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AIM AND SCOPE

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REVIEW

Biomarkers in colorectal cancer: Current clinical utility and future perspectives

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Abstract

Colorectal cancer (CRC) is a major cause of cancer death worldwide. CRC has poor prognosis and there is a crucial need for new diagnostic and prognostic biomarkers to avoid CRC-related deaths. CRC can be considered a sporadic disease in most cases (75%-80%), but it has been suggested that crosstalk between gene mutations (*i.e.,* mutations of *BRAF*, *KRAS*, and *p53* as well as microsatellite instability) and epigenetic alterations (*i.e.,* DNA methylation of CpG island promoter regions) could play a pivotal role in cancer development. A number of studies have focused on molecular testing to guide targeted and conventional treatments for patients with CRC, sometimes with contrasting results. Some of the most useful innovations in the management of CRC include the possibility to detect the absence of *KRAS*, *BRAF*, *NRAS* and *PIK3CA* gene mutations with the subsequent choice to administer targeted adjuvant therapy with anti-epidermal growth factor receptor antibodies. Moreover, CRC patients can benefit from tests for microsatellite instability and for the detection of loss of heterozygosity of chromosome 18q that can be helpful in guiding therapeutic decisions as regards the administration of 5-FU. The aim of this review was to summarize the most recent evidence on the possible use of genetic or epigenetic biomarkers for diagnosis, prognosis and response to therapy in CRC patients.

Key words: Biomarkers; Colorectal cancer; Epigenetics; Tumor markers; DNA methylation

Core tip: Colorectal cancer (CRC) is one of the leading causes of cancer death in the world today. Therefore, any improvement in early diagnosis, selection of appropriate treatment regimen, and effective follow up can be crucial in decreasing related mortalities.

This review discusses the most useful and promising genetic and epigenetic biomarkers for CRC. There is growing evidence that these biomarkers could help future development of more personalized treatment approaches.

Vacante M, Borzì AM, Basile F, Biondi A. Biomarkers in colorectal cancer: Current clinical utility and future perspectives. *World J Clin Cases* 2018; 6(15): 869-881 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/869.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.869

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer death worldwide, with an estimated 2.2 million new cases and 1.1 million deaths in the next ten years[1]. Therapeutic strategies for stage Ⅰ, Ⅱ, and Ⅲ disease includes surgery, adjuvant chemotherapy only for selected patients with stage Ⅱ and most patients with stage Ⅲ CRC, and radiotherapy for patients with stage Ⅱ and Ⅲ rectal cancers[2,3]. Palliative therapies are used for patients with metastasis or stage Ⅳ colorectal cancers that are not resectable; in these patients, the objective is to control symptoms and increase survival[4]. CRC has poor prognosis and there is a crucial need for new diagnostic and prognostic biomarkers to avoid CRC-related deaths[5]. Many recent studies have focused on molecular testing to guide targeted and conventional treatments for patients with CRC[6]. The molecular analysis of biomarkers for CRC is making great progress, but the inclusion of novel molecular tests into routine clinical practice faces huge challenges such as a better comprehension of genetic mutations in CRC, the need for laboratory techniques able to measure the resulting phenotypes and genotypes, and the achievement of regulatory qualification for clinical use. In 2011, a National Comprehensive Cancer Network (NCCN) Task Force aimed to assess the clinical utility of tumor markers for different cancer types (including CRC), and underlined common difficulties that clinicians may experience in the management of oncological patients, and then suggested recommendations for the community interested in developing tumor markers[6]. Many of the published findings on molecular biomarkers are controversial, and currently the most reliable molecular marker in clinical practice is the *KRAS* gene for patients receiving epidermal growth factor receptor (EGFR) - targeted therapy for CRC metastatic disease[7]. In 2017, an Expert Panel of The American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology developed guidelines that aimed to determine standard molecular biomarker testing of CRC tissues in order to direct EGFR therapies and standard chemotherapy regimens. The Expert Panel carried out a literature search that included more than 4000 scientific papers and concluded that mutations in EGFR signaling pathway genes may predict negative response to EGFR-directed therapies for CRC[8]. The process of carcinogenesis in CRC is related to different mechanisms that include, among others, chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI)[9]. In 1990, Fearon and Vogelstein described a classical genetic model for colorectal cancerogenesis characterized by the accumulation of mutations in the adenomas, the subsequent mutational activation of the *KRAS* oncogene , and the inactivation of the genes encoding *p53*[10]. Recent studies suggested crosstalk between gene mutations (*i.e*., mutations of *BRAF*, *KRAS*, and *p53* and microsatellite instability) and epigenetic alterations (*i.e.,* DNA methylation of CpG island promoter regions) in cancer development; in fact, gene mutations could potentially affect epigenetic patterns and epigenetic changes could guide mutation processes and genome instability[11]. CRC can be considered a sporadic disease in most cases (75%-80%), as a consequence of the accumulation of both mutations and epigenetic alterations of numerous genes[12]. A number of studies on DNA methylation concluded that there are no less than three subtypes of CRC in relation to the rate of DNA methylation and mutations in key genes for CRC[13]. The interaction of both gene mutations and epigenetic changes could be responsible for the development of malignant adenocarcinomas as a result of the interference on signaling pathways that control cell growth and tumor progression[14]. Currently, research has moved towards the identification of mutations in key genes involved in the progression of cancer (*i.e., APC*, *CTNNB1*, *BRAF* and *KRAS*), which are implicated in the WNT and the RAS-RAF-mitogen-activated protein kinase (MAPK) signaling cascades, and, eventually, in the classical adenoma-carcinoma sequence pathway (Table 1). The aim of this review was to summarize the most recent evidence on the possible use of genetic or epigenetic biomarkers for diagnosis, prognosis and response to therapy in CRC patients.

TISSUE- BASED BIOMARKERS

BRAF

BRAF is a gene that encodes a serine-threonine protein kinase and is a regulator of the MAPK pathway that is located downstream of *KRAS*. *BRAF* represents a prognostic biomarker and a possible target for therapies in patients with CRC[15]. Activating mutations of *BRAF* occur most frequently in codon 600, and are demonstrable in different types of cancers, for example CRC (10%), melanoma (50%)[16], and lung tumors (1%–2%)[17]. The conversion of valine 600 to glutamic acid (V600E) accounts for 80% of the *BRAF* mutations in CRC. There is evidence that *KRAS* and *BRAF* mutations are mutually exclusive events in cancer progression and

Table 1 Examples of biomarkers for colorectal cancer diagnosis, progression, prognosis and treatment

Biomarker		Prognostic factor	Predictive factor
BRAF mutations	Specific phenotype and metastasis; resistance to anti-EGFR mAb	Yes[6,110]	Yes[111], Potentially[6,110]
KRAS mutations	Heterogeneity of CRC; resistance to anti-EGFR mAb	Yes potentially[110]	Yes[6,110,111]
MSI	Resistance to 5-FU	Yes[6,110], No[111]	-
APC mutations	Poorer overall survival	Yes[66]	Yes[65]
Micro-RNA	Early detection of CRC, prognostic stratification and therapy-response prediction	Yes[72]	Yes[73]
PIK3CA mutations	Poor prognosis and particular clinico-pathological characteristics; resistance to anti-EGFR mAb	Yes[82]	Yes[110]
Loss of *PTEN*	High tendency to develop metastasis; Resistance to anti-EGFR mAb	-	Yes potentially[110,111]
TP53 expression	Poor prognosis	Yes potentially[110], No[111]	-
Loss of *NDST4*	Adverse prognosis; molecular predictor of metastasis	Yes[95]	Yes[95]
Loss of *18qLOH*	Poor prognosis	Yes[111], Potentially[110]	-
IGFR-1R	High levels in metastastic CRC; poor overall survival	Yes[104]	Yes[104]

National Comprehensive Cancer Network Guidelines[6]; European Society for Medical Oncology Guidelines[110]; American Society of Clinical Oncology Guidelines[111]. CRC: Colorectal cancer; EGFR: Epidermal growth factor receptor; MSI: Microsatellite instability; FU: Fluorouracil.

development[18]. Many studies highlighted different responses to anti-EGFR treatment according to *BRAF* status, with a failing rate of anti-EGFR up to 12%-15% in *BRAF* (V600E) mutation carriers[19]. Some studies showed a high methylation rate (CIMP-high) in *BRAF* mutation carriers compared to *BRAF* wild-type (WT) cancer; furthermore, it has been demonstrated a marked association between BRAF mutation and MSI[20]. BRAF mutant cancers are characterized by high prevalence in women and in elderly patients (> 70 years)[21], four or more positive lymph nodes, high-grade histology, defective mismatch repair status, and are mainly sited in the right side of the colon, while wild type tumors can generally affect any part of the colon and rectum[22]. Many retrospective studies underlined the poor prognosis in patients with *BRAF* mutations. Roth *et al*[23] evaluated the prognostic role of *KRAS* and *BRAF* in 3278 patients with stage Ⅱ and Ⅲ colon cancer patients receiving irinotecan added to fluorouracil (FU)/leucovorin (FA) as adjuvant treatment. The results confirmed that the *KRAS* mutation status does not have significant prognostic value, while *BRAF* is prognostic for overall survival in MSI low and stable tumors, especially in stage Ⅱ patients[23]. Similar results were observed in a study by Yokota *et al*[24] carried out in 229 patients on the prognostic impact of *KRAS*/*BRAF* mutations in advanced and recurrent CRC patients receiving chemotherapy treatment. *KRAS* and *BRAF* mutations were observed in 34.5% and 6.5% of patients, respectively. The overall survival in patients with *KRAS* and *BRAF* mutations (27.7 and 11.0 months respectively) was significantly poorer than that observed in patients with wild type forms of these genes. The results confirmed that *BRAF* mutations can be considered a strong prognostic factor for poor survival in advanced and recurrent CRC[24]. Nowadays, there is growing interest in the understanding of treatment implications of *BRAF* mutations. The MRC FOCUS trial evaluated the effects of FU, FU/irinotecan or FU/oxaliplatin administration in in 711 patients with advanced CRC and showed, as previously reported, that patients with *BRAF* mutations had a lower overall survival compared to patients with *BRAF*-WT. It is noteworthy that the response to chemotherapy treatment was not influenced by *BRAF* status, suggesting that *BRAF* mutations should not be considered as predictive biomarkers for irinotecan or oxaliplatin[25]. A number of studies highlighted that *BRAF* mutations in CRC can predict the lack of response to anti-EGFR treatment. Bokemeyer *et al*[26] analyzed pooled individual patient data from the CRYSTAL and OPUS randomized clinical trials (RCTs). The results of these RCTs showed that when cetuximab was added to first line chemotherapy treatment in patients with *KRAS*-WT CRC, there was a significant improvement in overall survival, progression-free survival, and best overall response rate. No significant differences were observed in the outcome between *BRAF* mutation carriers and *BRAF*-WT receiving EGFR-targeting therapies. Patients with *BRAF* mutations had a poorer prognosis compared to those with BRAF-WT[26]. A meta-analysis by Mao *et al*[27] carried out on 11 studies (7 studies for unselected mCRC patients and 4 studies for patients with *KRAS*-WT metastatic CRC),demonstrated that the *BRAF*(V600E) mutation is related to a lack of response in *KRAS*-WT metastatic CRC patients receiving anti-EGFR monoclonal antibodies. Another meta-analysis that included 463 patients with *RAS*-WT/*BRAF* mutant status CRC reported similar results. The analysis included 9 phase Ⅲ trials and 1 phase Ⅱ trial (6 first-line and 2 second-line trials, plus 2 trials involving chemorefractory patients). The addition of anti-EGFR monoclonal antibodies cetuximab and panitumumab in the *BRAF* mutant subgroup did not lead to any improvement in outcome compared to standard therapy or best supportive care. These results underlined the importance of *BRAF* mutation evaluation before starting anti-EGFR monoclonal antibody therapies[28]. Because of their growing importance, the NCCN guidelines strongly recommend *BRAF* and *RAS* (*KRAS* exon 2 and non-exon 2; *NRAS*) mutation testing for diagnosis of stage Ⅳ CRC[6]. Based on this evidence, *BRAF* mutations may be used as a biomarker to screen metastatic CRC

patients who could benefit from therapy with anti-EGFR antibodies.

KRAS

The *KRAS* gene encodes a small GTPase transductor protein that regulates cellular growth and differentiation[29]. The *KRAS*-WT protein is transitorily activated during signal transduction, but mutations in the *KRAS* gene could lead to the continuous activation of this signal transduction pathway and, as a result, to cell transformation and inefficacy of therapy with anti-EGFR antibodies[14]. Most activating mutations of *KRAS* involve codons 12 (82%-87%) and 13 (13%-18%), and only rarely codons 61, 63 and 146. Mutations in codon 12 are linked to mucinous CRC, while mutations in codon 13 are predominantly non-mucinous, showing more aggressive behavior and a tendency to develop metastasis[30]. A number of studies pointed out the key role of *KRAS* mutations as predictive markers for anti-EGFR therapy. An open-label, randomized, multicenter, phase Ⅲ study by Van Cutsem *et al*[31] showed that the administration of cetuximab in patients with metastatic *KRAS*-WT CRC receiving irinotecan, FU, and leucovorin (FOLFIRI) resulted in significant benefits as regards overall survival, progression-free survival and response compared with FOLFIRI alone. These results confirmed the importance of *KRAS* mutation status as a strong predictive biomarker for the efficacy of cetuximab plus FOLFIRI[31]. The benefits from cetuximab in advanced CRC patients with *KRAS*-WT, but not in those with *KRAS* mutation, were also reported in a RCT by Karapetis *et al*[32]. The Authors analyzed tumor samples from 394 patients with CRC, who were given cetuximab plus best supportive care (BSC) or BSC alone. Of these patients 42.3% showed at least one mutation in exon 2 of the *KRAS* gene. In CRC patients with *KRAS*-WT, cetuximab significantly improved overall survival and progression-free survival when compared with BSC alone. These differences were not observed in CRC patients with *KRAS* mutations. The presence of *KRAS* mutations represents a negative predictive factor, and plays a crucial role in the decision about the use of anti-EGFR therapy (Figure 1).

Microsatellite instability

Microsatellites are short tandem repeats of DNA sequences positioned throughout the human genome. MSI is a hypermutable phenotype caused by a deficient DNA mismatch repair (MMR) system, mainly due to the inactivation of the four MMR genes (*MSH2*, *MLH1*, *MSH6* and *PMS2*) that leads to a failure in the correction of the insertion or the deletion of repeating units during DNA replication [33]. MSI is observed in about 15% of all CRCs; 3% of these are associated with Lynch syndrome (Hereditary non polyposis colorectal cancer or HNPCC), and the other 12% are due to sporadic, hypermethylation of the promoter of the *MLH1* gene, in patients with the CpG island methylator phenotype[34]. CRCs with microsatellite instability are more frequent in the right colon, are mucinous with signet ring cell morphology, show poor differentiation and strong lymphocyte infiltration. Overall, CRC patients with MSI have a better prognosis that those without MSI and show a different response to chemotherapy treatment[35]. It has been observed that stage Ⅱ or stage Ⅲ CRC patients with stable or low MSI could benefit from adjuvant chemotherapy with 5-fluorouracil, while patients with stage Ⅱ CRC and high MSI show a 3-fold increase in mortality, probably due to the immunosuppressive effects of the therapy[36]. On the contrary, a retrospective study carried out by Fallik *et al*[37] on a small number of patients (n = 72) with metastatic CRC showed that the administration of irinotecan could be useful in MSI tumors even if these results need further clarification and are not yet applicable in routine clinical practice. A meta-analysis of eight independent studies conducted by Des Guetz *et al*[38] included a total of 287 patients who received 5FU-based chemotherapy, and 678 patients who were treated with other chemotherapy regimens (5FU or capecitabine with oxaliplatin and/or irinotecan). The data were analysed with a random-effect model due to heterogeneity between studies. The authors concluded that MSI status is not a predictive factor for the effect of chemotherapy, with comparable results in both MSI-High and MSI-stable metastatic CRC tumors[38]. MSI can be considered a promising prognostic marker for CRC patients and MSI status can be assessed through a panel of five markers (*BAT25*, *BAT26*, *D2S123*, *D5S346*, and *D17S2720*) and the use of polymerase chain reaction (PCR). MSI-high is characterized by instability at two loci or more, and MSI-Low by instability at one locus[39]. Currently, the main clinical use of MSI testing is to detect patients with Lynch syndrome. About 15% of all CRCs show MSI, and among these 75%–80% are characterized by acquired methylation of *MLH1*; 2%–3% of all CRCs show germ-line mutations in one of the MMR genes[40]. There is growing interest in MSI testing as regards the adjuvant setting to guide therapeutic choices; however, the implication of MSI in the metastatic setting is not well recognized.

EPIGENETIC MARKERS IN CRC

CpG island methylator phenotype

The term "epigenetics" refers to modifications in the phenotype or gene expression that do not implicate DNA sequence changes. Among these, DNA methylation is one of the most studied CRC biomarkers and plays a pivotal role in the alteration of gene expression observed in cancerogenesis[41] (Table 2). Hypermethylation of CpG islands sited in the promoter regions of tumor suppressor genes is a well-recognized mechanism for gene inactivation[42]. The inactivation of gene transcription is due to changes in the chromatin structure of a gene promoter that becomes inaccessi-

Table 2 Examples of epigenetic biomarkers for colorectal cancer

Epigenetic markers	
Methylated genes/loci	
p14 ARF, p15 INK 4b, p16 INK4a	Cell cycle regulation
hMLH1, MGMT	DNA repair system; progression from adenoma to cancer
DAPK	Apoptosis
THBS1	Angiogenesis inhibition
SPARC	Lymphovascular invasion, metastasis
TIMP3	Metastasis suppression
CDH1, CDH13	Cell adherence
Methylation biomarkers	
VIM, SEPT9, SFRP2	Biomarkers for CRC and as DNA-based colon cancer screening tests
TWIST1, IGFBP3, GAS7, ALX4, SDC2	Higher methylation levels in CRC compared to normal subjects (promising diagnostic biomarkers)
Candidate biomarkers	
Methylated *UGT1A1*	Affects irinotecan treatment (*in vitro*)
Methylated *DYPD, UMPK*, and *SPARC*	Affect 5-FU treatment (*in vitro*)
TFAP2E	No responsiveness to oxaliplatin, irinotecan, and 5-FU

CRC: Colorectal cancer; FU: Fluorouracil.

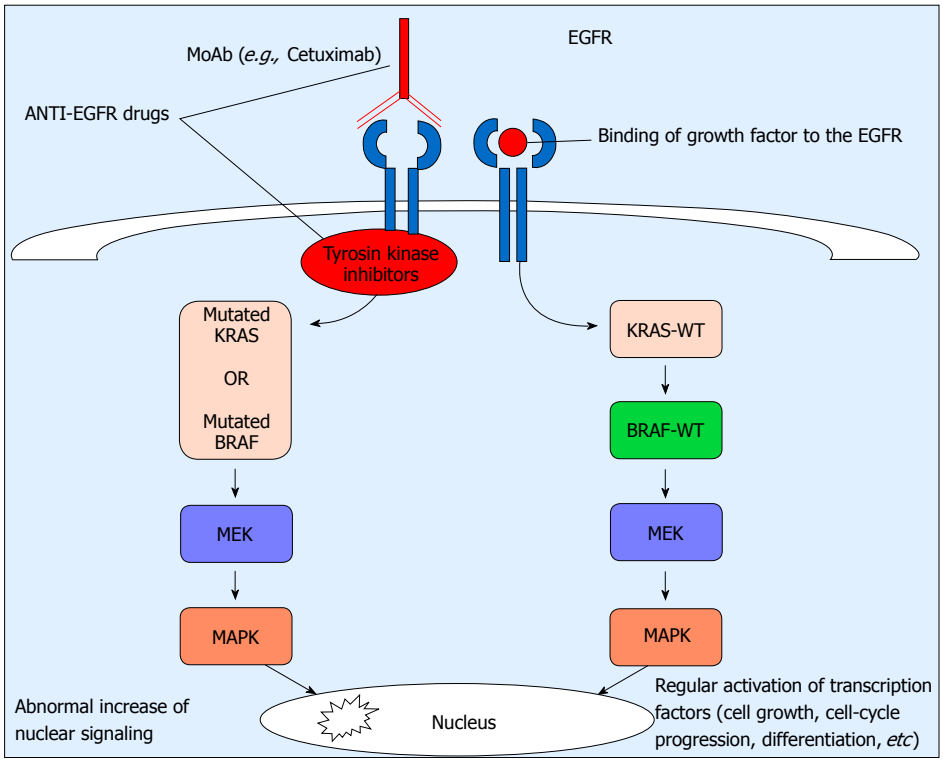

Figure 1 Epidermal growth factor receptor pathway in patients with wild-type and mutant *BRAF* and *KRAS*. On the right side of the figure, the normal epidermal growth factor receptor (EGFR) pathway is characterized by the binding of growth factor to the EGFR that leads to regular activation of transcription factors and cell-cycle progression; On the left side, mutations in *BRAF* or *KRAS*, which are mutually exclusive, cause the activation of the EGFR pathway and therefore an abnormal increase of nuclear signaling and no response to monoclonal antibodies. EGFR: Epidermal growth factor receptor; MEK: Mitogen-activated protein kinase kinase; MAPK: Mitogen-activated protein kinase; MoAb: monoclonal antibodies; WT: Wild type.

ble to transcription factors[42]. This epigenetic alteration is able to inactivate a number of cellular pathways that include, for example, DNA repair system (*hMLH1*, *MGMT*), apoptosis (*DAPK*), angiogenesis inhibition (*THBS1*), metastasis suppression (*TIMP3*), cell cycle regulation (*p14 ARF*, *p15 INK 4b*, *p16 INK4a*), and cell adherence (*CDH1*, *CDH13*)[43,44]. There is evidence of a strong correlation between CIMP-high and right colon cancer, microsatellite instability and a high rate of *BRAF* mutation[44]. Some studies showed that abnormal methylations of DNA repair genes, for example, *MGMT* and *MLH1*, may lead to the progression from adenoma to cancer. The mechanisms involved are the creation of a more prone state for G->A mutations, as frequently observed in *KRAS* in the case of methylated *MGMT* and a favorable condition for MSI in the case of methylated *MLH1*[45,46]. Lee *et al*[47] suggested that the CIMP could be used as a predictive marker for anti-EGFR therapy.

However further prospective studies are needed to confirm this hypothesis. Methylated genes such as *MLH1*, *VIM* and *SEPT9*, could be used as biomarkers for colorectal cancer and as DNA-based colon cancer screening tests. Methylated Vimentin (mVim) is a validated stool-based biomarker for early detection of colorectal cancer available in the US (ColoGuard assay; LabCorp)[48]. The methylated *VIM* gene is observed in most CRC (53%–84%). The test is PCR based and is able to measure methylated *VIM* and DNA integrity with high sensitivity and specificity (83% and 82%, respectively)[49]. A recent meta-analysis of 25 studies by Nian *et al*[50] pointed out that methylated *SEPT9* (Epi proColon; Epigenomics AG) can be considered as an effective blood-based assay in CRC detection, mostly for advanced tumors. The proportion of heterogeneity due to threshold effect was 0.02, which indicated the absence of significant thread hold effect among the included studies. Meta-regression demonstrated that study types, country (Asian population or not), sample size (less or greater than 300) kits used (Epipro colon or not), and risk of bias of included studies were all sources of heterogeneity of sensitivity and specificity[50]. Perez-Carbonell *et al*[51] carried out a systematic analysis of a panel of methylated CRC-specific genes (*SEPT9*, *TWIST1*, *IGFBP3*, *GAS7*, *ALX4* and *miR137*) and observed that methylation levels of all these genes were significantly higher in CRC compared to normal subjects ($P < 0.0001$), mainly as regards miR137 and *IGFBP3* (86.7% and 83%, respectively). The combination of these two genes showed a sensitivity of 95.5% and a specificity of 90.5% for the detection of CRC, thus representing a promising diagnostic biomarker. Moreover, the results of this study underlined that hypomethylation of *IGFBP3* could represent an independent risk factor for poor prognosis in patients with stage Ⅱ and Ⅲ CRC. Interestingly, in stage Ⅱ and Ⅲ CRC patients who showed hypermethylation of *IGFBP3*, adjuvant chemotherapy with 5FU did not improve overall survival or disease free progression[51]. Methylated *IGFBP-3* could be used as a potential target for the development of novel anticancer drugs, for example demethylating agents. Further studies are needed to clarify the association between methylated *IGFBP-3* and low recurrence-free survival, and to report the efficacy of demethylating agent alone or combined with adjuvant therapy in CRC patients[52]. A study by Tang *et al*[53] underlined the importance of methylated secreted frizzled-related protein 2 (*SFRP2*) as a possible marker for CRC detection and staging. *SFRP2* can be isolated from CRC tissues, serum and fecal DNA, with sensitivity for CRC that ranges from 66.9% to 88.2%. A higher specificity of *SFRP2* methylation levels for CRC was observed in serum compared to tissue and stool DNA. Furthermore, there was a significant association of serum *SFRP2* with low differentiation grade, serosal or subserosal infiltration, lymph node metastasis and TNM stage of CRC[53]. Other promising blood biomarkers include methylated thrombomodulin (*THBD*) that detected 71% of all CRCs at a specificity of 80%[54], and methylated syndecan 2 (*SDC2*) that showed a sensitivity of 92% for CRC at stage Ⅰ[55]. There is emerging evidence that epigenetic mechanisms could affect the response to chemotherapy[56]. Increased thymidylate synthetase (*TYMS*) expression, which is regulated by histone acetylation and deacetylation, seems to be the main mechanism involved in the development of resistance to 5-FU. A study by Watson *et al*[57] showed that CRC patients with *TYMS* amplification receiving post-resection 5-FU-based chemotherapy, showed shorter median survival. Other genes involved in pyrimidine metabolism that could determine resistance to 5-FU, thus guiding the chemotherapy choice for CRC, include thymidine phosphorylase (*TYMP*), uridine monophosphate/cytidine monophosphate kinase (*UMPK*), and dehydrogenase (*DYPD*) genes[53]. A clinical trial by Ebert *et al*[58] examined an initial cohort of 74 patients, followed by four cohorts of patients (total $n = 220$) and showed that CRC patients with high levels of methylation of the gene encoding transcription factor AP-2 epsilon (*TFAP2E*) did not benefit from chemotherapy treatment with 5-FU, irinotecan or oxaliplatin ($P < 0.001$). *TFAP2E* resistance is mediated through its downstream target gene DKK4, encoding dickkopf homolog 4 protein. In CRC patients with *TFAP2E* hypermethylation, targeting of *DKK4* could represent a possible option to bypass the resistance to chemotherapy mediated by *TFAP2E*[58]. Some studies showed a possible association between methylation of the *SPARC* gene (coding for the matricellular protein osteonectin)[59], and methylation of the *UGT1A1* gene (coding for the UDP glucuronosyltransferase-1A1 enzyme)[56] to a reduction of chemosensitivity to 5-FU or irinotecan. Amatu *et al*[60] carried out a phase Ⅱ study with dacarbazine in CRC patients who did not respond to standard chemotherapy (oxaliplatin, irinotecan, fluoropyrimidines, and cetuximab or panitumumab if *KRAS*-WT). Dacarbazine is an antineoplastic alkylating agent that acts by DNA methylation and causes base pair mismatch. Considering all CRC patients, 40% present hypermethylation of the *MGMT* gene and dacarbazine is effective only in tumors that lack *MGMT*[60].

APC

Adenomatous polyposis coli (*APC*) is a suppressor gene that was detected by genetic linkage analysis in familial adenomatous polyposis (FAP). Mutated APC is also responsible for most sporadic CRCs[61]. *APC* acts as an antagonist of the WNT signaling pathway and regulates many cell activities such as migration and adhesion, transcriptional activation, and apoptosis[62]. Around 70%-80% of patients with CRC show the loss of *APC*[63]. A meta-analysis by Liang *et al*[64] evaluated the associations between three APC polymorphisms (*D1822V*, *E1317Q*, and *I1307K*) and the risk of CRC.

The results showed a low association between *E1317Q* and the risk of CRC, especially for adenomas. Ashkenazi Jews *I1307K*-variant carriers showed a significantly increased risk of CRC compared to *I1307K* wild-type carriers. In this meta-analysis, there was no evidence of heterogeneity between studies; however, all the included studies were case-control studies with high likelihood of recall bias and selection bias[64]. Another recent meta-analysis highlighted that hypermethylated *APC* promoter was more frequent in adenoma than in normal control samples. Moreover, *APC* hypermethylation levels were higher in CRC patients at stage Ⅰ compared to normal controls. The authors concluded that *APC* hypermethylation could represent an important biomarker for early CRC diagnosis and a possible treatment target for personalized therapy. Interestingly, the results did not show a significant association between APC promoter methylation and overall survival in CRC patients. The heterogeneity in the meta-analysis was 43%, and there was no publication bias. However, only publications in English and Chinese were included in the study, thus suggesting the possible existence of selection bias[65]. Another study showed that *APC* mutation/high miR-21 in patients with advanced CRC had poorer overall survival. The mutation of *APC* and expression of miR-21 might be useful clinical predictors for CRC[66-68].

microRNA

microRNAs (miRNAs) are small non-coding RNA sequences that can control the expression of genes at the post-transcriptional level[69]. miRNAs play crucial roles in cancer biology and are involved in a number of cellular processes such as proliferation, apoptosis, differentiation, invasion and metastasis[70]. There is growing evidence that carcinogenesis and tumor progression could be associated with abnormalities of miRNAs[71]; thus, miRNAs could represent valuable biomarkers for early detection of cancer, prognostic stratification and therapy-response prediction[72,73]. miRNAs can be isolated from a variety of biological samples, including blood, saliva and stools[74]. A recent study identified a set of 19 differentially expressed miRNAs. Among these, the up-regulation of hsa-miR-183-5p and hsa-miR-21-5p, and the down-regulation of hsa-miR-195-5p and hsa-miR-497-5p were associated with CRC through the interplay with the *MMR* pathway and transforming growth factor β, *WNT*, *RAS*, *MAPK*, and *PI3K* signaling pathways[68]. miR-21 is one of the most studied miRNAs[75]; a recent meta-analysis by Peng *et al*[67] investigated the role of miR-21 in CRC and reported a sensitivity of 0.64, a specificity of 0.85 and an area under the curve of 0.85, as regards diagnostic test accuracy. Samples taken from blood circulation showed corresponding values of 0.72, 0.84, and 0.86 respectively. As regards diagnostic meta-analysis of miR-21-related combination biomarkers, the above values were 0.79, 0.79 and 0.86, respectively. The highest predictive power was observed for miRNA combination markers in circulation (0.85, 0.86, and 0.92 respectively). These results suggested that circulating (especially in serum) miR-21 could represent a promising diagnostic biomarker, while tissue miR-21 could be a useful prognostic marker for CRC. Meta-regression analysis found that ethnicity, sample size, and sample source did not have a significant effect on the pooled results ($P > 0.10$). Also, there was no heterogeneity from the threshold effect.

OTHER PROMISING BIOMARKERS FOR CRC

Phosphatidylinositide-3-kinases

Phosphatidylinositide-3-kinases (PI3K) are lipid kinases that are involved in the regulation of cellular behavior, including proliferation, adhesion and survival[76]. PI3K signaling is a major pathway for *RAS*-mediated proliferation, transformation and tumor progression[77]. Abnormalities in PI3K signaling are frequently observed in human cancer[78] and mutations in the *PIK3CA* gene, the gene coding for the catalytic subunit p110alpha of PI3K, have been described in many cancers, including CRC[79]. These mutations in CRC are associated with right side location, mucinous histological type, *KRAS* mutation, loss of *MGMT* expression and a high degree of methylation (CIMP)[78]. *PIK3CA* mutation is also associated with a significant reduction in survival in CRC patients with *BRAF*-WT[80]. Mutations at *PIK3CA* exon 9 and exon 20 trigger different biologic effects and are responsible for the promotion of cancerogenesis. A genetic and biochemical analysis conducted by Zhao *et al*[81] demonstrated that coexistent mutations in both exons 9 and 20, but not in exon 9 or 20 alone, result in an increase of tumorigenic effects with worse cancer-specific survival. Jehan *et al*[82] analyzed data from 220 patients who received adjuvant chemotherapy and/or radiotherapy and showed that *PI3KCA* amplification could represent an independent prognostic marker for better survival and a promising marker to detect CRC patients that may benefit the most from adjuvant therapy. Recent studies proposed mutated *PIK3CA* as a biomarker to detect CRCs sensitive to aspirin. Liao *et al*[83] carried out a study in 964 patients with CRC and observed that patients with mutated-*PIK3CA* who started aspirin therapy after diagnosis, showed higher colorectal cancer-specific survival (multivariate hazard ratio for cancer-related death, 0.18; 95%CI, 0.06 to 0.61; $P < 0.001$ by the log-rank test) and overall survival (multivariate hazard ratio for death from any cause, 0.54; 95%CI, 0.31 to 0.94; $P = 0.01$ by the log-rank test), as compared to patients with *PIK3CA*-WT[83]. Domingo *et al*[84] studied 896 participants in the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime trial, and confirmed the role of mutated *PIK3CA* as a predictive molecular biomarker in CRC patients for adjuvant aspirin therapy. A population-

based cohort study of 740 stage Ⅱ and Ⅲ CRC patients, showed a 31% improvement in cancer-specific survival in aspirin users compared to non-users (adjusted HR = 0.69, 95%CI: 0.47–0.98). These outcomes were more evident in patients with high *PTGS2* (prostaglandin-endoperoxide synthase 2, also known as cyclooxygenase-2 or COX-2) expression compared to those with low *PTGS2* expression. Further trials are needed to better detect CRC patients who may receive a survival benefit from aspirin therapy[85].

PTEN

PTEN is a tumor suppressor gene that regulates the cell-survival signaling pathway initiated by PI3K. *PTEN* mutations are associated with advanced and metastatic tumors[86] and *PTEN* promoter hypermethylation is frequently observed in MSI-high sporadic CRCs[87]. Patients with *PTEN* expression showed significantly longer overall survival compared to patients with *PTEN* loss tumor[88]; other studies reported an association with poor prognosis in stage Ⅱ patients only[86] or in CRC patients with liver metastasis[89]. *PTEN* could represent a useful predictive marker for *KRAS*-WT patients treated with anti-EGFR therapy[90].

TP53

The *TP53* gene encodes a tumor suppressor protein that is involved in the regulation of cell cycle, apoptosis, senescence, and DNA repair. *TP53* mutations may result in altered function of TP53 protein, which plays a pivotal role in tumorigenesis. *TP53* mutations are observed in about 60% of colorectal tumors and can be found in both adenomas and in malignant cells[91]. There is evidence that the expression of *p53* mRNA could represent a useful predictor of survival in patients with stage Ⅲ CRC or rectal cancer[92].

NDST4

NDST4 is a tumor suppressor gene located at chromosome 4q26. Most CRCs showed a significant decrease in *NDST4* expression compared to normal colonic mucosa and some studies showed that the loss of *NDST4* was associated with higher pathological stages and poor survival[93]. *NDST4* belongs to the N-deacetylase/N-sulfotransferase (heparan glucosaminyl) (*NDST*) family, and regulates heparan sulfate (HS) biosynthesis on a core protein to form heparan sulphate proteoglycans (*HSPGs*)[94]. The loss of *NDST4* function could lead to an increase in the invasive ability of cancer cells through changes of the interaction between cell adhesion receptors and their ligands. The genetic loss of *NDST4* could represent a biomarker of adverse prognosis for patients with CRC[95].

Chromosome 18q loss of heterozygosity

Loss of heterozygosity of chromosome 18q (18qLOH) is a genetic alteration frequently observed in CRC[94] and many key genes (*i.e., DCC*, *SMAD2* and *SMAD4*), involved in CRC tumorigenesis, are located on chromosome 18q[95,96]. A study by Sarli *et al*[97] carried out in 118 patients, reported a decreased overall survival for patients with CRC stage Ⅲ and 18qLOH compared to non-18qLOH patients. The authors concluded that 18qLOH could represent an informative genetic marker, and has the potential to be used to predict recurrences and survival in resected stage Ⅲ CRCs[97]. A meta-analysis of 27 studies on the prognostic significance of 18q LOH showed that chromosome 18q allelic imbalance and *DCC* loss of expression could be considered as negative predictive factors for survival. In this metanalysis there was evidence of significant heterogeneity and publication bias[98]. However, these findings suggested that 18q LOH/*DCC* status could help to detect CRC patients who may benefit from adjuvant chemotherapy after potential curative surgery[99]. Boulay *et al*[100] analyzed 202 colorectal tumour biopsies from a previous randomised study of adjuvant chemotherapy, and observed that patients with the loss of 18q (and *SMAD4* deletion) could obtain less benefit from adjuvant 5-FU treatment.

IGFR-1R

The type 1 insulin-like growth factor receptor (IGF-1R) is a transmembrane glycoprotein composed of two extracellular subunits and two cytoplasmic subunits with tyrosine kinase activity. Overexpression of IGFR-1R has been observed in various tumors (*i.e.,* primary renal cancer cells, and preinvasive breast lesions), and its activation is involved in cell proliferation, differentiation, angiogenesis, and apoptosis[101,102]. IGF-1R undergoes nuclear translocation and interacts with chromatin, under the regulatory effect of IGF[103]. IGF-1R has become a target of new treatments, especially monoclonal antibodies or tyrosine kinase inhibitors. In vitro studies demonstrated that chemotherapy resistance in CRC cell lines was associated with overexpression of IGF-1R within the nuclear compartment. Recently, Codony-Servat *et al*[104] carried out a study in four cohorts of patients with metastatic CRC (total *n* = 470), and showed that IGF-1R nuclear location might lead to chemotherapy and targeted agent resistance. Metastatic CRCs presented higher levels of IGF-1R compared to untreated primary cancers and showed poor overall survival. It is noteworthy that ganitumab, an IGF-1R blocking monoclonal antibody, and dasatinib, an SRC inhibitor, augmented the nuclear localization of IGF-1R. Based on these results, IGF-R1 could represent a new potential biomarker for poor prognosis in patients with metastatic CRC[104].

CONSENSUS MOLECULAR SUBTYPES CLASSIFICATION OF CRC

The consensus molecular subtypes (CMS) classification is a recent CRC classifications based on comprehensive gene expression profiling[105,106]. CRC can be separated

into 4 groups called *CMS1*, *CMS2*, *CMS3* and *CMS4*, and each group shows a unique biology and gene expression pattern: *CMS1* (MSI immune, 14%), with higher mutation levels, presence of MSI and marked immune activation; *CMS2* (canonical, 37%), found in epithelial CRCs, with higher *CIN*, and strong *WNT* and *MYC* signaling activation; *CMS3* (metabolic, 13%), observed in epithelial CRCs with evident metabolic disorders; and *CMS4* (mesenchymal, 23%), with noticeable TGF-beta activation, angiogenesis and stromal invasion. The remaining 13% may show mixed characteristics due to transition phenotype or intratumoral heterogeneity[106]. A recent retrospective study by Okita *et al*[107] carried out in 193 patients with metastatic CRCs, showed that the biological features of CMS may affect the efficacy of chemotherapy. In fact, the results of the study demonstrated that in *CMS4* subtype, chemotherapic regimens containing irinotecan showed more benefit than those containing oxaliplatin for progression-free survival [hazard ratio (HR) = 0.31, 95%CI: 0.13-0.64] and overall survival (HR = 0.45, 95%CI: 0.19-0.99). As regards anti-EGFR therapy, *CMS1* showed worse progression-free survival (HR = 2.50, 95%CI: 1.31-4.39) and overall survival (HR = 4.23, 95%CI: 1.83-9.04), while *CMS2* had better progression-free survival (HR = 0.67, 95%CI: 0.44-1.01) and overall survival (HR = 0.49, 95%CI: 0.27-0.87) compared to the other subtypes[107]. There is evidence that CMS classification could represent the starting point for future clinical stratification and subtype–based targeted interventions for CRC. A study by Isella *et al*[108] identified 5 CRC intrinsic subtypes (CRIS) characterized by unique molecular, functional and phenotypic features: (1) CRIS-A: mucinous subtype, glycolytic metabolism, with marked MSI, mutated BRAF or KRAS; (2) CRIS-B: active TGF-β signaling, epithelial–mesenchymal transition, bad prognosis; (3) CRIS-C: high EGFR signaling, and sensitivity to EGFR inhibitors (*i.e.,* cetuximab); (4) CRIS-D: high WNT signaling, *IGF2* gene amplification/overexpression (which has been involved in reduction of sensitivity to EGFR blockade in patients with *KRAS*-WT CRCs)[109]; and (5) CRIS-E: Paneth-like phenotype and *TP53*-mutated genotype. CRIS subtypes categorized independent groups of primitive and metastatic CRCs effectively, representing a great opportunity to enhance patients' management with regard to precision medicine.

CONCLUSION

Research is moving towards a better comprehension of the mechanisms underlying the pathophysiology and the management of colorectal cancer. Recently, new treatment regimens have been developed, mainly for advanced CRC stages. Some of the most useful innovations in the management of CRC include the possibility to detect the absence of *KRAS*, *BRAF*, *NRAS* and *PIK3CA* gene mutations with the subsequent choice to administer targeted adjuvant therapy with anti-EGFR antibodies. Moreover, CRC patients can benefit from tests for MSI and for the detection of 18qLOH that can be helpful in guiding therapeutic decisions as regards the administration of 5-FU. Future therapies for CRC could include targeted therapy against membrane receptors, for example other EGFR ligands, platelet-derived growth factor receptors, and insulin-like growth factor 1 receptor. It seems reasonable to think that in the future, molecular screening will help to recognize patients suitable for specific targeted treatments and to fully characterize cancers. The objective of future research will be to detect biomarkers that could provide a cost-effective and non-invasive diagnosis of CRC; other goals are the identification of the best prognostic panel of biomarkers and the characterization of predictive biomarkers to help in the selection of the most appropriate therapy.

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REVIEW

Inflammation and de-differentiation in pancreatic carcinogenesis

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Abstract

Pancreatic cancer is a malignancy with an extremely poor prognosis. Chronic pancreatitis is a well-known risk factor for pancreatic cancer. Inflammation is thought to influence carcinogenesis through DNA damage and activation of intracellular signaling pathways. Many transcription factors and signaling pathways co-operate to determine and maintain cell identity at each phase of pancreatic organogenesis and cell differentiation. Recent studies have shown that carcinogenesis is promoted through the suppression of transcription factors related to differentiation. Pancreatitis also demonstrates transcriptional changes, suggesting that multifactorial epigenetic changes lead to impaired differentiation. Taken together, these factors may constitute an important framework for pancreatic carcinogenesis. In this review, we discuss the role of inflammation and de-differentiation in the development of pancreatic cancer, as well as the future of novel therapeutic applications.

Key words: Pancreatitis; Inflammation; Organogenesis; Differentiation; Transcription factor; Pancreatic cancer

Core tip: Inflammation is involved in carcinogenesis by causing DNA damage. Recent studies show that

carcinogenesis is promoted by reprogramming factors and by suppressing transcription factors related to acinar cell differentiation. Pancreatitis also shows such transcriptional changes, suggesting that epigenetic changes by several causes leading to the impaired differentiation may constitute an important framework for pancreatic carcinogenesis. New diagnostic, preventive and/or treatment strategies based on the findings described in this review are expected to be clinically applied in the near future.

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INTRODUCTION

The worldwide incidence of pancreatic cancer is approximately 330000 cases in 2012, with trends indicating that rates are higher in men and in developed countries. The number of deaths due to pancreatic cancer are also estimated to be approximately 330000 people a year; it ranks 11th in cancer-related deaths[1,2]. The mean survival time is 19 mo and the 5-year survival rate is 5% or less; these figures indicate that pancreatic cancer has one of the worst prognoses across all forms of malignancy[2,3]. The early stages of pancreatic cancer are almost always asymptomatic. As a result, by the time symptoms become apparent, the disease is already at a very advanced stage. Because the 5-year survival rates of stage Ⅰ and Ⅳ pancreatic cancers are 43% and 7.7% respectively, early diagnosis and treatment are especially crucial to improve the overall prognosis of the disease.

One option, to aid in the earlier diagnosis of pancreatic cancer, is to elucidate more thoroughly the mechanism of carcinogenesis and identify high-risk groups to follow carefully. Well-known risk factors include smoking, obesity, diabetes, and chronic pancreatitis[4]. In particular, the risk of pancreatic cancer in patients with chronic pancreatitis is 13.3 times greater than that of healthy controls, suggesting that inflammation is deeply involved in the pathogenesis of pancreatic cancer[5,6].

It is well known that the *KRAS* mutation and mutational inactivation of the *CDKN2A*, *TP53*, and *SMAD4* tumor suppressors play important roles in the development of pancreatic cancer[4,7-9]. Furthermore, recent studies have shown that carcinogenesis is promoted by reprogramming factors and by suppression of transcription factors related to differentiation[10,11]. Interestingly, pancreatitis also shows the above transcriptional changes, suggesting that multifactorial epigenetic changes that result in impaired differentiation have an important role in pancreatic carcinogenesis.

In this review, we will discuss the mechanisms of pancreatic carcinogenesis from the perspective of pancreatic inflammation and cell differentiation.

INFLAMMATION AND PANCREATIC CARCINOGENESIS

In 1863, Rudolph Virchow first reported inflammatory cells in cancer tissues and hypothesized that inflammation promoted carcinogenesis[12]. In 1915, Yamagiwa induced skin cancer on the ears of rabbits by repeatedly painting them with coal tar, and experimentally revealed a case of carcinogenesis due to inflammation[13]. Furthermore, several cancers are known to be epidemiologically related to inflammatory diseases. For example, *Helicobacter pylori*-related gastritis patients have a 2.6-fold increased risk of gastric cancer[14]. Viral hepatitis and inflammatory bowel disease are risk factors for liver cancer and colon cancer, respectively. Previous epidemiological studies have demonstrated that non-steroidal anti-inflammatory drugs such as aspirin, lowers the overall risk of colon cancer[15,16]. Taken together, these results suggest that inflammation is frequently associated with carcinogenesis.

Chronic pancreatitis is a risk factor for pancreatic cancer[6]. Patients with hereditary pancreatitis, a rare cause of chronic pancreatitis and a strong risk for pancreatic cancer (49% of the patients develop pancreatic cancer by age 75 years), suffer from recurrent pancreatitis with pancreatic exocrine insufficiency and diabetes mellitus from a young age[17]. Mutations of the cationic trypsinogen (*PRSS1*) and serine protease inhibitor Kazal type 1 (*SPINK1*) genes cause hereditary pancreatitis[18,19]. Because the risk of developing pancreatic cancer does not change with the presence or absence of *PRSS1* or *SPINK1* gene mutations, it is unlikely that the gene itself functions as an oncogene or tumor-suppressor gene[19,20]. The increased carcinogenic risk in hereditary pancreatitis patients is presumed to be carcinogenesis due to prolonged inflammation.

Notably, Bailey *et al*[21] conducted unsupervised clustering of pancreatic cancer RNA sequencing data, and they classified pancreatic cancers into four subtypes: Squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine. Each subtype differently expresses unique transcription factors and downstream targets, which are important in lineage specification and differentiation during pancreas development. Among them, the immunogenic subtype is associated with a significant immune infiltrate[21], which may be associated with pancreatitis and carcinogenesis.

The relationship between pancreatic cancer and inflammation has also been explored in experiments using genetically engineered mice. When *Kras* mutations were introduced during the embryonic stage in mice, pancreatic intraepithelial neoplasia (PanIN) formation was promoted while pancreatic cancer developed at a lower frequency[22]. The introduction of *Kras* mutations

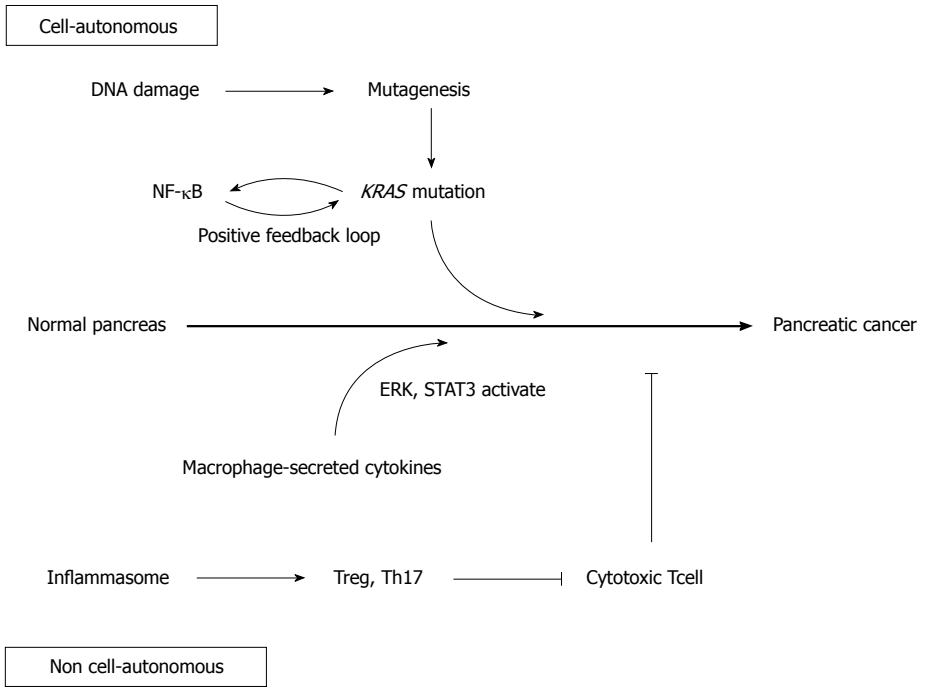

Figure 1 Inflammation induces carcinogenesis both cell-autonomously and non-cell-autonomously. DNA damage caused by inflammation contributes to mutagenesis. Nuclear factor κB and *KRAS* activate each other and sustained *KRAS* activity promotes carcinogenesis. Macrophage-secreted cytokines activate the ERK and STAT3 signaling pathways in epithelial cells. Inflammasomes inactivate cytotoxic T cells *via* the activation of Th17 and regulatory T cells. NF-κB: Nuclear factor κB.

alone induced pancreatic cancer development over 1 year; however, when *Trp53* and *Cdkn2a* defects were introduced, it only took 7 and 18 wk, respectively, to develop pancreatic cancer[23]. Furthermore, when pancreatitis was induced by administering caerulein in *Kras* mutant mice, carcinogenesis occurred at 12 wk[24]. These results demonstrated that some secondary abnormalities in *Kras*-mutated mice are necessary for rapid progression to invasive cancer, and that inflammation promotes carcinogenesis in conjunction with *Kras* mutations.

DNA damage caused by inflammation may contribute to carcinogenesis (Figure 1)[25]. Inflammatory cytokines produce reactive oxygen species, which randomly oxidize DNA to cause genetic mutation[26]. NO, induced by inflammation, also inhibits DNA repair enzymes to promote mutations[27]. In fact, the duration of chronic pancreatitis correlates positively with the incidence of *KRAS* mutations, suggesting that DNA damage accumulates due to the persistence of inflammation, promoting further carcinogenesis[28].

Although random genetic mutations caused by inflammation may contribute to carcinogenesis, work done by Guerra *et al*[29] suggests an alternative role of inflammation in the development of carcinogenesis. Guerra *et al*[29] used a Cre Tet-off system to control the expression of mutant *Kras* in mice. When mutant KRas was expressed during the embryonic stage, PanIN was formed at 1-3 mo. However, when mutant KRas was expressed in adult mice 2 mo after birth, PanIN was not formed. Furthermore, even when *Cdkn2a* or *Trp53* gene deficiencies were simultaneously introduced into adult mutant *Kras* mice, PanIN did not develop[29]. These results suggest that the carcinogenic potential through genetic mutation differs between the embryonic and adult stages in mice. Moreover, when pancreatitis was induced by administering caerulein to adult mutant *Kras* mice, PanIN developed and rapidly progressed to pancreatic cancer[30]. However, PanIN did not develop after deletion of *Cdkn2a* or *Trp53* in adult mice accompanied with caerulein pancreatitis. From these results, mutant *Kras* and inflammation are necessary components of pancreatic carcinogenesis in adult mice, with inflammation contributing to carcinogenesis by means other than the introduction of specific gene mutations as a result of DNA damage. Recent studies revealing the association of various signaling pathways and microenvironments with inflammation and pancreatic carcinogenesis may support this concept.

CELL-AUTONOMOUS INTRACELLULAR SIGNALING PATHWAYS IN PANCREATIC INFLAMMATION AND CARCINOGENESIS

Nuclear factor κB (NF-κB) is involved not only in inflammation but also in cell differentiation and proliferation, both of which are activated in pancreatic cancer[31,32]. Mutant KRas is known to activate interleukin-1alpha (IL-1α) *via* AP-1. IL-1α polyubiquitinates tumor necrosis fa-

ctor receptor-associated factor 6 and activates IKK2/β, which activates NF-κB. NF-κB subsequently upregulates *IL-1α* and *p62* transcription, which in turn re-activates NF-κB in a positive feedback loop[33]. Because activated NF-κB activates KRas, another positive feedback loop is generated, resulting in sustained KRas activity which may promote pancreatic cancer development[34].

Additionally, Toll like receptor 4 (TLR4) and TLR7 are upregulated within the pancreatic cancer microenvironment[35,36]. TLRs are receptors that recognize pathogen-associated molecular patterns and diverse byproducts of inflammation and cellular injury. Activated TLRs induce the activation of NF-κB pathway within acinar cells, which may further promote the development of pancreatic cancer.

NON CELL-AUTONOMOUS INTRACELLULAR SIGNALING PATHWAYS IN PANCREATIC INFLAMMATION AND CARCINOGENESIS

The IL-6 / STAT3 pathway is also involved in pancreatic cancer and inflammation[37]. While caerulein-induced pancreatitis transiently activates STAT3, prolonged activity and PanIN development were both observed in *Kras* mutant mice[38]. In these mice, pancreatic *Kras*-mutant epithelial cells recruited macrophages, which secreted IL-6, result in the STAT3 activation in epithelial cells and formation of PanIN. Conversely, inactivation of IL-6 trans-signaling or inhibition of STAT3 resulted in decreased PanIN formation[39].

Various studies have revealed that macrophages play an important role in pancreatitis, and are likely to be related to pancreatic carcinogenesis[40]. As mentioned above, macrophages secrete IL-6 and activate the STAT3 signaling pathway to promote pancreatic carcinogenesis. In addition, macrophages are observed around acinar ductal metaplasia (ADM) lesions, which are precancerous lesions formed in response to pancreatitis. They secrete inflammatory cytokines such as TNFα, and the chemokine regulated upon activation of normal T cell expressed and presumably secreted (RANTES). They also promote ADM formation through activation of NF-κB and matrix metalloproteinase-9[41,42]. Macrophages that migrate around ADM and PanIN are polarized dominantly from M1 to M2 by stimulation of IL-13. M2 macrophages secrete CCL2 and IL-1ra, which activate the ERK signaling pathway and promote the growth of PanIN[43].

Th17 is associated with many inflammatory conditions, such as inflammatory bowel diseases. In the pancreas, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is also activated in pancreatitis[44]. Macrophages expressing NLRP3 inactivate cytotoxic CD8+ T cells through the activation of Th17 and regulatory T cells, which also contribute to the promotion of pancreatic cancer development[45].

PANCREATIC ORGANOGENESIS AND DIFFERENTIATION

The Guerra *et al*[29] study demonstrated that *KRAS* gene mutations induce PanIN formation in the embryonic, but not the adult stage. From these results, cell differentiation status at the embryonic or adult stage may control organ carcinogenesis. Research on the inflammation and differentiation of pancreatic cells has been increasing in recent years, and elucidation of pancreatic embryology on a cellular level would provide great understanding to pancreatic cancer development.

Pancreatic development begins with the evagination of dorsal mesenchyme of foregut endoderm on embryonic day 26 (E26) in humans and E9.5 in mice[46-48] (Figure 2). The ventral pancreatic bud emerges at 6 d in humans and at 12 h in mice after the appearance of the dorsal pancreatic bud. Branching begins immediately after evagination. Stalk elongation and gut rotation occur on the ventral and dorsal side, while fusion of the ventral and dorsal pancreas occurs during E12 to E13 in mice and E37 to E42 in humans. During E13-14 in mice, there is a dramatic increase in endocrine cells, particularly β-cells, known as "secondary transition". Similarly, acinar cells develop and acinar enzyme gene expression increases. After E15 in mice, the destiny of pancreatic cells is determined.

Pancreatic tissue consists of acinar, duct, and endocrine cells. Lineage tracing using CreERT mice revealed that multipotent progenitor cells differentiate into respective cell populations[49]. Multipotent progenitor cells co-express homeobox protein PDX1, Sry-box protein SOX9, and basic helix-loop-helix (bHLH) protein PTF1A. As differentiation continues, the expression of PDX1, SOX9 and PTF1A are restricted in endocrine, duct, and acinar cells respectively. During early branching morphogenesis, the branch tip is composed of PDX1, PTF1A, and Cpa1 positive multipotent progenitor cells that can differentiate into all three type of cells; however, cells in the tip area lose their multipotency and change into pro-acinar cells after E14[50]. The trunk region is composed of bipotent progenitor cells that can differentiate into either duct or endocrine cells[51]. Some of these cells express neurogenin 3 (NGN3) and will differentiate further into endocrine cells[52].

Various transcription factors and signaling pathways are involved in acinar cell development. NR5A2 is a member of the nuclear hormone receptor family, and is responsible for pancreatic exocrine secretion in the mature pancreas[53]. NR5A2 regulates the various stages of development and is required for OCT4 expression in the epiblast[54]. It is also required for gastrulation and acinar cell maturation during secondary transition[55,56]. Since there is decreased expression of pancreas-related transcription factors during secondary transition, NR5A2 is thought to regulate pancreatic differentiation in cooperation with other transcription factors at this stage[56].

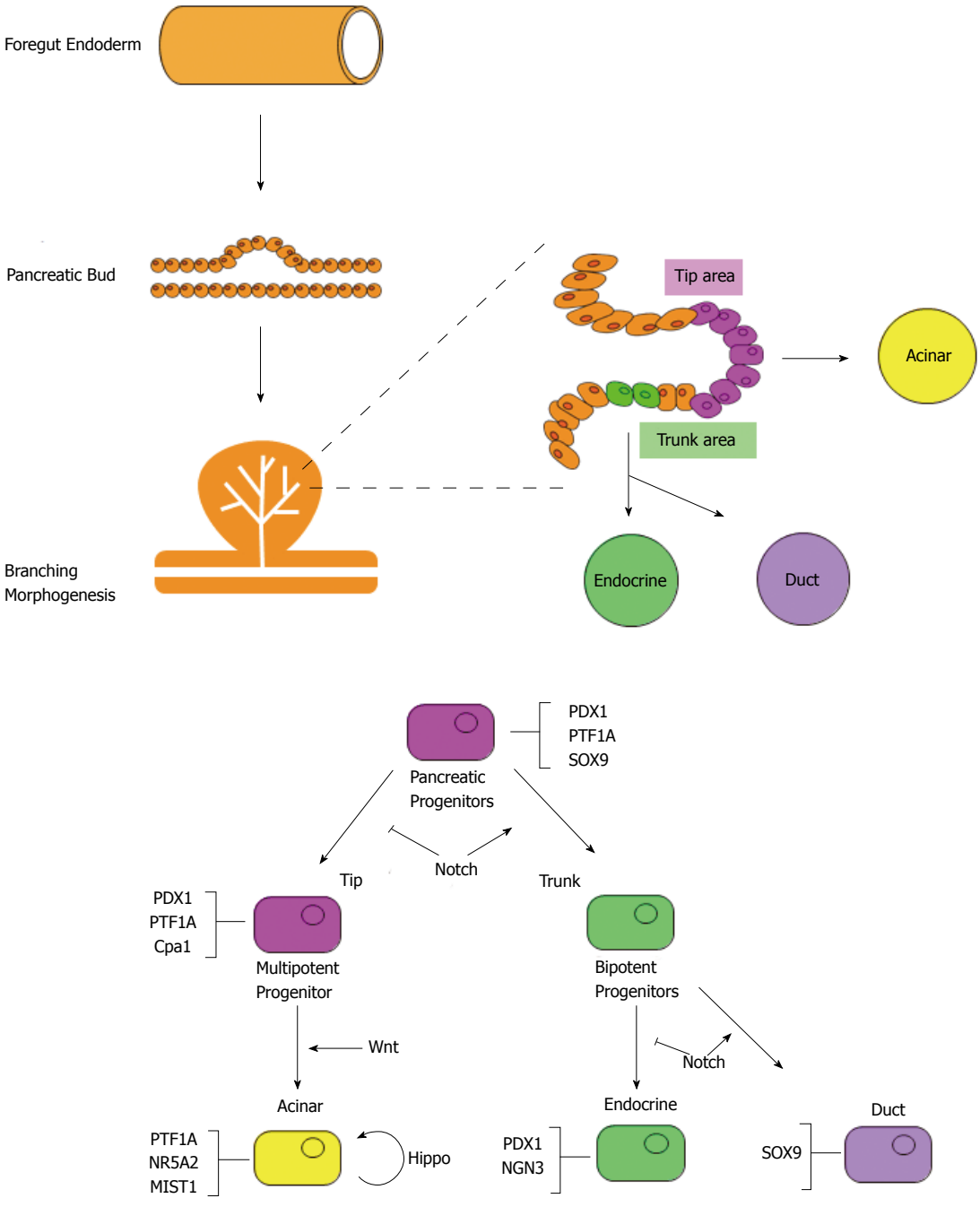

Figure 2 Pancreatic organogenesis and cell differentiation. The pancreatic bud arises from the endoderm foregut. During early branching morphogenesis, the branch tip is composed of multipotent progenitor cells that change into acinar cells. The trunk region is composed of bipotential progenitor cells that can differentiate into either duct or endocrine cells. As differentiation continues, the expression of *PTF1A*, *NR5A2*, and *MIST1* is restricted in acinar cells.

MIST1 is a bHLH transcription factor, highly expressed in acinar cells, as well as the stomach, prostate, and seminal vesicles[57]. Mice with *Mist1* gene knockout developed highly disorganized acinar cells with impaired exocytosis[58]. Furthermore, ADM formation and susceptibility to caerulein pancreatitis were increased in these mice[59]. MIST1 is thought to be required for the maintenance of acinar cell identity.

The Wnt/β catenin signaling pathway is necessary for differentiation of acinar cells. Pancreatic hypoplasia was observed in *β-catenin* knockout mice[60]. Furthermore, acinar cell proliferation was promoted by deficiencies in the *Apc* gene, which has endogenous β-catenin inhibitory activity. Because this abnormal proliferation stops when *c-myc* is deleted, *c-myc* is considered to be an important downstream component of the Wnt/β catenin pathway[61].

The Hippo signaling pathway has been associated with pancreatic development. Deletion of the core Hippo kinase genes *Mst1* and *Mst2* induced pancreatic hypoplasia *via* YAP, the downstream mediator. Interestingly, in *Mst1* and *Mst2* double knockout mice,

expression levels of MIST1, PTF1A, and NR5A2 were equivalent to those seen in wild type mice, with normal pancreatic sizes at birth. However, after 1 mo, the acinar cells changed to duct-like cells while the overall size of the pancreas was approximately half that of wild type mice. This suggests that the Hippo signaling pathway is necessary to maintain acinar cell identity and pancreas size after birth in mice[62].

The Notch signaling pathway is also indirectly related to acinar cell differentiation *via* lateral inhibition. NGN3 is a transcription factor that promotes differentiation to endocrine cells. Cells expressing NGN3 upregulate the expression of DLL1, which is a Notch ligand. DLL1 binds to the Notch receptor of surrounding cells and activates the Notch signaling pathway, thereby upregulating HES1 expression. HES1 inhibits NGN3 and suppresses endocrine cell proliferation. HES1 also maintains the expression level of PTF1A in multipotent progenitor cells and is thought to contribute to multipotent progenitor cell proliferation[63].

PANCREATIC CELL DE-DIFFERENTIATION, INFLAMMATION, AND CARCINOGENESIS

As described above, pancreatic cell differentiation and their identities are maintained by the cooperation of various transcription factors and signaling pathways. However, recent research has revealed that differentiated pancreatic cells show plasticity under specific circumstances. Acinar cells transdifferentiate or de-differentiate into duct cells and endocrine cells after pancreatic duct ligation. During this change, cells express SOX9 and HNF1β multipotency factors[64,65]. The conversion from an acinar cell to embryonic progenitor phenotype that exhibits ductal markers, is called ADM. ADM is thought to be a reversible process and is frequently observed in pancreatic inflammation and injury. However, it becomes irreversible when combined with a *Kras* mutation. This alteration results in a lesion that is considered a precancerous stage of pancreatic cancer[66,67].

Epigenetic factors play crucial roles in differentiation and carcinogenesis. A recent study showed that Brg1, a catalytic ATPase subunit of the SWI/SNF chromatin remodeling complex, is inactivated in approximately 10% of pancreatic cancer[68]. Brg-1 binds to the SOX9 promoter and regulates the expression of SOX9. Acinar cell-specific deletion of Brg-1 attenuates ADM/PanIN formation in *Kras* mutant mice[69].

NR5A2 suppression and forced expression of SOX9 or PDX1 can induce ADM[11,70-72]. These results suggest that transcriptional changes that cause the loss of acinar cell identity promote ADM formation. Interestingly, although the pancreatic tissues of *Nr5a2*$^{+/-}$ mice are histologically normal, transcriptome analyses of *Nr5a2*$^{+/-}$ mice show inflammasome upregulation. In humans, similar transcriptomic changes occur in the pancreas with low levels of NR5A2 expression. Furthermore, NR5A2 is relocated from the promoters of differentiation-specific genes to the promoters of inflammation-related genes. AP-1 is upregulated in these mice and the deletion of *Jun* results in the downregulation of AP-1 and NR5A2 binding to AP-1 and inflammatory gene promoters[73].

In another study, temporal activation of reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, *c-Myc*) in the pancreas of *Kras* mutant mice promoted ADM formation and pancreatic cancer[10] (Figure 3). In previous transcriptome analyses, when the reprogramming factors are activated, acinar cell-related genes *Ptf1a* and *Mist1* were downregulated. In addition, when pancreatitis was induced *via* caerulein administration in *Kras* mutant mice, similar transcriptional patterns were observed. Conversely, forced expression of *Ptf1a* or *Mist1* in *Kras* mutant mice with caerulein-induced pancreatitis suppressed PanIN formation. These results demonstrate the crucial role of epigenetic regulation in the initiation of pancreatic carcinogenesis.

FUTURE PERSPECTIVES

A growing body of research in pancreatic carcinogenesis demonstrates that the loss of acinar cell identity caused by the suppression of transcriptional networks by reprogramming factors plays a crucial role in ADM formation. In addition, *Kras* mutation and epigenetic regulation play important roles in pancreatic carcinogenesis. Furthermore, inflammation induces an intracellular transcriptional state similar to the de-differentiated state of pancreatic cells, implying that inflammation, cell differentiation, and carcinogenesis are very closely related.

Some questions remain to be resolved. Inflammation may induce not only de-differentiation but also stem cell damage and impaired differentiation, and subsequently cause carcinogenesis. Further research is needed to determine the origin of pancreatic cancer. There is a strong association between chronic pancreatitis and pancreatic cancer. However, only 1.34% of pancreatic cancers are thought to be caused by chronic pancreatitis[74]. Furthermore, pancreatic cancer concomitant with intraductal papillary mucinous neoplasm, a premalignant lesion of pancreatic cancer, is not associated with pancreatitis or pancreatic atrophy[75]. However, these epidemiological and pathological data do not completely deny the connection between carcinogenesis and inflammation. One possible explanation is that pro-inflammatory states may exist in the absence of histologically observed pancreatitis[73]. Further studies are required to clarify the inflammation-like changes in "inflammation-absent" pre-neoplastic pancreatic lesions. This may subsequently allow the identification of high-risk patients.

Many novel therapeutic strategies for pancreatic cancer are aimed at reprogramming pancreatic cancer cells to behave like normal pancreatic cells[76]. For example, PD 325901 inhibits MEK1/2 and induces PanIN

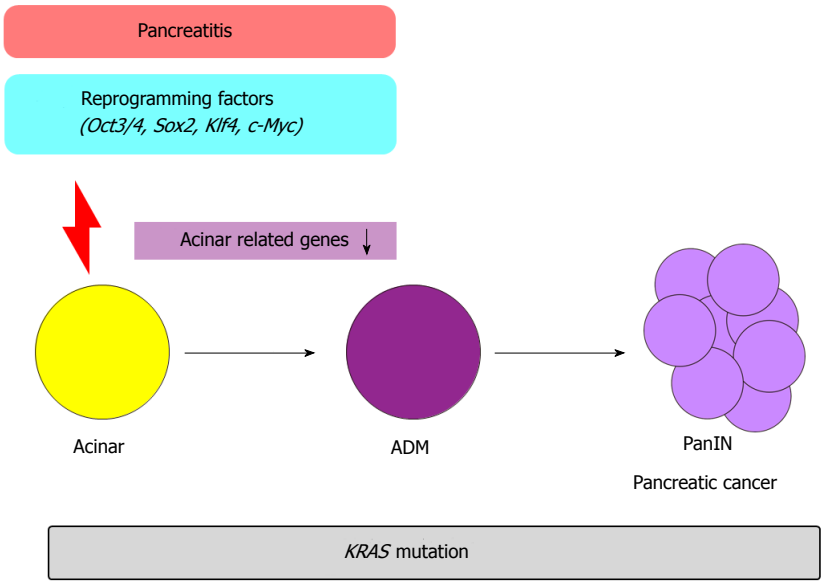

Figure 3 Pancreatic cell de-differentiation, inflammation, and carcinogenesis. Carcinogenesis is promoted by reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*). When the reprogramming factors are activated, acinar cell-related genes are suppressed. Pancreatitis also shows such transcriptional changes.

re-differentiation into acinar cells[77]. Another study has shown that the overexpression of bHLH transcription factors E47 and PTF1A resulted in increased acinar cell gene expression, suppressing cancer proliferation[78,79]. It is highly expected that in the near future, new diagnostic and/or treatment strategies based on the findings described in this review will be clinically applied, improving the prognosis of patients with pancreatic cancer.

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MINIREVIEWS

Management of gastroesophageal reflux disease: Patient and physician communication challenges and shared decision making

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Abstract

Gastroesophageal reflux disease (GERD) is a common upper esophageal condition and typical symptoms can include heartburn and sensation of regurgitation while atypical symptoms include chronic cough, asthma, hoarseness, dyspepsia and nausea. Typically, diagnosis is presumptive given the presence of typical and atypical symptoms and is an indication for empiric therapy. Treatment management can include lifestyle modifications and/or medication therapy with proton pump inhibitor (PPI) class being the preferred and most effective. Complete symptom resolution is not always achieved and long-term PPI therapy can put patients at risk for serious side effects and needless expense. The brain-gut connection and hypervigilance plays an important role in symptom resolution and treatment success, especially in the case of non-PPI responders. Hypervigilance is a combination of increased esophageal sensory sensitivity in combination with exaggerated threat perception surrounding esophageal symptoms. Hypervigilance requires a different approach to GERD managements, where continued PPI therapy and surgery are usually not recommended. Rather, helping physicians and patients understand the brain-gut connection can guide and improve care.

Education and reassurance should be the main pillars or treatment. However, it is important not to suggest the symptoms are due to anxiety alone, this often leads to patient dissatisfaction. Patient dissatisfaction with treatment reveals the need for a more patient-centered approach to GERD management and better communication between patients and providers. Shared decision making (SDM) with the incorporation of patient-reported outcomes (PRO) promotes patient adherence and satisfaction. SDM is a joint discussion between clinician and patient in which a mutually shared solution is explored for GERD symptoms. For SDM to work the physician needs to capture patients' perceptions which may not be obtained in the standard interview. This can be done through the use of PROs which promote a dialogue with patients about their symptoms and treatment priorities in the context of the SDM patient encounter. SDM could potentially help in the management of patient expectations for GERD treatment, ultimately positively impacting their health-related quality of life.

Key words: Gastroesophageal reflux disease; Psychosocial; Patient-physician communication; Shared decision making; Patient-reported outcomes; Patient satisfaction

Core tip: Gastroesophageal reflux disease management can be complex and is affected by psychosocial factors. Physician-patient communication improvement and shared decision making are two approaches that could improve patient-reported outcomes and patient satisfaction.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common upper esophageal condition that affects 33% of the general population and the prevalence in the developed world is constantly rising[1,2]. GERD presents with a host of problematic esophageal and extra-esophageal symptoms contributing to wide variations in clinical practice in both the diagnosis and treatment of GERD. The economic impact of GERD per patient per year is estimated to be $3441 where proton pump inhibitor (PPI) therapy might be the most cost-effective strategy[3].

Managing patient symptoms lies at the center of patient care according to the Institute of Health Care Improvement's Triple Aim[4]. Similarly, the Montreal Guidelines, places core emphasis on the patient experience of "troublesome symptoms" when diagnosing and managing GERD. Hence, care of GERD goes beyond reflux reduction and should strive to incorporate patients' goals as well as address underlying other biopsychosocial factors that influence patient symptoms. At every point in the diagnosis and management of GERD, there exist opportunities for physicians to improve care and patient outcomes. Satisfaction with treatment relies largely on meeting patient expectations and good patient-physician communication[5-7]. The purpose of this review is to present the treatment options of GERD and explore the biopsychosocial aspects of symptoms. We will address how to improve current GERD treatment through addressing physician-patient communication challenges and the opportunities offered by shared decision making (SDM).

DEFINITION

GERD is defined as a group symptoms or a presence of mucosal damage caused by abnormal reflux of highly-acidic gastric content into the esophagus or beyond, including into the oral cavity or respiratory pathways[8]. The symptoms of GERD are classified as typical symptoms that include heartburn, sensation of regurgitation and atypical symptoms which are associated with chronic cough, asthma, hoarseness caused by laryngitis, dyspepsia and nausea[9]. Another group of symptoms are defined as alarm symptoms since they can be potentially associated with life-threatening conditions (chest pain/myocardial infarction, dysphagia/esophageal stricture or malignancy)[9,10]. About 70% of GERD patients have non-erosive reflux disease (NERD). These patients report symptoms related to acid exposure, but do not have mucosal damage[11]. Untreated and chronic GERD may lead to serious complications including peptic stricture, Barrett's esophagus and esophageal adenocarcinoma[12].

DIAGNOSIS OF GERD

In most cases the diagnosis is presumptive. The accurate diagnosis of GERD relies on the careful questioning of the patient by the provider. Many patients do not report their symptoms of GERD and receive no treatment[15]. Facilitating effective communication between patient and provider at the beginning of treatment has been shown to improve patient experience and satisfaction. The presence of typical and atypical symptoms and the absence of alarm symptoms is considered an indication for empiric therapy[13]. A positive response to PPI therapy is used as a conformation of initial GERD diagnosis[14]. This approach to diagnosis of GERD has a high specificity with low sensitivity. Counterintuitively, studies have demonstrated that patients are consciously aware of only 2 to 3 percent of acid reflux events[15]. Additionally, many

patients present with atypical symptoms that are not used as clear markers for diagnosis[15]. The frequent lack of clinical correlation between the patient's perception of typical symptoms and episodes of reflux points to the complex nature of GERD symptom production which will be explored in detail in later sections. The older proactive testing with barium contrast radiography has fallen out of favor due to low sensitivity and specificity. The most reliable method of diagnosis remains direct visualization and identification of esophageal injury obtained by endoscopy of the upper GI tract including tissue biopsy demonstrating mucosal damage[8,16]. This diagnostic method is not, however, bulletproof. Most patients with typical symptoms of GERD do not present with abnormal findings on the upper gastrointestinal endoscopy exam. The upper GI endoscopy is usually reserved for evaluation of GERD-associated complications and placement of wireless pH probes. Wireless pH probes are used in ambulatory 24-h pH monitoring allowing direct measurement of esophageal exposure to gastric acid. This diagnostic method can be used to quantify a reflux frequency and provide information on the association between the timing of symptoms and actual reflux episodes[8]. The widespread use of 24-h pH probes has led to the identification of a subset of patients with typical GERD symptoms who do not respond to PPI' s. These PPI-refractory symptoms have been shown, with the use of pH-impedance testing, to be related to continued episodes of reflux[47]. This testing method has also demonstrated that only 5%-15% of reflux events correspond to patient symptoms[47]. One advantage of this diagnostic procedure is that it is associated with very little discomfort to patients allowing them to resume their normal lives during the testing period[17-19]. The most common complication associated with this method are poor data reception, dysphagia, increased number of reflux episodes, early capsule detachment and failure of scheduled detachment[20]. The more traditional method of ambulatory esophageal acid monitoring is through the placement of transnasal catheter with pH sensor capability. The method is shown to be a very accurate, however, its utilization is hindered by patient discomfort and limitation of daily activity[21].

THERAPY

The initial treatment of GERD should include lifestyle modifications with education about the factors precipitating physiological and pathological reflux[22,23]. This includes advice on diet, alcohol and tobacco use, sleep position and weight loss. Although many patients are advised to avoid certain foods, there is little evidence this is helpful. Rather losing weight, stopping smoking, elevating the bed headrest and avoiding late evening meals can substantially reduce symptoms[24].

The next step in treatment of GERD is initiation of acid suppression therapy. Several classes of medications are used for acid suppression: antacids, histamine-receptor antagonists and PPIs. The PPIs are the preferred medication for treatment of GERD. They have been shown to be a highly effective tool against injuries associated with erosive gastritis and their effect is achieved much faster than other medication alternatives[25]. Proven effectiveness and wide popularity of PPIs has resulted in FDA approval of over-the-counter sale of this group of medications.

Surgical therapy is usually reserved for patients who do not respond well to acid suppression medication, patients who prefer surgical approach, and patients who present with complications due to GERD[15]. Prior to recommending surgery, it needs to be established heartburn is due to GERD and not another reason. The majority of these patients undergo Nissen fundoplication, however, several alternative techniques such as endoscopic radiofrequency energy delivery technique and minimally invasive surgical procedures have also been used[26]. Long-term complications of these surgical procedures include bloating and gas-bloat syndrome, dysphagia, diarrhea, recurrent heartburn and recurrent atypical symptoms[27]. Bariatric surgery for weight loss has been evaluated for its effect on GERD. Evidence shows improvement of GERD symptoms, mostly due to weight loss, although some patients develop GERD symptoms after surgery[28,29].

The majority of patients will not require surgery. Acid suppression such as PPIs remains the most common treatment for GERD. However, emerging studies indicate a presence of side effects with long-term use of these drugs. The chronic usage of PPIs has been associated with malabsorption of calcium, magnesium and Vitamin B_{12} which can ultimately lead to an increased risk for bone fractures[30,31]. Various studies have also indicated a potential link between PPI use and increased incidence of community acquired pneumonia[32] and enteric infections[33,34]. PPIs are also found to interact with cytochrome P450 isozyme 2C19 which can result in interference with metabolism of other co-administered drugs (clopidogrel) prompting an FDA warning[32]. Recent studies have found increased risk of chronic kidney disease with PPI use[35-40]. Finally, a Nationwide study in Denmark found an association between PPI use and microscopic colitis[41]. Hence, use of these medications, especially over the long-term, may need to be weighed against their potential risk of side effects. Patients who have a positive response to PPI therapy can be reluctant to taper off and stop treatment.

Limiting unnecessary PPI exposure should therefore a treatment goal to reduce risk of the above mentioned side effects. In observational primary care and community-based studies, 45% of participant reported persistent, troublesome heartburn symptoms despite PPI therapy[2]. One study noted that 42% of PPI non-responders remained on a PPI with no clinical benefit even after showing they had no acid reflux[42]. Up to 50% patients with GERD symptoms do not respond to a double-dose[16,43]. These numbers suggest that many patients are taking PPIs without any clinical benefit. Effective communication with patients should

include discussion of persisting troublesome symptoms. Providers and patients often do not explicitly address these concerns. Even in patients who have responded to PPIs, long term use is often unnecessary. The majority of PPI responders can successfully step-down their use of PPIs without negatively affecting their quality of life (QOL)[44,45]. Overuse and misuse of PPIs leads to needless expense, increased risk, and no benefit to patient experience or satisfaction. Providers must take the time to communicate the relative risks and benefits of PPI treatment, especially the benefits of discontinuation.

PSYCHOSOCIAL FACTORS CONTRIBUTING TO PATIENT OUTCOME AND PATIENT SATISFACTION

Understanding the factors associated with PPI treatment non-response continues to be a challenge. Possible factors conjectured include persistent or weakly acid reflux, and an impaired esophageal mucosa. However, there is more going on here than just acid exposure and tissue damage. Taken from another perspective, one study found that more than half of a general population sample reported symptoms of heartburn, and severity of their symptoms was the same as reported by patients seen in a gastroenterology[1]. This suggests that care seeking for GERD is not related to symptoms or mucosal damage alone, and should be considered within a wider context.

The central importance of the brain-gut bi-directional communication pathway cannot be overstated. The central nervous system (CNS), through neural, hormonal, and immunological bi-directional communication with the gut, maintains normal gastrointestinal functioning and helps modulate disease activity[46]. Psychological factors, such as stress, can influence gut functioning and also influence perception of peripheral gut nerve input to the CNS all of which may impact clinical outcomes in GERD[46]. Thus, there is a continuous feedback loop between the brain and the gut and it is increasingly recognized that you cannot treat one without the other.

The brain-gut axis can be helpful in explaining why symptoms can persist despite treatment. Hypervigilance to gut input is thought to play a central role in understanding why some patients continue to report symptoms despite healing of the esophageal mucosa. Hypervigilance is a combination of increased gut sensory sensitivity in combination with exaggerated threat perception surrounding gut symptoms. Kahrilas and colleagues defined it as the "cognitive-affective process that stems from hyperawareness of discomfort. This heightened awareness or sensitivity is coupled with behavior that is out of proportion to the prior symptom experience, serving to amplify the 'threat-level' of symptoms and their potential consequences" [47]. In other words, some patients are highly sensitive to gut inputs. These patients feel discomfort at levels where other people may not notice and/or be bothered by it (visceral hypersensitivity). Hypervigilance is the combination of increased symptoms due to visceral sensitivity as well as a high level of threat associated with these symptoms ("In order to be in this much pain, there must be something really wrong"). Hypervigilance often leads to avoidance of situations that may trigger symptoms, such as eating certain foods, restaurants and even sleep[1,48,49]. These patients strictly monitor their symptoms and become caught in a negative feedback loop of discomfort, pain and anxiety. Indeed, anxiety has been associated with persistent reflux symptoms despite PPI therapy and increased visceral hypersensitivity[50]. In one study, hypervigilance accounted for 50% of patient-reported symptom severity while psychological distress (depression, anxiety, somatization) was found to be within normal limits in the treatment refractory group[51]. More medicine and more diagnostic procedures will not help these patients. Similarly, avoiding surgery in these patients is critical as outcomes may be poor in this patient population. Rather, helping physicians and patients better understand and appreciate the brain-gut connection can guide and improve care.

Physicians have to treat the whole person and focus on the patient experience. Physicians must recognize these underlying patient dynamics and not ignore or discount them. More PPI, more testing or surgery is not the answer. However, suggesting their symptoms are due to their anxiety is not helpful either. Patients as a rule do not react well to being told that their symptoms are "all in their head" as it communicates their doctor is not taking them seriously or minimizing their suffering. Instead, physicians should provide education and assurance. Education about the origin of the symptoms should include an explanation of the brain-gut axis and an explanation on how hypersensitive gut nerves can be responsible for their symptoms. Usually pain and discomfort are symptoms that warn us for harm, but in this case, the nerves may be over responding and the signal (pain) is not useful anymore. Reassurance that there is no need for continued testing, surgery or even PPI or other medication treatment is needed as well. Low-dose imipramine has shown initial promise in this patient population[52], but only improved QOL, not symptoms nor visceral hypersensitivity. Better success has been found with behavioral interventions[46]. These focus on increasing their coping skills and resilience while reducing disability[53]. Some approaches may even target hypersensitivity directly. Given the complexity of the origin and treatments of GERD symptoms and potential reluctance of patients to entertain the influence of the brain-gut axis, effective physician-patient communication is important in the treatment of GERD.

PATIENT-CENTERED COMMUNICATION

Meaningful and effective physician-patient communication can be influenced by many factors including medical, ethical, and socioeconomic issues[54]. Differing opinions, patient autonomy, cost and truthful assessment could

potentially cause conflict. A physician should be able to identify pitfalls and learn how to navigate these circumstances in order to provide optimal patient care.

Physician-patient communication should be patient-centered[55]. Epstein and Street defined patient-centered communication as: "(1) Eliciting, understanding, and validating the patient's perspective (*e.g.*, concerns, feelings, expectations); (2) Understanding the patient within his or her own psychological and social context; (3) Reaching a shared understanding of the patient's problem and its treatment; and (4) Helping a patient share power by offering him or her meaningful involvement in choices relating to his or her health."

Patient-centered communication positively affects patient satisfaction, recall, understanding, and adherence and health outcomes[55]. Increase in malpractice and in missed opportunities to empower patients to self-manage their illness are two negative consequences of not employing patient-centered communication[56].

A limited earlier review of studies on verbal and nonverbal physician behaviors during a patient interview found several to have a positive effect on health outcomes[56]. Some of the verbal behaviors include: empathy, psychosocial talk, time spent in health education and information sharing, humor, courtesy, and clarification. Several of the nonverbal behaviors found to be beneficial include: head nodding, arms and legs that are uncrossed and leaning forward.

There is very limited research on physician-patient communication within the context of GERD. Research has shown a disparity between patients and providers regarding GERD management and its impact. Patient satisfaction with prescription treatment for symptom management is often overestimated by providers[57-61]. The severity of symptoms are often underestimated by providers when compared to patients' reports[59,62]. There is also a disconnect with what providers and patients see as most problematic symptoms for QOL[57]. This evidence supports the need for a more patient-centered approach to GERD management and better communication between patients and providers.

In a study of the impact of patient education and GERD management, a survey of outpatients indicated that only 66% of patients thought they had a comprehensive discussion of factors affecting GERD with their physician[63]. These patients are also significantly more knowledgeable about when to take their medication than those who did not have a comprehensive discussion with their physician. This emphasizes the need for better discussion between physician and patient.

The type of practitioner may also impact a GERD patient's perception. A study comparing the satisfaction of patients with GERD who saw gastroenterologists to those who saw a family physician indicated that the latter were significantly more satisfied with the care information they received and thought their doctors spent more time with them[64]. This implies that patients form a closer relationship and a more beneficial communication with their family physicians which could lead to a more effective treatment.

Patient-reported outcomes (PRO) tools can help advance physician-patient communication by capturing patients' perceptions of GERD management via specific targeted questions which patients may not provide in the standard interview to their provider. These tools can facilitate treatment management by measuring the impact of GERD from the patients' perspectives. Improved communication regarding treatment expectations can also help with a more patient-centered approach. Patients should be educated that treatments may not provide full symptom relief and residual symptoms may persist.

The GERD Impact Scale (GIS) is a commonly used PRO. It has eight questions exploring the frequency of symptoms over the past week: acid-related symptoms, chest pain, extra-esophageal symptoms, and the impact of symptoms on sleep, work, meals and special occasions. Two other tools include the Quality of Life in Reflux and Dyspepsia that informs treatment response and gives a patient-centered measure of progress and the Reflux Disease Questionnaire, a patient-centered self-administered instrument that tracks symptom improvement[65]. Using these PRO's at the time of diagnosis and at each subsequent visit helps fill the gap in physician appreciation of patient's ongoing symptoms and suffering.

Physicians have frequently been shown to underestimate the severity and impact of GERD symptoms on their patient's lives while simultaneously overestimating treatment effects[57,66]. Systematically tracking patient response and patient experience fosters a collaborative discussion between physician and patient. Patients are more likely to be satisfied if they feel they are taken seriously by their physician as well as if the consultation is interactive[67]. Employing validated PRO instruments at diagnosis and during ongoing pharmacotherapy demonstrates physician concern for the GERD patient. Patients feel that their physician is serious about providing enduring symptom relief when they monitor their progress over time. Additionally, if treatment is not successful, physicians recognize treatment failures faster allowing them to adjust treatment strategies. In some treatment refractory patients this may include behavioral health referral for gut-centered cognitive behavioral therapy. Patients may be much more receptive to this discussion and referral if the physician has been employing PRO tools during ongoing care and use these as part of SDM.

SHARED DECISION MAKING IN THE DIAGNOSIS AND MANAGEMENT OF GERD

Despite the fact that GERD represents one of the most common diseases encountered by primary care providers as well as gastroenterologists, there remain large gaps in actual clinical practice especially in the areas of patient-

physician communication and patient satisfaction. Bytzer highlighted elements on how a physician can improve patient satisfaction in GERD treatment: improve communication between physician and patient in addition to providing accurate diagnosis and effective treatment, encouraging adherence, and managing patient expectations[67]. In often rushed clinical encounters, the patient and provider often collude in minimizing patient concerns and symptoms: the patient does not want to disappoint the doctor and so may not proactively discuss continuing troublesome symptoms and the provider misinterprets the patients' lack of complaint as treatment success and moves on, thereby missing opportunities to optimize care and patient satisfaction. This kind of dysfunctional communication dynamic spans across medical disciplines. In order to combat this lack of patient-provider communication, experts have proposed a new model for clinical practice: SDM.

SDM aims to create a two-way partnership between patient and clinician encouraging not only the exchange of information but also factoring in patient values and treatment preferences. At its core, to be considered SDM, care must include a discussion of the treatment options and the pros and cons of each relevant option, a discussion of patient values and preferences, and finally a mutual decision by patient and provider including follow-up plans. Put more simply, SDM is a process, a conversation between the clinician and patient who, jointly, arrive at a solution to the patient's problem[68]. Many providers already engage patients in some of these processes; however all of these elements must occur in the clinical encounter for the care to be considered SDM. Studies assessing provider adherence to SDM principles and care have demonstrated clinicians often overestimate their level of patient engagement and involvement.

While the evidence is still growing, the SDM approach has been shown to increase patient satisfaction and treatment adherence especially in chronic conditions. The strongest evidence supports an increase in patient satisfaction when utilizing an SDM approach[69]. It has been more difficult to demonstrate improved health outcomes or decreased levels of health utilization[69]. The latter was thought to be a potential by-product of SDM care rather than a goal of SDM.

Often, providers use decision aids or communication tools to promote the SDM clinical conversation. Tools such as patient decision or conversation aids are not necessary for care to count as SDM - also the evidence that these tools improve care remains low[70]. In fact, while tools and decision aids and choices are critical elements of SDM, the concept focuses heavily on the conversation, evident caring, and mutually respectful relationship of the physician and patient[71].

SDM has been studied in many conditions including multiple sclerosis[72], Coronary Heart Disease[73], and depression[74]. The European Crohn's and Colitis Organization's review on treatment withdrawal in Inflammatory Bowel Disease briefly mentioned SDM[75]. Surprisingly, SDM has not been studied in GERD. The SDM approach to GERD treatment management can be a way for clinicians to provide more patient-centered care and improve patient satisfaction. Every step in GERD management - diagnosis, medication trials and adjustments, further work-up for refractory symptoms provides an opportunity for the practice of SDM. Clinicians need to identify which troublesome symptoms matter most to their patients. This will necessarily vary from patient to patient. Without this conversation, clinicians may not focus on what the patient feels is most important. One way for clinicians to gather this information on an ongoing basis employs the use of PROs discussed above. In the absence of decision aids and conversation aids, PRO tools can help the clinician hone in on continuing patient concerns and track treatment progress overtime.

Medication adherence and proper dosing including the time of dose also need to be monitored and addressed with patients. The SDM approach encourages patients to share their concerns and includes their experience as a central part of care decisions. Finally, optimal care, which includes SDM approaches, should include basic patient education about the brain-gut bidirectional pain pathway. This educational information can provide the patient with a framework to understand that not all of their symptoms will resolve. Utilizing the SDM process can help clinicians optimize treatment, but may also help the patient understand, accept, and manage residual persisting symptoms potentially avoiding unnecessary invasive testing and expense.

Employing PRO tools as part of the SDM model may help improve the use of PPI therapy in several ways. Patients who have a good initial response to PPIs can be monitored and maintained on the lowest dose necessary to control symptoms. PROs can also help the clinician explore reasons for treatment failure including checking for adherence and proper dosing 30 min prior to eating or the need for dose-escalation. Long-term PPI therapy carries increased risk of enteric infections and community acquired pneumonia, increased hip and vertebral fractures possibly due to the decreased absorption of calcium, and secondary hypergastrinemia and rebound acid hypersecretion[24]. Limiting unnecessary PPI exposure should be a treatment goal and PROs can help guide optimal care. Many patients remain on excessive doses of PPIs exposing them to risk and expense. The majority of PPI responders can successfully step-down their use of PPIs without negatively affecting their QOL[44,45].

Overuse and misuse of PPIs leads to needless expense, increased risk, and no benefit to patient experience or satisfaction. PROs can help physicians track this initial treatment response and better engage patients in an ongoing conversation about their troublesome symptoms and QOL. One study revealed that physicians alter their treatment decision 35% of the time based on information gleaned from the GIS (a common PRO)[59]. Clinicians need to find efficient, effective ways to gather critical clinical information from patients. PROs may be

one of many tools clinicians can use to promote dialogue with patients about their symptoms and treatment priorities in the context of the SDM patient encounter.

Lifestyle modifications remain a potent but often neglected area of treatment recommendation and disease modification for GERD patients. Providers should return again and again to these proven strategies. Weight loss, smoking cessation, avoiding trigger foods, decreased alcohol use, avoiding late night meals and elevating the head of the bed have all been shown to reduce GERD symptoms and improve QOL[24]. Continued engagement with patients on these conservative, lifestyle management strategies promotes patient self-management and has been shown to improve perceived symptoms[76,77]. The SDM approach can help facilitate a conversation with the patient on lifestyle changes. While a detailed discussion is outside the scope of this article, Motivational Interviewing may also be a supporting technique for use in the SDM patient care approach[78].

By applying SDM principles in the management of GERD, both the generalist and specialist can target specific areas where physicians have frequently been shown not to follow treatment guidelines. It also could decrease the chance of a breakdown in patient-physician communication.

CONCLUSION

GERD management can be complex, involving multiple avenues of trial and error, from lifestyle modifications to medication therapy. PPI therapy can be successful for some, but often does not provide complete resolution of symptoms. Long-term PPI therapy can put patients at risk for serious side effects and needless expense. The brain-gut connection may be important in explaining non-PPI responders. Emerging consensus has focused on the relatively new concept of hypervigilance to best understand this challenging population of patients. Given that the goal of treatment is managing symptoms, patient-physician communication is important. The paucity of literature on physician-patient communication in the treatment of GERD calls for more research in this area. Further, a disparity between patients and providers regarding GERD management can also impact patient satisfaction. This necessitates understanding and validating a patient's perspectives and values pertaining to his or her illness and choices, in addition to effectively obtaining information. SDM with the incorporation of PROs includes the patient in their treatment, promoting patient adherence and satisfaction. SDM manages patient expectations of GERD management, ultimately impacting their health-related QOL.

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MINIREVIEWS

Non-small bowel lesion detection at small bowel capsule endoscopy: A comprehensive literature review

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Abstract

Small bowel capsule endoscopy is a minimally-invasive endoscopic investigation that is often used in clinical practice to investigate overt or occult gastrointestinal (GI) bleeding among other clinical indications. International guidance recommends small bowel capsule endoscopy as a first-line investigation to detect abnormalities in the small bowel, when gastroscopy and colonoscopy fail to identify a cause of GI bleeding. It can diagnose with accuracy abnormalities in the small bowel. However, there has been increasing evidence indicating that small bowel capsule endoscopy may also detect lesions outside the small intestine that are within the reach of conventional endoscopy and have been probably missed during prior endoscopic investigations. Such lesions vary from vascular deformities to malignancy and their detection often alters patient management, leading to further endoscopic and/or surgical interventions. The current study attempts to review all available studies in the literature and summarise their relevant findings.

Key words: Obscure gastrointestinal bleeding; Small bowel capsule endoscopy; Non-small bowel lesions; Overt gastrointestinal bleeding; Occult gastrointestinal bleeding; Iron deficiency anaemia

Core tip: Video capsule endoscopy can accurately diagnose small bowel pathology, but often also detects abnormalities in the upper and lower gastrointestinal tract within the reach of conventional endoscopy, that have probably been previously overlooked.

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INTRODUCTION

More than a decade ago, the emergence of novel modalities for the diagnosis and treatment of small bowel diseases revolutionised the landscape of gastrointestinal endoscopy. Small bowel capsule endoscopy (SBCE), a non-invasive method of direct visualisation of the small intestine, was introduced in clinical practice both in the United States and Europe in 2001. Since then, the use of SBCE has steadily increased with a broadening spectrum of clinical indications, and the most common application is the investigation of iron deficiency anaemia (IDA) and/or obscure gastrointestinal (GI) bleeding[1-3]. Traditionally, obscure GI bleeding has been defined as overt or occult GI haemorrhage following normal upper and lower endoscopic examinations. However, the American College of Gastroenterology (ACG) recently challenged the current nomenclature, proposing that the term "obscure GI bleeding" should be reserved only for cases where a source of bleeding was not detected following conventional upper and lower GI endoscopic examinations and small bowel evaluation[2]. Overt GI bleeding refers to patients presenting with either melaena or hematochezia, whereas occult GI bleeding refers to those presenting with IDA in the absence of visible blood loss to the patient or the physician, with or without guaiac-positive stools[1].

The ACG recommends that SBCE should be performed as a first-line investigation for the examination of the small bowel, following visualisation of the upper and lower GI tract, although sometimes a second-look endoscopy may be indicated[1]. Similarly, the British Society of Gastroenterology (BSG) in its recently published guidelines on the management of IDA recommended that following direct visualisation of the upper and lower GI tract, further assessment of the small bowel should be performed in the presence of symptoms indicating small bowel disease, or in cases where the haemoglobin level cannot be restored or maintained following iron replacement therapy. In these cases, evaluation of the small intestine is indicated, and this can be performed by SBCE, which has a diagnostic yield of 40%-55% and the advantage of being a minimally invasive endoscopic investigation, although other options include radiological investigations (Magnetic resonance imaging enteroclysis, computed tomography enterography, barium studies) or enteroscopy. Findings detected with SBCE are often within the reach of conventional endoscopes, hence a second-look gastroscopy (OGD) or colonoscopy may be of some value[2]. In line with other institutional guidelines, the European Society of Gastrointestinal Endoscopy (ESGE) also recommends the use of SBCE as a first-line modality for the investigation of obscure GI bleeding[3].

ROLE OF SBCE IN THE INVESTIGATION OF OBSCURE GI BLEEDING

Up to 30% of patients investigated for IDA may remain without a definite diagnosis after evaluation of the upper and lower GI tract with conventional endoscopies and serological testing for coeliac disease[4]. Similarly, in 5% of patients presenting with overt GI bleeding, a definite diagnosis is not reached after upper and lower GI endoscopy[5]. The advent of SBCE reportedly led to the identification of a small-bowel culprit lesion in approximately two thirds of cases with 'obscure' GI bleeding[6-13]. SBCE allows the evaluation of the entire small bowel in up to 90% of the patients, with a diagnostic yield of 38%-83% in patients with potential small bowel haemorrhage[14]. SBCE has a high positive (94%-97%) and negative predictive value (83%-100%) in the evaluation of GI bleeding[15-16]. Additionally, SBCE findings reportedly may lead to a therapeutic intervention or overall a change in clinical management in 37%-87% of cases[16-17]. The main limitations of SBCE include a lack of specificity and a 10%-36% false-negative rate, as well as failure to identify the major duodenal papilla in a significant proportion of patients, which potentially could lead to important duodenal lesions being missed[18-22].

Previous studies or anecdotal reports on SBCE referred to patients with non-small bowel lesions missed during preceding OGD or colonoscopy, indicating that these lesions were probably overlooked during conventional endoscopy. Non-small bowel lesions are defined as lesions proximal to the papilla of Vater and distal to the ileocaecal valve. The current study attempts to review all available studies in the literature and summarize their findings.

LITERATURE STUDY

An extensive bibliographical search was performed *via* the online databases PubMed and EMBASE. The keywords used were the following: non-small bowel lesions, capsule endoscopy, obscure GI bleeding, small bowel bleeding, unexplained IDA. All selected studies were manually examined to identify further relevant reports. This review included all original research papers published in full. Only those written or translated into English were included in the full text assessment. A subset of ten articles was relevant to this review.

NON-SMALL BOWEL LESIONS DETECTED BY SMALL BOWEL CAPSULE ENDOSCOPY

Kitiyakara *et al*[23] reviewed a prospective database of 140 consecutive patients that were referred to a tertiary

University teaching hospital in Sydney, Australia, for further management of obscure GI bleeding. The referred patients had on average a mean of 2.3 OGDs and 2.2 colonoscopies, with no definitive diagnosis. Amongst them, 131 had small-bowel follow-through and 61 enteroscopy carried out[23]. A definitive or likely cause of bleeding was identified in 66% of cases. Interestingly, in 6.4% the culprit lesion was within the reach of conventional endoscopy[23]. Amongst patients with abnormalities in the upper GI tract, 3 women had gastric antral vascular ectasia (GAVE) and one had an inflammatory-appearing polyp. On the other hand, amongst patients with abnormalities identified distal to the ileocaecal valve, 2 were diagnosed with an adenocarcinoma of the caecum, one had a possible caecal tumour and 2 had an angiodysplasia of the caecum. In 5 out of 9 patients with non-small bowel lesions detected by SBCE, there was active bleeding at the time of the examination. Subsequently, all patients received appropriate management, based on the findings of the SBCE[23].

In 2008, Elijah *et al*[24] reported that amongst 201 consecutive SBCE performed in their centre for obscure GI bleeding between March 2003 and November 2004, 78 (38.8%) had a lesion that was within the reach of conventional endoscopy. All patients had at least one gastroscopy and colonoscopy carried out prior to the capsule endoscopy. The majority of patients were diagnosed either with erosions or vascular lesions (*i.e.*, angiectasias or GAVE). Amongst these patients, 21 had an endoscopic intervention carried out and one had surgery, as a result of the SBCE findings[24].

Riccioni *et al*[25] carried out a retrospective study to assess whether it is worthwhile performing SBCE in patients with unexplained IDA. About 138 patients (in a total of 650 consecutive patients) were investigated for unexplained IDA. In 2 out of 3 patients (n = 91), SBCE identified at least one gastric or small bowel lesion likely accounting for IDA. The SBCE findings in decreasing order of frequency included angiodysplasias (in 51 patients), jejunal and/or ileal micro-ulcerations (in 12), tumours (in 8), Crohn's disease, jejunal villous atrophy, erosive gastritis, a solitary ileal ulcer, and a small bowel polyp (in 1). In 4 patients blood was present in the lumen without visible mucosal lesions. Although the primary aim of this study was not the evaluation of SBCE in the detection of non-small bowel lesions, it is noteworthy that 4 patients were found to have unexplained IDA secondary to erosive gastritis, that surprisingly was not seen during OGD[25]. At the end of the follow-up period, an improvement in haemoglobin levels after treatment (either medical, endoscopic or surgical) was reported, and complete resolution of IDA was achieved in 96.25% of patients with positive SBCE[25].

Tacheci *et al*[26] reported the results on 118 consecutive SBCE performed in two University hospitals for obscure GI bleeding. Overall, gastric lesions were detected in 37% of patients and were considered significant (potentially haemorrhagic) in 21%. 17% of the detected lesions were underestimated or missed at conventional endoscopy. The most frequently detected lesions were haemorrhagic erosions. 10% of the lesions were identified as the source of GI bleeding [26].

Vlachogiannakos *et al*[27] published a study including 317 patients (out of 605 in total) who had SBCE performed for obscure (occult or overt) GI bleeding. The patients had a median of 2 OGDs and 2 colonoscopies before the SBCE[27]. Interestingly, small bowel follow-through had also been performed in 114 patients and push enteroscopy in 84. A definite or likely cause of GI bleeding was found in 215 patients in the small bowel and in 11 cases (3.5%) the source of bleeding was outside the small bowel and within the reach of conventional endoscopes. Most non-small bowel lesions were identified in the caecum (7/11)[27]. Of those 7 cases, 3 were diagnosed with a carcinoma of the caecum. Another patient had a bleeding diverticulum in the caecum (preceding colonoscopies had dismissed diverticular disease as a cause of overt bleeding due to the fact that no signs of bleeding were seen at the time of the examination). In addition, 2 patients had an angiodysplasia of the caecum and a young patient with anaemia, weight loss and bouts of abdominal pain, had multiple aphthoid ulcers in the caecum. This patient was later diagnosed with Crohn's disease. In this study, there were also 4 patients with non-small bowel lesions identified in the upper GI tract: 2 were diagnosed with angiodysplasia(s), one patient with longstanding anaemia and a medical history of scleroderma was diagnosed with GAVE (previously described as antral gastritis on repeated OGDs) and the last patient had a carcinoma of the cardia[27]. Given the relatively low incidence of non-small bowel lesions detected by SBCE in this study (3.5%), the authors concluded that second-look endoscopy in a tertiary centre prior to SBCE would not be a cost-effective strategy and may in fact result in a delayed diagnosis[27].

Hoedemaker *et al*[28] prospectively collected data of consecutive SBCE studies performed in a tertiary-care centre in the Netherlands between 2003 and 2009. A total of 595 patients were included, the majority referred for obscure GI bleeding or suspected Crohn's disease. Most patients underwent conventional endoscopic examinations prior to referral for SBCE (mean number 1.1) and approximately 20% of patients had small-bowel-follow-through examination while about 10% underwent push enteroscopy[28]. In 14.3% of patients, abnormalities were identified within the reach of OGD and colonoscopy, and only 2% of those lesions had been previously detected. The majority of the non-small bowel abnormalities were located in the terminal ileum (n = 21) and colon (n = 19), followed by abnormalities seen in the stomach (n = 15), the duodenum (n = 12), proximal jejunum (n = 10), and in other or multiple locations. The most frequent findings were angiodysplasias (37.6%), followed by erosions, active bleeding without definite mucosal pathology

and inflammatory lesions. Regarding patients originally referred for suspected Crohn's disease, abnormalities were seen in the terminal ileum in 33.6%. It is interesting that the terminal ileum had been previously intubated during colonoscopy in only about 30% of cases[28]. The study however, was limited by the fact that follow-up data on patients diagnosed with a non-small bowel lesion at SBCE were lacking.

Riccioni *et al*[29] prospectively reviewed data from 637 patients who underwent SBCE for obscure GI bleeding following a "normal" OGD and colonoscopy. 21.6% of these patients had a definite or likely cause of bleeding identified exclusively in the stomach, whereas 6.5% had a definite or likely cause in the colon; 21% had a combination of small bowel and non-small bowel lesions[29]. Regarding patients with abnormal findings detected in the upper GI tract, 79/138 had multiple gastric and duodenal erosions, 11/138 had gastric or duodenal ulcers, 13/138 were diagnosed with GAVE, 11/138 with isolated or multiple angiodysplasias, 10/138 had multiple erosions in the distal duodenum (previously described as "non-specific duodenitis"), 8/138 were found to have inflammatory-appearing polyps and in the remaining patients (out of 138), SBCE documented the presence of fundic and esophageal varices, antral adenocarcinoma, neoplastic recurrence on gastric anastomosis, gastric leiomyoma, and spontaneous mucosal bleeding without visible lesions[29]. Regarding patients with lesions identified in the lower GI tract, 24/41 were found to have isolated or multiple angiodysplasias in the caecum and/or ascending colon, and 8/41 had erosions or small ulcers at the ileocaecal valve or in the caecum. Of the remaining patients (out of 41), 3 had a haemorrhagic-appearing caecal mucosa without obvious lesions (all 3 were diagnosed with adenocarcinoma of the colon on repeat colonoscopy and were treated accordingly), 3 had non-specific "irregularity" of the mucosa of the right colon, 2 had a large bleeding caecal polyp and one patient had diverticular disease of the right colon with active bleeding[29]. About 75.3% of patients with gastric lesions and 65.8% with colonic lesions did not have further presentations with obscure GI bleeding following diagnosis reached by SBCE and effective endoscopic and/or surgical management[29].

Akin *et al*[30] recently reviewed prospectively collected databases of patients referred to a tertiary teaching hospital in Turkey for potential small bowel bleeding, after inconclusive upper and lower conventional endoscopy. These patients were referred for SBCE and 114 met the inclusion criteria of the study[30]. In 50% of cases a definite or likely cause of the bleeding was identified and amongst them, 8 patients (approximately 7%) were reported to have non-small bowel lesions within the reach of conventional endoscopy[30]. The majority of these findings were identified in the caecum (5/8). Overall, 5 out of 8 patients had angiodysplasia(s) and 4 of them had active bleeding at the time of examination. In a patient with occult GI bleeding GAVE was found. Previous endoscopic examination of the upper GI tract misdiagnosed the above finding as antral gastritis. In a patient with past medical history of Billroth Ⅱ gastrectomy, active bleeding from an anastomotic ulcer was detected. Another patient had active bleeding distal to the duodenal bulb at the time of the SBCE examination, without a definitive lesion seen. A subsequent second-look endoscopy confirmed the presence of an angiodysplasia. Finally, a patient investigated for anaemia and abdominal pain was found to have a caecal ulcer on a caecal fold. A repeat colonoscopy with biopsies was performed and histologically "chronic active colitis" was shown[30].

Juanmartiñena Fernández *et al*[31] retrospectively analyzed data from 2217 consecutive SBCE performed in a tertiary centre in Spain between 2008 and 2016. 52.3% of the patients were referred for occult GI bleeding. The rest were referred for Crohn's disease, abdominal pain, chronic diarrhoea or other indications[31]. SBCE detected gastroduodenal lesions in 566 patients. More than 80% had previously had 1.29 ± 1.1 (1-10) gastroscopies carried out, the vast majority within 30 mo prior to the SBCE. Among patients with gastric or duodenal lesions detected at SBCE, 75.4% and 86.4% respectively did not have these abnormalities found at prior endoscopies. Lesions identified more frequently in the stomach included erosions, vascular lesions and findings suggestive of chronic gastritis, while lesions found more frequently in the duodenum included erosions, erythema or vascular lesions[31]. Lesions revealed by SBCE led to a change to the initial therapeutic strategy in 60.6% of the patients. In 12.8% an endoscopic intervention was carried out (most frequently argon plasma coagulation for vascular changes) and in 1.2% a surgical intervention was performed[31]. Juanmartiñena Fernández *et al*[32] also analyzed 526 consecutive SBCE performed in their centre between 2008 and 2011, in order to assess detection of colonic lesions identified at SBCE[32]. Interestingly, 85.7% had a prior colonoscopy done within two years from the SBCE. Colonic abnormalities were detected in 47 patients (9%) and in 33 out of 47 cases synchronous small bowel lesion(s) were detected. In 66.6% out of them, capsule endoscopy identified findings, which had been overlooked during prior endoscopy. The most frequent findings were vascular lesions (41.8%) and colonic ulcers (20.8%). Treatment changes after SBCE led to an overall change to the initial therapeutic strategy in almost 60% of the patients[32]. Findings are summarized in Table 1.

DISCUSSION

Obscure GI bleeding, either overt or occult, is a common presentation, encountered in 5%-10% of cases of GI bleeding[30]. Conventional upper and lower GI endoscopy often fails to identify the source of bleeding and cannot visualise the entire GI tract. Similarly, radiology may detect small bowel masses and/or large ulcerating lesions but lacks sensitivity in detecting subtle mucosal

Table 1 Summary of publications studying non-small bowel lesions detected at capsule endoscopy

References	Presentation (GI bleeding)	Mean duration (mo)[1]	No of SBCE (*n*)	NSBL detection (*n*)	Most frequent site of NSBL	Most frequent lesion(s)
Kitiyakara *et al*[23]	Obscure	23.1	140	9	Colon	GAVE
Elijah *et al*[24]	Obscure	Not specified	201	78	Only upper GI reported	Vascular lesions
Riccioni *et al*[25][2]	Occult	Not specified	138	Not specified	Not specified	Angiody-splasia
Tacheci *et al*[26]	Obscure	Not specified	118	20	Only upper GI reported	Erosions
Vlachogiannakos *et al*[27]	Obscure	8.6	317	11	Colon	Angiodysplasia and cancer
Hoedemaker *et al*[28]	Obscure	Not specified	595	85	Terminal Ileum	Angiody-splasia
Riccioni *et al*[29]	Obscure	Not specified	637	179	Stomach/ duodenum	Gastric - duodenal erosions
Akin *et al*[30]	Obscure	Not specified	114	8	Caecum	Angiody-splasia
Juanmartiñena Fernández *et al*[31]	Obscure or other indications	19.8	2217	447	Only upper GI reported	Erosions
Juanmartiñena Fernández *et al*[32]	Obscure or other indications	25	526	24	Only lower GI reported	Vascular lesions

[1]Mean duration of presenting symptom; [2]Riccioni *et al*[25] studied the role of small capsule endoscopy in investigating unexplained iron deficiency anaemia. SBCE: Small capsule endoscopy; NSBL: Non-small bowel lesion (defined as lesions within the reach of conventional upper and lower gastrointestinal endoscopy. This may include the terminal ileum; IDA: Iron deficiency anaemia; GI: Gastrointestinal.

abnormalities[33]. Push enteroscopy identifies a potential source of bleeding in up to 40% of patients presenting with obscure GI bleeding. The main limitations of push enteroscopy are operator-dependency, the fact that it does not allow visualisation of the entire small bowel, and that it is an invasive procedure[25].

The introduction of SBCE in clinical practice, a minimally-invasive modality of visualising the entire small bowel, led to the detection of a small-bowel source of obscure GI bleeding in approximately two thirds of cases [6-13]. Another novel modality of visualising directly the small bowel is device-assisted enteroscopy (DAE). DAE includes double-balloon enteroscopy, single-balloon enteroscopy, spiral enteroscopy and balloon-guided endoscopy. DAE shares almost the same limitations as push enteroscopy, but has the advantage of real-time inspection of the lumen and the option of tissue sampling and endoscopic treatment if required[3,24].

SBCE allows the evaluation of the entire small bowel in up to 90% of cases, has a diagnostic yield of up to 83% in patients with potential small bowel bleeding and its findings may lead to a change in management in 37%–87% of cases[14-17]. Several comparative studies demonstrated SBCE superiority over barium follow-through (31% *vs* 5%)[7], push enteroscopy (50% *vs* 24%)[34], CT enteroclysis (59% *vs* 36%)[35], intraoperative enteroscopy (74.4% *vs* 68%)[36], and angiography (72% *vs* 56%)[37]. In comparison to double-balloon enteroscopy, it has a similar diagnostic yield in detecting small-bowel lesions (55.3% *vs* 60.5%)[38]. Thus, many gastrointestinal societies, such as ACG, BSG and ESGE recommend the use of SBCE as first-line investigation for obscure GI bleeding following normal OGD and colonoscopy[1-3].

Until recently, the focus of most studies has been the actual findings within the small bowel. However, there has been increasing evidence suggesting that non-small bowel lesions detected by SBCE are sometimes within the reach of conventional endoscopy and have probably been missed at previous upper and lower GI endoscopy. In 2004, Tang *et al*[39] reported that among 46 patients that underwent SBCE for obscure GI bleeding, 5 had a lesion likely overlooked during prior endoscopies[39]. To the best of our knowledge, since then, there have only been very few studies published to date relevant to non-small bowel lesions overlooked by OGD and colonoscopy.

The reason why such lesions are often missed cannot be determined with confidence. A possible explanation for overlooking a non-small bowel lesion may be the small size or unusual site, posing a challenge in its detection. Additionally, air insufflated during conventional endoscopy may lead to suboptimal appearance of the lesion, as a consequence of vasculature compression, especially for vascular or subtle mucosal abnormalities. It is also interesting that in most studies included in this review, GAVE was misinterpreted as antral gastritis in a significant proportion of patients. In 2006, Sidhu *et al*[40] reported 6 cases of GAVE detected during SBCE that were previously missed at conventional endoscopy, most frequently misdiagnosed as antral gastritis. In addition, luminal endoscopy performed in anaemic patients or in patients with low blood pressure may result in the findings being less prominent, especially if sedation is also administered. A non-bleeding lesion may also be harder to detect. As suggested by Kitiyakara *et al*[23], SBCE may induce bleeding by traumatizing the mucosa which subsequently "reveals"

the lesion. With regard to colonoscopy, failure to reach the caecum either due to actual inability to reach it, or due to misidentification of the caecum by the endoscopist and premature termination of the endoscopy, may lead to missed pathology. Intubation of the ileocaecal valve and inspection of the terminal ileum also appears to be invaluable. Lesions behind colonic haustral folds and poor bowel preparation especially in the right colon are other possible explanations for missed lesions.

The prevalence of non-small bowel lesions missed at conventional endoscopy or push enteroscopy varied significantly between studies, from 3.5% to more than 30%[23-32]. Vlachogiannakos *et al*[27] report a statistically significant difference in the rates of such lesions being missed at endoscopy between different healthcare centres. In most studies, the relevant lesion was detected in the lower GI tract more frequently than in the upper GI tract. Regarding patients with overlooked lesions located in the upper GI tract, antrum is a frequent site where such lesions are found[23-32]. Interestingly, colonic diagnoses were made using a SBCE, which is not designed to explore and examine the colon. Vascular lesions (either angiodysplasia or GAVE) were the most frequently detected abnormality. Other common findings included ulcers or erosions, tumours, polyps, inflammation, or GI bleeding due to diverticular disease. Although not assessed in all of the included studies, in the majority of patients the diagnosis was followed by interventional endoscopic or surgical treatment and/or conservative medical therapy. Treatment changes after SBCE most frequently included iron supplements, argon plasma coagulation for vascular lesions (angiodysplasia) and surgery for patients diagnosed with cancer. Lesions revealed by SBCE led to a change to the initial therapeutic strategy in up to 60% of patients[31,32]. In one of the studies, an improvement in haemoglobin levels after treatment and complete resolution of IDA was achieved in more than 95% of patients with positive findings at SBCE[25].

In conclusion, SBCE is a minimally-invasive endoscopic investigation that can accurately diagnose small bowel pathology, but often also detects abnormalities in the upper and lower GI tract that are within the reach of conventional endoscopy. The prevalence of such lesions that have been overlooked at conventional endoscopy is somewhat alarming, especially when considering the wide range of missed pathology that may include benign lesions, such as gastric or duodenal erosions, or significant abnormalities, such as malignant tumours. Great care should be taken in performing endoscopy carefully and under optimal conditions to maximize diagnostic accuracy and avoid unnecessary repeat examinations, leading to an increased cost and potentially hazardous delays in reaching a diagnosis. SBCE is a safe and reliable means of investigating further the GI tract, provided the procedure is carried out correctly and adequately trained healthcare professionals are interpreting the results. Our study is limited by the fact that most cases presented in the literature, which are summarised in the current review, are retrospectively assessing patient data; therefore prospective studies are mandated to validate the findings.

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ORIGINAL ARTICLE

Case Control Study

Genetic associations of inflammatory bowel disease in a South Asian population

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Abstract

AIM

To estimate prevalence and phenotypic associations of selected inflammatory bowel disease (IBD)-associated genetic variants among Sri Lankan patients.

METHODS

A case study of histologically confirmed ulcerative colitis (UC) or Crohn's disease (CD) patients with $\geqslant$ 1 year disease duration, who were compared to unrelated, gender-matched, healthy individuals as controls, was conducted at four major centers in Sri Lanka. Phenotypic data of the cases were obtained and all participants were genotyped for 16 selected genetic variants: *IL12B*:*rs1045431*, *IL23R*:*rs11805303*, *ARPC2*:*rs12612347*, *IRGM*:*rs13361189*, *IL26/IL22*:*rs1558744*, *CDH1*:*rs1728785*, *IL10*:*rs3024505*, *FCGR2A*:*rs3737240*, *PTGER4*:*rs4613763*, *IL17REL/PIM3*:*rs5771069*, *HNF4a*:*rs6017342*, *STAT3*:*rs744166*, *SMURF1*:*rs7809799*, *LAMB1*:*rs886774*, *HLA-DRB5*, *DQA1*, *DRB1*, *DRA*:*rs9268853*, *MST1*, *UBA7*, and *APEH*:*rs9822268*. The genotypes of all variants were in Hardy-Weinberg Equilibrium ($P > 10^{-3}$). To account for multiple hypothesis testing, *P*-values < 0.003 were considered significant.

RESULTS

A total of 415 patients and 465 controls were recruited. Out of the single nucleotide polymorphisms (SNPs) tested, the majority were not associated with IBD in Sri Lankans. Significant positive associations were noted between *rs886774* (*LAMB1*-gene) and UC (odds ratio (OR) = 1.42, $P = 0.001$). UC patients with *rs886774* had mild disease (OR = 1.66, $P < 0.001$) and remained in remission (OR = 1.48, $P < 0.001$). A positive association was noted between *rs10045431* (*IL 12B* gene) and upper gastrointestinal involvement in CD (OR = 4.76, $P = 0.002$).

CONCLUSION

This confirms the heterogeneity of allelic mutations in South Asians compared to Caucasians. Most SNPs and disease associations reported here have not been described in South Asians.

Key words: Inflammatory bowel disease; Genetics of inflammatory bowel disease; Ulcerative colitis; Crohn's disease; *LAMB1* gene mutation; *IL-12B* gene mutation

Core tip: This is a case-control study looking at the prevalence of genetic mutations, ones that are commonly associated with inflammatory bowel disease (IBD) among Caucasians, in a South Asian population from Sri Lanka. Most allelic variants studied were not seen in this population, confirming the heterogeneity of the genetic composition of IBD between South Asians and Caucasian patients. We found positive associations between *rs886774* (*LAMB1*-gene) and ulcerative colitis, which was also associated with a milder disease and increased remission rate. Patients with upper gastrointestinal involvement of Crohn's disease were more likely to have the mutation *rs10045431* (*IL 12B* gene).

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the intestines that includes Crohn's disease (CD) and ulcerative colitis (UC). It was initially considered a disease of developed countries but it has now become a global health problem[1]. In Europe, the annual incidence of IBD per 100000 people is reported to range from 3-7 cases for CD and 4-11 cases for UC[2]. Although the evidence based in the Asian region is limited, studies such as the Asia Pacific Crohn's and Colitis Epidemiology Study carried out in Australia, China, Hong Kong, Indonesia, Macau, Malaysia, Singapore, Sri Lanka and Thailand have demonstrated an overall incidence per 100000 people of 0.76 for UC and 0.54 for CD[3,4].

The prevalence of IBD is relatively higher in East Asia compared to South Asia. Japan has the highest prevalence (121.9 per 100000) for UC in East Asia[5], while India has the highest prevalence for UC (44.3 per 100000) in South Asia[5-7]. The reported prevalence and incidence of IBD per 100000 people in Sri Lanka are 6.5 (UC-5.3, CD-1.2) and 1.6 (UC-1, CD-0.6),

respectively[4,8]. Genetic heterogeneity within the region, along with diverse socio-economic, environmental and cultural factors, may contribute to these differences.

Since identification of the Neucleotide Oligomerisation Domain 2 (*NOD2*) gene in 2001, a multitude of genome-wide association scans (GWAS) and candidate gene association studies have identified more than 160 genes associated with IBD in Caucasians[8-10]. However, genetic contribution to IBD varies between regions and ethnicities, and there is only limited data for Asians[11]. Results from a large trans-ancestry study demonstrated a wide heterogeneity of genetic risk between European, East Asian and South Asian populations[14]. Therefore, it is important to study genetic associations of IBD for individual Asian ethnic populations.

Many genetic variants that are correlated with increased disease risk in Caucasians, such as variants found in *NOD2/CARD15*, autophagy-related protein 16-liked 1 (*ATG16l1*), immunity-related GTPase family (IRG)-M, interleukin 23 receptor (*IL23R*), tumour necrosis factor superfamily gene (*TNFSF*)*-15*, Toll-like receptor (*TLR*)*-4, DLG-5*, and *SLC22A4* genes, have been investigated in Asian populations. A systematic review and meta-analysis by Ng *et al*[13] in 2012 based on results of 93 reports from eight countries with data from 17976 patients found that only *ATG16L1*, *IL23R*, *TNFSF15*, *TNF308*, *CTLA-4* and *MHC* were significantly associated with IBD among Asians. However, more studies representative of the Asian population are required to identify additional underlying genetic risk factors[3,6]. This study was conducted in Sri Lankans, a population that had never before been studied in South Asia, with the objective of identifying prevalence and phenotypic associations of common genetic risk alleles for IBD.

MATERIALS AND METHODS

Study population

This multicenter, case-control study was conducted among 415 patients with IBD and 465 healthy controls from five major centers in three major cities of Sri Lanka. Patients were recruited from Gastroenterology Units of Colombo North Teaching Hospital, Ragama, National Hospital of Sri Lanka, Colombo, Colombo South Teaching Hospital, Kalubovila, Teaching Hospital, Kandy and Teaching Hospital Karapitiya, Galle. These centers collectively provide tertiary level specialist gastroenterology care for the majority of Sri Lankan patients.

Cases were patients with endoscopically and histologically confirmed IBD, who had the condition for more than one year duration. From the commencement of data collection, consecutive, consenting patients were recruited from the five study centers. Approximately equal numbers of unrelated, healthy, gender-matched subjects, with no chronic bowel symptoms, from the above five locations were recruited as controls.

Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya and Hospital ERCs where relevant.

Data collection

Data were obtained using an interviewer-administered, structured questionnaire. Clinical data were obtained by direct questioning and by review of medical records. Phenotypic data (type, location, severity, treatment types, response to treatment and complications) of patients were recorded. Patients were categorized into UC and CD using clinical, endoscopic and histological features. Disease characteristics were listed according to the Montreal classification[15]. Comorbid conditions, details of the disease and treatment were confirmed using medical records. Complicated disease was defined as having stricturing or penetrating disease in CD, and extensive colitis or pancolitis in UC. Patients with a disease course that was frequently relapsing, steroid-dependent, steroid refractory or requiring biologics was classified as treatment refractory. The presence of disease complications was considered if either perforation, significant bleeding, requirement for colectomy or malignant changes had taken place.

Single nucleotide polymorphism selection and genotyping

Previous candidate gene and GWAS studies were reviewed to select 16 frequently replicated single nucleotide polymorphisms (SNPs) that were associated with inflammatory bowel disease. DNA from the cases and controls were extracted from stored peripheral blood samples using Qiagen QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) to yield DNA concentration > 10 ng/μL. These DNA samples were quantified, normalized and arrayed on 96-well plates. Thereafter, genotyping was carried out for 16 SNPs, which confirmed IBD susceptibility loci, using the Agena MassARRAY system (Agena Bioscience, San Diego, United States) and by following the manufacturer's instructions. Genotypes of all variants were in Hardy-Weinberg Equilibrium ($P > 10^{-3}$ in the control population).

Statistical analysis

After Bonferroni correction, a *P*-value of < 0.003 was considered significant to account for multiple hypotheses. Association analysis utilized logistic regression within STATA version 13 (Chicago, IL, United States) with routines available from http://www-gene.cimr.cam.ac.uk/clayton/software/stata. Different genetic models were tested using statistical modeling in univariate and multivariate analyses for associations with UC and CD. Individual SNPs and various combinations were tested against disease phenotypes. Chi-square tests/Fisher's exact tests were used where appropriate for significance testing.

RESULTS

The demographic and clinical characteristics of patients

Table 1 Characteristics of the patient population, *n* (%)

Characteristic	CD (*n* = 153)	UC (*n* = 258)	*P*[1]
Male gender	77 (50.3)	123 (47.7)	0.80
Age in years (mean, SD)	41.0 (16.9)	47.6 (14.9)	< 0.01
Race			
Sinhala	129 (84.31)	229 (88.75)	
Tamil	11 (7.19)	13 (5.06)	
Muslim	11 (7.19)	13 (5.03)	
Other	2 (1.31)	3 (1.17)	
Body mass index mg/m^2 (mean, SD)	21.4 (4.6)	22.9 (4.5)	< 0.01
Family history of IBD	7 (4.6)	12 (4.7)	0.98
Comorbidities			
Diabetes	11 (7.1)	41 (15.9)	0.01
Hypertension	16 (10.5)	37 (14.3)	0.26
BA/COPD	9 (5.8)	22 (8.5)	0.33
Tuberculosis	7 (4.6)	1 (0.4)	< 0.01
Tobacco smoking	25 (16.3)	49 (18.9)	0.39
Disease characteristics			
Duration of the disease (yr)	4.8 (4.2)	7.3 (5.7)	< 0.01
Extensive disease in UC	76 (29.5)	-	-
Upper GI disease in CD	11 (7.2)	-	-
Severe/complicated disease	47 (30.7)	130 (50.4)	< 0.01
Maintained remission	142 (92.9)	245 (95.0)	0.83
Treatment refractory disease	24 (15.68)	24 (9.3)	< 0.05
Use of biologics	16 (10.5)	7 (2.7)	< 0.01

[1]Unadjusted univariate *P* value. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; GI: Gastrointestinal; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease.

are summarized in Table 1.

The results of the case-control comparison of variants in cases and controls is included in Table 2. The variant alleles of *rs11805303*, *rs1558744* and *rs886774* occurred at a higher frequency in cases than in controls.

The presence of variant alleles was tested for the phenotypes (either CD or UC) that are currently established for Western populations. Only SNP *rs886774* was associated with the described phenotype (Table 3).

Most of the tested phenotypic characteristics were not associated with individual SNPs and combinations that were tested. Table 4 shows SNPs that were significantly associated with the clinical characteristics of UC and CD.

DISCUSSION

The aim of this study was to identify the association of selected SNPs with IBD, its clinical manifestations and treatment outcomes. Of the 16 SNPs tested, only the variant allele of the *LAMB1* gene (*rs886774*) was associated with the main phenotype of UC in this population. We also present a few disease characteristics that are associated with the *LAMB1* gene (*rs886774*) and the *IL 12B* gene (*rs10045431*) that have not been reported previously among South Asians.

The most significant mutation associated with UC in this study was *rs886774* of the *LAMB1* gene. The *LAMB1* gene codes for a subunit of Laminin, which is a component of the cell basement membrane. Mutation *rs886774* in the *LAMB1* gene has been reported in GWAS to be associated with increased susceptibility to UC[16]. Although mutations in this gene are postulated to alter intestinal permeability, a study carried out in the Netherlands failed to demonstrate an association with disrupted intestinal permeability[17]. In this Sri Lankan patient population with UC, *rs886774* was associated with mild disease [odd ratio (OR) = 1.66, $P < 0.001$] and maintained remission (OR = 1.48, $P < 0.001$). Therefore, this study's findings indicate that although rs886774 increases susceptibility to UC, patients with this mutation develop a milder version of the disease that is easier to control. This is consistent with our clinical observations that Sri Lankan patients with UC tend to have a milder and easily controllable form of the disease[18].

The variant allele of the *IL-12B* gene (*rs10045431*) that is known to increase susceptibility to CD in Caucasians[19] was absent in a study conducted among North Indian patients with CD[20]. Similarly, we did not observe a significant association of this mutation with the main phonotype of CD (OR = 2.5, $P = 0.178$ for homozygous individuals). However, among patients with CD, *rs10045431* was associated with upper gastrointestinal involvement (OR = 4.42, $P = 0.002$) in our population. This relationship had not been demonstrated in IBD patients prior to this study.

The variant allele (*rs11805303*) in the region of *IL23R*, which is an extensively studied genetic association of CD, was not present in this group of patients[21,22]. In contrast to Caucasians, this allele of *IL23R* was reported by several study groups to be associated with UC in Chinese patients[23-25]. This variant, however, has not been observed in South Asia[26], which is in agreement with the findings of our study.

Variant *rs9268853*, located in the MHC class Ⅱ

Table 2 Results of the case's control analysis for the association of single nucleotide polymorphisms with inflammatory bowel disease

SNPs	Variant allele	Genotypes	Controls (465), *n* (%)	Cases (415), *n* (%)	Odds ratio[1]	95%CI		*P*
rs10045431	C	AA	5 (1.08)	5 (1.2)				
		CA	114 (24.52)	83 (20)	0.77	0.56	1.06	0.11
		CC	346 (74.41)	327 (78.8)	1.06	0.30	3.69	0.93
rs11805303	T	CC	93 (20)	53 (12.77)				
		TC	236 (50.75)	207 (49.88)	1.54	1.05	2.26	0.03
		TT	136 (29.25)	155 (37.35)	2.00	1.33	3.01	0.00
rs12612347	G	AA	67 (14.41)	69 (16.63)				
		GA	229 (49.25)	191 (46.02)	0.81	0.55	1.19	0.29
		GG	169 (36.34)	155 (37.35)	0.89	0.60	1.33	0.57
rs13361189	C	TT	267 (57.42)	235 (56.63)				
		CT	172 (36.99)	153 (36.87)	1.01	0.76	1.34	0.94
		CC	26 (5.59)	27 (6.51)	1.18	0.67	2.08	0.57
rs1558744	A	GG	347 (74.62)	289 (69.64)				
		AG	116 (24.95)	118 (28.43)	1.22	0.90	1.65	0.19
		AA	2 (0.43)	8 (1.93)	4.80	1.01	22.79	0.04
rs1728785	A	CC	261 (56.13)	253 (60.96)				
		CA	184 (39.57)	139 (33.49)	0.78	0.59	1.03	0.08
		AA	20 (4.3)	23 (5.54)	1.19	0.64	2.21	0.59
rs3024505	A	GG	373 (80.22)	322 (77.59)				
		GA	89 (19.14)	89 (21.45)	1.16	0.83	1.61	0.38
		AA	3 (0.65)	4 (0.96)	1.54	0.34	6.95	0.57
rs3737240	T	CC	262 (56.34)	215 (51.81)				
		TC	172 (36.99)	167 (40.24)	1.18	0.90	1.56	0.24
		TT	31 (6.67)	33 (7.95)	1.30	0.77	2.19	0.33
rs4613763	C	TT	461 (99.14)	408 (98.31)	1.98	0.57	6.80	0.28
		CT	4 (0.86)	7 (1.69)	0.89	0.77	1.01	0.07
		CC	0 (0)	0 (0)				
rs5771069	A	GG	264 (56.77)	248 (59.76)				
		GA	160 (34.41)	144 (34.7)	0.96	0.72	1.27	0.77
		AA	41 (8.82)	23 (5.54)	0.60	0.35	1.02	0.06
rs6017342	A	CC	217 (46.67)	223 (53.73)				
		CA	200 (43.01)	154 (37.11)	0.75	0.57	0.99	0.04
		AA	48 (10.32)	38 (9.16)	0.77	0.48	1.23	0.27
rs744166	G	AA	86 (18.49)	100 (24.1)				
		AG	238 (51.18)	203 (48.92)	0.73	0.52	1.03	0.08
		GG	141 (30.32)	112 (26.99)	0.68	0.47	1.00	0.05
rs7809799	G	AA	405 (87.1)	361 (86.99)				
		GA	58 (12.47)	50 (12.05)	0.97	0.65	1.45	0.87
		GG	2 (0.43)	4 (0.96)	2.24	0.41	12.32	0.35
rs886774	G	AA	154 (33.12)	104 (25.06)				
		GA	214 (46.02)	199 (47.95)	1.38	1.01	1.89	0.05
		GG	97 (20.86)	112 (26.99)	1.71	1.18	2.47	0.00
rs9268853	C	TT	210 (45.16)	203 (48.92)				
		CT	208 (44.73)	164 (39.52)	0.82	0.62	1.08	0.16
		CC	47 (10.11)	48 (11.57)	1.06	0.68	1.65	0.81
rs9822268	A	GG	284 (61.08)	280 (67.47)				
		GA	163 (35.05)	117 (28.19)	0.73	0.55	0.97	0.03
		AA	18 (3.87)	18 (4.34)	1.01	0.52	1.99	0.97

[1]Reports the odds of being a case for heterozygous and homozygous individuals with the recessive allele compared to the controls. SNPs: Single nucleotide polymorphisms.

molecule/*HLA DRB9* region, is also significantly associated with UC, which has been previously reported among Caucasians[27,28]. In our population, this SNP was not associated with UC. Interestingly, our UC patients with this variant allele had a trend towards less extensive disease compared to others (OR = 0.59, *P* = 0.009). Furthermore, CD patients with this variant were more likely to receive biologics compared to others (OR = 3.36, *P* = 0.004). This variant was not associated with any of the other characteristics of severe CD in this population.

The majority of previously reported variants associated with IBD in Caucasians and Asians of Chinese origin were not replicated in this study. This difference may be due to other factors such as gene-gene interactions or gene-environment interactions. It is also possible that other undiscovered genetic variants unique to South Asian populations, which were not investigated in this study, may contribute. Furthermore, it is noted that familial aggregation is lower among South Asian IBD patients. This contributed to the hypothesis that genetic contribution to IBD is lower among Asians compared to their Caucasian counterparts, which is refuted by some

Table 3 Associations of variants with Crohn's disease and ulcerative colitis

SNPs	Candidate gene	Associated subtype	Heterogenous		Homogenous	
			odds ratio[1]	*P*	odds ratio[1]	*P*
rs10045431	*IL 12B*	CD	0.579	0.027	2.491	0.178
rs11805303	*IL23R*	CD	0.909	0.609	1.505	0.010
rs12612347	*ARPC2*	UC	0.896	0.479	0.991	0.957
rs13361189	*IRGM*	CD	1.093	0.578	1.355	0.331
rs1558744	*IFN-c, IL26, IL22*	UC	1.043	0.811	5.560	0.036
rs1728785	*CDH1*	UC	0.829	0.244	1.410	0.314
rs3024505	*IL10*	UC	1.194	0.351	2.446	0.244
rs3737240	*FCGR2A*	UC	1.182	0.291	1.187	0.564
rs4613763	*PTGER4*	CD	2.325	0.273	[2]	-
rs5771069	*IL17REL/PIM3*	UC	0.915	0.589	0.599	0.109
rs6017342	*HNF4a, SERINC3*	UC	0.690	0.021	0.920	0.746
rs744166	*STAT3*	CD	0.841	0.266	0.900	0.541
rs7809799	*SMURF1*	UC	1.149	0.542	2.747	0.270
rs886774[3]	*LAMB1*	UC	1.163	0.330	1.494	0.001
rs9268853	*HLA DRB5*	UC	0.684	0.017	1.049	0.850
rs9822268	*APEH*	UC	0.748	0.748	1.116	0.779

[1]Odds ratios when comparing patients with healthy controls; [2]No heterozygous individuals were present in this study population; [3]Significantly associated with the relevant phenotype after Bonferroni correction. SNPs: Single nucleotide polymorphisms; CD: Crohn's disease; UC: Ulcerative colitis.

Table 4 Association of single nucleotide polymorphisms with clinical characteristics of ulcerative colitis and Crohn's disease

Characteristic	SNPs	OR[1]	*P*	95%CI	
Risk for UC	rs11805303	1.35	0.009	1.08	1.69
Extensive disease in UC	rs9268853	0.59	0.009	0.37	0.82
Upper GI disease in CD	rs10045431	4.42	0.002	1.75	12.92
Mild disease in UC	rs886774	1.66	< 0.001	1.13	2.17
Maintained UC remission	rs886774	1.48	< 0.001	1.19	1.85
Use of biologics in CD	rs9268853	3.36	0.004	1.48	7.58

[1]Univariate odds for the presence of single nucleotide polymorphisms in patients with characteristics tested against healthy controls. OR: Odds ratio; SNPs: Single nucleotide polymorphisms; GI: Gastrointestinal; CD: Crohn's disease; UC: Ulcerative colitis.

scientists[12].

We only studied 16 selected SNPs that were reported to be associated with IBD in previous studies, and which were known to be polymorphic in the Sri Lankan population. The limited number of patients with IBD and the genetic variants included in this study may be a limitation. Hence, more comprehensive studies, including GWAS that involves larger and wider, cross country patient populations throughout South Asia, are needed.

In conclusion, this study confirms the heterogeneity of allelic mutations in South Asians compared to Caucasians. Most of the SNPs and disease associations reported here have not been previously studied in South Asians. Further studies involving a broader South Asian population are required to confirm or refute these findings.

ARTICLE HIGHLIGHTS

Research background

Genetic factors play an important role in the etiology and nature of inflammatory bowel disease (IBD). Genome-wide association studies and meta-analyses have discovered 230 disease loci linked to IBD and its various phenotypic characteristics. A majority of these studies are conducted among Caucasian populations.

Research motivation

Genetic factors that determine disease patterns are known to vary across different populations and regions. Hence, there is an increased need to study the South Asian population in whom there is only sparse evidence of genetic associations of IBD.

Research objectives

We aimed to study the association of 16 selected single nucleotide polymorphisms (SNPs) in a South Asian multiethnic population of IBD patients in Sri Lanka.

Research methods

A case-control multi-center study was conducted. Patients, who were diagnosed with IBD for over a 1 year duration, were recruited from the four main gastroenterology units in Sri Lanka. A roughly equal number of unrelated gender-matched healthy adult volunteers were recruited. DNA was extracted from peripheral blood, and genotyping was performed for 16 selected SNPs using the Agena MassARRAYay system. Data on disease characteristics including disease behavior, treatment response and severity were obtained. Genotypes of all variants were in Hardy-Weinberg Equilibrium. Data analysis included testing for individual SNPs and various combinations with ulcerative colitis (UC), Crohn's disease (CD) and different clinical characteristics of these diseases.

Research results

A total of 415 (CD = 158, UC = 258, indeterminate colitis = 4) patients and 465 controls were studied. SNP *rs886774* (*LAMB1*-gene) was associated

with UC [odds ratio (OR) = 1.42, $P = 0.001$]. Other tested mutations failed to demonstrate an association with UC or CD in this population. The following phenotypic associations were noted within the patient population: among UC patients, *rs886774* was associated with mild disease (OR = 1.66, $P < 0.001$) and remained in remission (OR = 1.48, $P < 0.001$), and SNP *rs10045431* (*IL 12B* gene) was associated with upper gastrointestinal involvement in CD (OR = 4.76, $P = 0.002$).

Research conclusions

This study demonstrated the presence of SNP *rs886774* (*LAMB1*-gene) among Sri Lankan patients with UC. Out of the SNPs tested, the majority were not associated with IBD in Sri Lankans. This confirms the genetic heterogeneity of South Asians compared to Caucasian populations.

Research perspectives

Future research should focus on genome-wide association scans and the identification of other genetic risk factors specific to South Asian populations.

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ORIGINAL ARTICLE

Case Control Study

Clinical relevance of atrial septal aneurysm and patent foramen ovale with migraine

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Abstract

AIM

To test the potential association between atrial septal aneurysm (ASA) and migraine in patent foramen ovale (PFO) closure patients through an observational, single-center, case-controlled study.

METHODS

We studied a total of 450 migraineurs who had right-to-left shunts and underwent PFO closure in a retrospective single-center non-randomized registry from February 2012 to October 2016 on the condition that they were aged 18-45 years old. Migraine was diagnosed according to the International Classification of Headache Disorders, 3rd edition and evaluated using the Headache Impact Test-6 (HIT-6). All patients underwent preoperative transesophageal echocardiography, contrast transthoracic echocardiography, and computed tomography or magnetic resonance imaging

examinations, with subsequent fluoroscopy-guided PFO closure. Based on whether they have ASA or not, the patients were divided into two groups: A (PFO with ASA, *n* = 80) and B (PFO without ASA, *n* = 370). Baseline characteristics and procedural and follow-up data were reviewed.

RESULTS

Compared to group B, group A had an increased frequency of ischemic lesions (11.3% *vs* 6.2%, *P* = 0.038) and migraine with aura (32.5% *vs* 21.1%, *P* = 0.040). The PFO size was significantly larger in group A (*P* = 0.007). There was no significant difference in HIT-6 scores between the two groups before and at the one-year follow-up after the PFO closure [61 (9) *vs* 63 (9), *P* = 0.227; 36 (13) *vs* 36 (10), *P* = 0.706].

CONCLUSION

Despite its small sample size, our study suggests that the prevalence of ASA in PFO with migraine patients is associated with ischemic stroke, larger PFO size, and migraine with aura.

Key words: Patent foramen ovale; Migraine; Atrial septal aneurysm; Contrast transthoracic echocardiography; Right-to-left shunt; Transesophageal echocardiography

Core tip: The aim of this study was to test the potential association between atrial septal aneurysm (ASA) and migraine in patent foramen ovale (PFO) closure patients. A total of 450 migraineurs who had right-to-left shunts and underwent PFO closure on the condition that they were aged 18-45 years old were observed. Compared to the PFO without ASA patients, the PFO with ASA patients had an increased frequency of ischemic lesions and migraine with aura. The PFO size was significantly larger in PFO with ASA patients. There was no significant difference in Headache Impact Test-6 scores between the two groups before and at the one-year follow-up after the procedure.

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INTRODUCTION

Migraine is common, with an estimated prevalence of 8%-12% in the general population (18% of women and 6% of men), and has been acknowledged as one of the most important causes of disability burdens[1]. Patent foramen ovale (PFO) is a remnant of the fetal anatomy with a slit-like interatrial opening that is present in approximately 27% of the general population[2]. Although not all migraineurs have a PFO, and not all PFO patients have migraine, interestingly, PFO is more prevalent in migraineurs (approximately 48% in migraineurs with aura, 23% in in migraineurs without aura, and only 20% in controls)[3]. The pathophysiological mechanisms between PFO and migraine remain entirely unknown. Anecdotally, the closure of a PFO for nonmigraine indications has been shown to ameliorate pre-existing migraine in numerous retrospective series published after 2000[4-8]. Therefore, the hypothesis of the right-to-left shunts (RLS) of chemical or physical triggers for migraine has been proposed.

Atrial septal aneurysm (ASA) is redundant septal primum tissue with excessive mobility of the fossa ovalis. The prevalence of ASA is approximately 2%-3% in the general population. An ASA increases the likelihood of the presence of a PFO, whereas the incidence of ASA in PFO patients is significantly higher than that of the general population[9]. With the continuous deeper study of PFO, ASA has been identified as an independent risk factor for cryptogenic stroke in PFO patients[10,11]. Patients with migraine appear to be at risk for silent stroke, which might be related to the presence of a PFO. However, the association of ASA and migraine in PFO patients remains unknown.

MATERIALS AND METHODS

Study population

In a retrospective single-center non-randomized registry from February 2012 to October 2016, we enrolled 450 patients diagnosed with migraine who had RLS and underwent transcatheter PFO closure at the First Affiliated Hospital of Xi'an Jiaotong University on the condition that they were aged 18-45 years old. All patients underwent preoperative contrast transthoracic echocardiography (cTTE), transesophageal echocardiography (TEE), and computed tomography (CT) or magnetic resonance imaging (MRI) examinations, with subsequent fluoroscopy-guided PFO closure. According to the International Classification of Headache Disorders 3rd edition, migraine was diagnosed by two neurologists[12], and evaluated by Headache Impact Test-6 (HIT-6) scores.

The patients gave their informed written consent to the procedures. The local ethics committee approved this study. Based on whether they had an ASA or not, the patients were divided into two groups: A (PFO with ASA, *n* = 80) and B (PFO without ASA, *n* = 370). Baseline characteristics and procedural and follow-up data were reviewed.

Echocardiography

All patients had a diagnostic cTTE and TEE study performed prior to the procedure. An ultrasound system with a 2-4 MHz transducer was used to perform cTTE and a 4-7 MHz transducer was used to perform TEE.

As reported by Agmon *et al*[9], an ASA was defined if the excursion of the septum primum into the left/right atriums exceeded 10 mm or the total excursion distance was more than 15 mm. The apical four-chamber view was generally selected when performing cTTE. The presence of RLS was identified when micro-bubbles were seen in the left atrium within the first three cardiac cycles after contrast appearance in the right atrium during normal respiration or the Valsalva maneuver. The severity of the RLS was semi-quantified into a four-level scale[13].

PFO closure

The procedure was performed under 2% lidocaine local anesthesia. All the operations were performed by the same interventional cardiologist and first assistant. The right femoral vein was accessed and intravenous heparin (80-100 IU/kg) was administered. The device implantation was guided only by fluoroscopy. The device size was determined according to the surgeon's preference. The Amplatzer PFO occluder (St. Jude Medical, Golden Valley, MN, United States) and the Cardi-O-Fix PFO occluder (Starway Medical Technology Inc., Beijing) were used during the study period. The occluder type included 18/18 mm, 18/25 mm, 30/30 mm, and 25/35 mm.

Follow-up

After the procedure, low-molecular-weight heparin (10 U/kg·h) was administered for 48 h. Aspirin 100 mg/d for 6 mo and clopidogrel 50-75 mg/d for 3 mo were administered to all patients following device implantation. All patients were followed at 1, 3, 6, and 12 mo post-procedure and yearly thereafter. The HIT-6 score was recorded to evaluate the severity of migraine. Transthoracic echocardiography (TTE) was performed to confirm early residual shunting and device embolization within 24 h following the procedure. cTTE was performed at 3 mo after the procedure to observe residual RLS. If there was no residual RLS, cTTE was not required in future follow-up examinations. If the RLS remained, cTTE was performed at 180-d follow-up after the procedure. All patients were followed after device implantation through questionnaires made by phone calls or office visits. For patients with symptoms of palpitation, Holter monitoring was performed to confirm the presence or absence of atrial fibrillation. Follow-up was completed in Oct 2017.

Statistical analysis

Data analyses were performed using SPSS version 24.0 (Statistical Package for Social Sciences, version 24.0, for Windows, SPSS, Chicago, IL, United States). Summary statistics for normally distributed quantitative variables are expressed as the mean ± SD. Differences in means for continuous variables were compared using Student's *t*-test. For non-normally distributed variables, we used the median and interquartile range (IQR). Differences in medians for non-normally distributed variables were compared using a Mann-Whitney *U* test. Categorical data are summarized as ratios and percentages. Chi-square tests or Fisher's exact tests were used for two-group comparisons. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

In total, 450 participants (group A: PFO with ASA, *n* = 80; group B: PFO without ASA, *n* = 370) were included in the study. The baseline characteristics of the two groups are listed in Table 1. There were no significant differences regarding age, weight, gender, hypertension, diabetes mellitus, hyperlipidemia, history of smoking, or baseline HIT-6 scores between the two groups (*P* > 0.05).

Compared with group B, group A exhibited an increased frequency of ischemic brain lesions, as observed with MRI/CT (11.3% *vs* 6.2%, *P* = 0.038). Migraine with aura was found to be more prevalent in group A (32.5% *vs* 21.1%, *P* = 0.040). The PFO size ranged from 1.0-9.3 mm (median 2.6 mm) in group A and 0.7-9.3 mm (median 2.1 mm) in group B. The PFO size was significantly larger in patients with ASA compared those without (*P* = 0.007).

Procedural characteristics

The Amplatzer PFO occluder was used in 146 patients (32.4%), and the Cardi-O-Fix PFO occluder was used in 304 patients (67.6%). Technical success was defined as the delivery and release of the device and was achieved in all patients. Procedural success, defined as implantation without in-hospital serious adverse events, was also achieved in all patients. Procedural complications included two arteriovenous fistulae, two false aneurysms, and one inguinal hematoma. There were no procedure-related deaths, strokes, or transient ischemic attacks (TIAs).

Follow-up

The mean follow-up period was 3 (2) years. Residual RLS was detected by cTTE in two (2.5%) cases 180 days after the procedure in group A, while there was no residual RLS detected by cTTE 180 days after the procedure in group B. No patients experienced TIAs or stroke after the procedure. Two (0.44%) cases of paroxysmal atrial fibrillation occurred (at 2 wk and 3 mo after the procedure). One reverted spontaneously to a sinus rhythm, and the other underwent pharmacological conversion to a sinus rhythm. No cases of occluder translocation, occlude erosion, pericardial effusion, or puncture site bleeding was found in our study.

We compared HIT-6 scores at different time points during the follow-up period after the procedure. At 3 mo after closure, the average HIT-6 scores were 41 (15) in group A and 40 (15) in group B. At 6 mo after closure,

Table 1 Baseline characteristics, *n* (%)

	Group A (*n* = 80)	Group B (*n* = 370)	Sig (*P*)
Age, yr, median (IQR)	34 (12)	34 (13)	0.968
Weight, kg, median (IQR)	60 (13)	59 (15)	0.549
Women	62 (77.5)	259 (70)	0.227
Hypertension	4 (5.0)	11 (3.0)	0.567
Diabetes mellitus	1 (1.25)	2 (0.5)	1.000
Hyperlipidemia	5 (6.3)	31 (8.4)	0.683
History of smoking	14 (17.5)	82 (22.2)	0.440
Ischemic lesions detected by CT/MRI	11 (11.3)	23 (6.2)	0.038
Migraine with aura	26 (32.5)	78 (21.1)	0.040

CT: Computed tomography; MRI: Magnetic resonance imaging; IQR: Interquartile range.

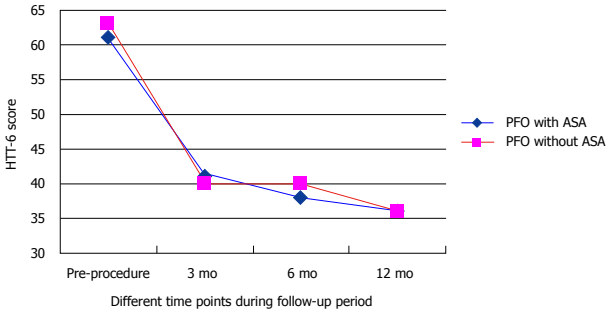

Figure 1 Comparison of migraine relief between two groups at different time points during the follow-up period. PFO: Patent foramen ovale; ASA: Atrial septal aneurysm; HIT-6: Headache Impact Test-6.

the average HIT-6 scores were 38 (11) in group A and 40 (10) in group B. At 12 mo after closure, the average HIT-6 scores were 36 (13) in group A and 36 (10) in group B; the average HIT-6 scores at baseline were 61 (9) and 63 (9) for group A and group B, respectively (Figure 1). At the one-year follow-up after the PFO closure, there was no significant difference in HIT-6 scores between the two groups (P = 0.706).

DISCUSSION

Since 1998, when Del Sette *et al*[14] found that 41% of a migraine group and 16% of a control group had PFO-RLS, the relationship between migraine and PFO has been extensively studied. Unfortunately, the current literature remains discordant as to whether a link exists between PFO and migraine. Some observational studies have shown that PFO and migraine are closely related. For most migraine patients with a PFO, migraine can be greatly alleviated after PFO closure[15,16]. However, other studies found no association between migraine and the presence of a PFO[17,18].

The reasons for the inconsistent results of the above research might be explained in different ways. First, many observational studies include different types of migraine populations, mainly cryptogenic stroke patients with migraine, while other studies with the opposite opinion mostly exclude these patients with pathological PFO[19]. Second, one of the factors that is most strongly associated with the occurrence of a cryptogenic stroke is the presence of a combination of a PFO with an ASA, and the incidence of migraine in these patients is also significantly higher[20,21]. Therefore, we hypothesized that the link between a PFO and migraine might be an ASA.

The main findings of our study suggest that the prevalence of ASA and migraine in PFO patients is associated with silent stroke, severe RLS, and migraine with aura. The incidence of ASA in the normal population is 1%-2.2%[22] when determined by autopsy and 1%-4.9% when determined by TEE[23].The incidence of ASA in cryptogenic stroke and TIAs is approximately 7.9%, which is significantly higher than that of the general population[9]. In 50%-89% of patients with an ASA, a PFO is also seen, and the PFO size is also larger when accompanied by an ASA[9]. The association between ASA and PFO has emerged as a factor that can potentially increase the risk of stroke occurrence or relapse. Because of the unknown mechanisms of migraine itself, the pathogenesis of silent stroke in migraine patients is also in the hypothesis stage. Previous studies showed that the possibility of stroke was significantly increased in patients with PFO combined with ASA, while a paradoxical embolism was considered to be the main mechanism of stroke. Overell *et al*[11] found that the risk of stroke was 4.96 times higher in patients with PFO with ASA compared with the normal population. Compared with the control group, the odds ratio for stroke was 6.14 in patients younger than 55 years old; and in patients with a simple PFO, the odds ratio for stroke was 3.10; if patients had a PFO with an ASA, the odds ratio for stroke was as high as 15.59. A prospective cohort study by Mas *et al*[24] found that the possibility of recurrent stroke or TIAs in simple PFO patients was 6% under 300 mg/d aspirin condition; if an ASA was combined with a PFO, the incidence increased to 15.6%. After 4 years of follow-up, the relative risk of recurrent stroke or TIA was 5.6 in simple PFO patients and 19.2 in PFO with ASA patients. Therefore, an ASA can increase the possibility of paradoxical embolisms in PFO patients. When a PFO is combined with ASA, the presence of an ASA can lead to increased PFO channel opening frequency and a wider opening. In addition, the presence of an ASA

can change the direction of blood flow, allowing the blood flow of the inferior vena cava into the PFO and promoting a RLS, thus resulting in cerebral ischemic events[25]. In this study, the prevalence of silent infarct-like lesions in patients with migraine and an ASA was higher, which is also consistent with previous study results.

In the current study, we found that patients with an ASA had a larger PFO than those without an ASA. The grade of the RLS in patients with an ASA was also larger than that of patients without an ASA. The size of the PFO directly correlated with the degree of the shunt. Larger PFO sizes allowed a higher number of microbubbles to enter systemic circulation. Larger shunts might also increase the likelihood of paradoxical embolization to the brain and, hence, explain the statistically increased stroke risk associated with migraine[20].

Our study also found that the incidence of migraine with aura was higher in people with an ASA. Wilmshurst *et al*[26] studied the incidence of migraine in 200 divers with decompression sickness. The results showed that the prevalence of migraine was higher in patients with a larger RLS (especially in those who showed a persistent RLS at rest). A large RLS may induce migraine, especially migraine with aura. Anzola *et al*[27] studied 420 cases of RLS and found that the degree of the RLS could predict the occurrence of migraine and that the degree of the RLS in migraine patients was larger than that of non-migraine patients.

Moreover, a recent study by Snijder *et al*[28] also confirmed this finding. A plausible hypothesis for mrgraine is that, *via* the PFO, a venous to arterial passage of activated platelets or chemical substances may trigger a headache by overwhelming the filtering capacity of the lungs[29]. Therefore, the size of the PFO and the degree of the RLS through it may be the major determinants for whether a PFO acts as a conduit for paradoxical embolization. By comparing migraine relief after PFO closure at different time points during the follow-up period in patients with or without an ASA, we found similar mean HIT-6 scores at 3, 6, and 12 mo after the procedure, which were all significantly decreased in comparison with the baseline values. However, regardless of whether patients had an ASA or not, there were no significant differences between the two groups. From the above information, we speculated that the PFO closure effects likely affected early judgments about headache relief. In our study, the incidence of a residual RLS was very low in both groups, which was associated with an accurate preoperative TEE examination. We speculate that the low incidence of residual shunts after the operation relieved migraine attacks and significantly reduced the HIT-6 scores.

This single-center, case-controlled study cohort, despite its small sample size, suggests that the prevalence of ASA with migraine in PFO patients is associated with ischemic stroke, larger PFO size, and migraine with aura.

ARTICLE HIGHLIGHTS

Research background

The relationship between patent foramen ovale (PFO) with atrial septal aneurysm (ASA) and migraine remains controversial. We examined this association through an observational, single-center, case-controlled study.

Research motivation

A PFO with ASA has been identified as a risk factor for ischemic stroke. Patients with migraine with aura appear to be at risk for silent brain infarction, which might be related to the presence of a PFO. However, the association between ASA and migraine in PFO closure patients has rarely been reported. Therefore, in addition to clarifying the relationship between PFO, ASA, and migraine, this study also hopes to provide guidance for the choice of migraine patients who can benefit more from PFO closure.

Research objectives

The research objective of this study was to test the potential association between ASA and migraine in PFO closure patients. Because ASA is a structural abnormality, our findings also verify the role of ASA in migraine with PFO patients. Further PFO and migraine studies should focus on the specific intra-atrial structural abnormality.

Research methods

We retrospectively analyzed 450 migraineurs who had right-to-left shunts and underwent PFO closure from February 2012 to October 2016. The patients were classified into two groups according to whether they had ASA or not: the PFO with ASA group and the PFO without ASA group. This study is a single-center, non-randomized, case-controlled study.

Research results

Our research found that the PFO with ASA patients had an increased frequency of ischemic lesions and migraine with aura. The PFO size was significantly larger in PFO with ASA patients. However, there was no significant difference in Headache Impact Test-6 scores between the PFO with ASA and without ASA groups before and after the PFO closure. Given its nature, the present study shares all of the limitations of case-controlled studies. In our study, the mean follow-up time was only 1 years. Although the effect of PFO closure on migraine usually appears within this time frame, the results may have been affected. The small sample size is another limitation of this study.

Research conclusions

This single-center, case-controlled study cohort, despite its small sample size, suggests that the prevalence of ASA with migraine in PFO patients is associated with ischemic stroke, larger patent foramen ovale size, and migraine with aura. That is to say, the presence/absence of an ASA is associated with differences in baseline characteristics but not with differences in severity of migraine as demonstrated by the similar score results.

Research perspectives

We used the anatomical abnormality of ASA as a breakthrough point, and concluded that patients with ASA have a large PFO diameter and a high incidence of ischemic stroke and migraine with aura. According to our experience, the direction of the future research should focus on the anatomical abnormality of PFO. And we also believe that the highest level of evidence in clinical studies is still a multi-center, prospective, randomized controlled study.

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ORIGINAL ARTICLE

Retrospective Study

Current trends of liver cirrhosis in Mexico: Similitudes and differences with other world regions

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Abstract

AIM

To investigate the main current etiologies of cirrhosis in Mexico.

METHODS

We performed a cross-sectional retrospective multicenter study that included eight hospitals in different areas of Mexico. These hospitals provide health care to people of diverse social classes. The inclusion criteria were a histological, clinical, biochemical, endoscopic, or imaging diagnosis of liver cirrhosis. Data were obtained during a 5-year period (January 2012-December 2017).

RESULTS

A total of 1210 patients were included. The mean age was 62.5 years (SD = 12.1), and the percentages of men and women were similar (52.0% *vs* 48.0%). The most frequent causes of liver cirrhosis were hepatitis C virus (HCV) (36.2%), alcoholic liver disease (ALD) (31.2%), and nonalcoholic steatohepatitis (23.2%), and the least frequent were hepatitis B virus (1.1%), autoimmune disorders (7.3%), and other conditions (1.0%).

CONCLUSION

HCV and ALD are the most frequent causes of cirrhosis in Mexico. However, we note that non-alcoholic fatty liver disease (NAFLD) as an etiology of cirrhosis increased by 100% compared with the rate noted previously. We conclude that NAFLD will soon become one of the most frequent etiologies of liver cirrhosis in Mexico.

Key words: Alcoholic liver disease; Hepatitis C virus; Nonalcoholic steatohepatitis; Liver cirrhosis

Core tip: In 2004, a Mexican study reported the most common causes of liver cirrhosis were alcoholic liver disease (39.5%), hepatitis C virus (36.6%), and non-alcoholic fatty liver disease (10.4%). We believe that the epidemiology of cirrhosis has changed because of the increasing prevalence of obesity, metabolic syndrome, and autoimmune diseases. Therefore, we performed a cross-sectional multicenter study that included eight hospitals of different areas of Mexico in order to know the current epidemiology of liver cirrhosis in this country.

Méndez-Sánchez N, Zamarripa-Dorsey F, Panduro A, Purón-González E, Coronado-Alejandro EU, Cortez-Hernández CA, Higuera de la Tijera F, Pérez-Hernández JL, Cerda-Reyes E, Rodríguez-Hernández H, Cruz-Ramón VC, Ramírez-Pérez OL, Aguilar-Olivos NE, Rodríguez-Martínez OF, Cabrera-Palma S, Cabrera-Álvarez G. Current trends of liver cirrhosis in Mexico: Similitudes and differences with other world regions. *World J Clin Cases* 2018; 6(15): 922-930 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/922.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.922

INTRODUCTION

Liver fibrosis develops as a result of chronic injury to the liver in conjunction with the excessive accumulation of extracellular matrix proteins, which occurs in most chronic liver diseases (CLDs)[1]. The accumulation of extracellular matrix proteins distorts the hepatic architecture by forming fibrous scar tissue, and the subsequent development of regenerative nodules within hepatocytes defines cirrhosis[2]. Cirrhosis is the end stage of CLD and leads eventually to portal hypertension, hepatocellular carcinoma (HCC), and liver failure[3].

Liver cirrhosis is a major and underestimated global public health problem as well as an important cause of morbidity and mortality. In 2010, cirrhosis was responsible for an estimated 2% of all deaths worldwide[4]. Current global estimates show that 844 million people have a CLD, and 2 million people die per year because of CLD[5]. The worldwide prevalence rate for CLD is 4.5% to 9%, causing approximately 633000 cases of liver cirrhosis per year[6]. In the United States, CLDs and liver cirrhosis are the 12th leading cause of mortality and

Table 1 Main causes of liver cirrhosis by hospital

Hospital	*n*	Virus		Alcohol	NASH	Autoimmune	Others
		B	C				
MSC&F	413	8	169	123	71	42	0
CHG	156	0	91	45	20	0	0
CMH	100	0	23	25	41	11	0
CMSSH	113	3	20	26	47	8	9
GHD	73	1	6	40	25	1	0
GHM	99	0	35	26	24	14	0
GRH IMSS No.1	82	0	72	4	0	6	0
HJM	174	1	22	88	53	7	3
Total	1210	13	438	377	281	89	12
Percentage		1.1	36.2	31.2	23.2	7.3	1
95%CI		0.62-1.8	33.5-38.9	28.6-33.8	20.9-25.7	6.0-8.9	0.56-1.7
							$P < 0.001$

The distribution of the etiology of liver cirrhosis was higher for hepatitis C virus 36.2%, alcoholic liver disease 31.2% and nonalcoholic steatohepatitis 23.2% and lower for hepatitis C virus 1.1%, autoimmune hepatitis 7.3% and other causes 1.0% ($P < 0.001$). MSC&F: Medica Sur Clinic and Foundation; HJM: Hospital "Juárez" of México; CHG: Civil Hospital of Guadalajara "Fray Antonio Alcalde"; CMSSH: Christus Muguerza "Super Specialty" Hospital; GHM: General Hospital of Mexico "Dr. Eduardo Liceaga"; CMH: Central Military Hospital; GHD: General Hospital of Durango; GRH IMSS No.1: Regional General Hospital IMSS 1; NASH: Nonalcoholic steatohepatitis.

account for about 60000 deaths per year[7]. In European countries, liver cirrhosis affects about 0.1% of the populations and causes about 170000 deaths per year[8].

The most common etiologies of liver cirrhosis in developed countries include chronic hepatitis C virus (HCV) infection, alcoholism, and nonalcoholic steatohepatitis (NASH), whereas viral hepatitis, especially that caused by hepatitis B virus (HBV) infection, are the main causes in developing countries[7]. However, in many countries, the proportion of liver cirrhosis caused by viral hepatitis is decreasing markedly and the proportion caused by NASH is increasing[9]. Nonalcoholic fatty liver disease (NAFLD), the predecessor condition of NASH, has a current prevalence of 25%-30% worldwide and the highest prevalence rates are in Western countries[10]. Some studies have reported that over 64 million people have NAFLD in the United States and 53 million have NAFLD in Europe[11]. Therefore, it is expected that NAFLD will become the leading cause of liver-related morbidity and mortality in the next 20 years as well as the main indication for liver transplantation[12]. Unfortunately, NASH is now the second most frequent indication for liver transplantation in the United States[13,14].

In Mexico, alcoholic liver disease (ALD) and HCV infection have been the most frequent causes of liver cirrhosis in the past decade[15]. Nevertheless, the rising prevalence of obesity[16], metabolic syndrome[17], and autoimmune diseases[18] has probably modified the epidemiology of cirrhosis in our country. Therefore, we aimed to investigate the main etiologies of liver cirrhosis in Mexicans. We believe that understanding the epidemiology of liver cirrhosis in the general population is the first step toward developing interventions to decrease this disease burden.

MATERIALS AND METHODS

A multicenter cross-sectional retrospective observational study was performed in eight tertiary referral hospitals from different cities of Mexico: Medica Sur Clinic and Foundation (Mexico City), Hospital "Juárez" of Mexico (Mexico City), Civil Hospital of Guadalajara "Fray Antonio Alcalde" (Jalisco), Christus Muguerza "Super Specialty" Hospital (Nuevo León), General Hospital of Mexico "Dr. Eduardo Liceaga" (Mexico City), Central Military Hospital (Mexico City), General Hospital of the Mexican Social Security Institute (Durango), and the General Regional Hospital, IMSS 1 (Cuernavaca). The hospitals in our sample come from three geographic regions of Mexico: North, Center, and Mexico City. These hospitals provide medical care to the Mexican population of all ages. The study was conducted from January 2012 to December 2017.

We included patients who were older than 20 years, of both genders, who had been diagnosed with liver cirrhosis of the compensated or decompensated stage. The medical records of all participants were reviewed to obtain information about liver disease categorization and biochemical and imaging data. All eligible patients had received a biochemical, clinical, imaging, or histological diagnosis of liver cirrhosis. The diagnosis of liver disease was categorized as HBV, HCV, autoimmune liver disease, ALD, NASH, or other conditions. Hereditary liver disease or liver cirrhosis resulting from hepatotoxic drugs or toxins was classified into the group of other causes.

We made the histological diagnosis of cirrhosis according to the American Association for the Study of Liver Diseases guidelines. The criteria for the categorization of viral hepatitis were positive serological enzyme-linked immunoassay test results for HCV antibody, immunoglobulin G to hepatitis core antigen, and positive surface antigen of HBV. ALD was diagnosed for patients with a history of ethanol consumption $\geqslant$ 30 g/d in men or $\geqslant$ 20 g/d in women and negativity to viral and autoimmune markers. Consumption of alcohol was assessed

Table 2 Main etiologies of liver cirrhosis by gender, *n* (%)

	Male (*n* = 629)							Female (*n* = 581)						
		Virus							Virus					
Hospital	*n*	B	C	Alcohol	NASH	Auto-inmune	Other	*n*	B	C	Alcohol	NASH	Autoinmune	Other
MSC&F	217	5	56	110	29	17	0	196	3	113	13	42	25	0
		(62.5)	(36.4)	(33.6)	(26.1)	(77.3)	0		(60.0)	(39.8)	(26.0)	(24.7)	(37.3)	0
CHG	96	0	44	42	10	0	0	60	0	47	3	10	0	0
		0	(28.6)	(12.8)	(9.0)	0	0		0	(16.6)	(6.0)	(5.9)	0	0
CMH	35	0	8	13	12	2	0	65	0	15	12	29	9	0
		0	(5.2)	(4.0)	(10.8)	(9.1)	0		0	(5.3)	(24.0)	(17.1)	(13.4)	0
CMSSH	70	2	11	23	11	2	5	43	1	9	3	20	6	4
		(25.0)	(7.1)	(7.0)	(7.1)	(9.1)	(71.4)		(20.0)	(3.2)	(6.0)	(11.8)	(9.0)	(80.0)
GHD	45	0	2	35	8	0	0	28	1	4	5	17	1	0
		0	(1.3)	(10.7)	(7.2)	0	0		(20.0)	(1.4)	(10.0)	(10.0)	(1.5)	0
GHM	45	0	11	25	9	0	0	54	0	24	1	15	14	0
		0	(7.1)	(7.7)	(8.1)	0	0		0	(8.5)	(2.0)	(8.8)	(20.9)	0
GRH IMSS No.1	14	0	12	1	0	1	0	68	0	60	3	0	5	0
		0	(7.8)	(0.3)	0	(4.5)	0		0	(21.1)	(6.0)	0	(7.5)	0
HJM	107	1	10	78	16	0	2	67	0	12	10	37	7	1
		(12.5)	(6.5)	(23.8)	(14.4)	0	(28.6)		0	(4.2)	(20.0)	(21.8)	(10.4)	(20.0)
Total	629	8 (100.0)	154 (100.0)	327 (100.0)	111 (100.0)	22 (100.0)	7 (100.0)	581	5 (100.0)	284 (100.0)	50 (100.0)	170 (100.0)	67 (100.0)	5 (100.0)
							$P < 0.001$							$P < 0.001$

MSC&F: Medica Sur Clinic and Foundation; HJM: Hospital "Juárez" of México; CHG: Civil Hospital of Guadalajara "Fray Antonio Alcalde"; CMSSH: Christus Muguerza "Super Specialty" Hospital; GHM: General Hospital of Mexico "Dr. Eduardo Liceaga"; CMH: Central Military Hospital; GHD: General Hospital of Durango; GRH IMSS No.1: Regional General Hospital IMSS 1; NASH: Nonalcoholic steatohepatitis.

using the Alcohol Use Disorders Identification Test[19], a widely used screening instrument for unsafe and noxious alcohol consumption.

Statistical analysis

Continuous variables with a normal distribution are expressed as the mean ± SD. Categorical variables are expressed as frequencies and percentages. The chi-squared test was used to identify differences between the underlying cause of liver cirrhosis and age groups, gender, and the hospital where patients were treated. Data were analyzed using the statistical program Stata version 14 (Stata Corp, College Station, TX).

RESULTS

The sample comprised 1210 patients (male: female ratio 1:1, mean age 62.5 ± 12.1 years). HCV infection was the most frequent etiology (36.2%), followed by ALD (31.2%), and NASH (23.2%). Other causes of liver cirrhosis included autoimmune liver diseases (7.3%), HBV infection (1.1%), and other conditions (1%) (Table 1). Women accounted for most of the cirrhotic patients with HCV infection (64.8%) and NASH-related cirrhosis (60.5%), and men accounted for 86.7% of patients with liver cirrhosis caused by ALD ($P < 0.001$). The underlying causes of liver cirrhosis and the gender distribution according to etiology are summarized in Table 2.

The prevalence of HCV infection, ALD, and NASH (38.6%, 32.6%, and 38.8%, respectively) was highest in the 61-70-year-old group. No significant differences in the etiology were found between age groups ($P = 0.166$) (Figure 1).

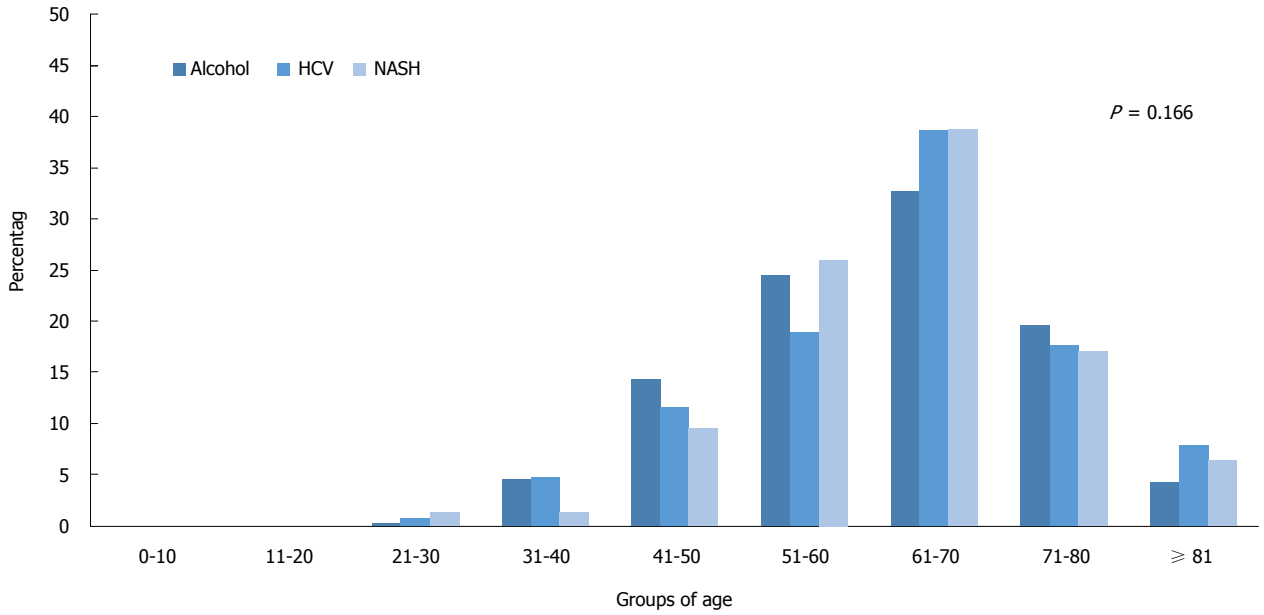

Figure 1 Main etiologies by age group were alcoholic liver disease (*n* = 377), nonalcoholic steatohepatitis (*n* = 281), and hepatitis C virus (*n* = 438). The percentage of these etiologies was higher for patients aged 61-70 years (32.6%, 38.8%, and 38.6%, respectively). However, no significant differences in etiology were found between age groups (*P* = 0.166). HCV: Hepatitis C virus; NASH: Nonalcoholic steatohepatitis.

DISCUSSION

Liver cirrhosis is the fourth leading cause of death in Mexico[20]. However, cirrhosis is the second leading cause of death in people aged 35-55 years[15]. In other countries, both developed and developing, CLD is also a major health problem[21-28] (Figure 2).

As expected, we found that the epidemiology of cirrhosis in Mexico has changed with time. Previous epidemiological studies in Mexico have reported that ALD was the main cause of liver cirrhosis[21,29]. However, our recent results show that HCV infection and ALD are currently the most common causes of liver cirrhosis in Mexico. A recent study of 578 Mexicans with CLD by Torres-Valadez *et al*[30]. reported similar findings in patients assessed for liver damage. These authors reported that the leading etiologies in patients with liver cirrhosis were ALD (45%), HCV (43%), and NASH (10%). Similar to our findings, this study found that ALD was more prevalent in men, and NASH and HCV infection were more prevalent in women.

We found that NASH was the third leading cause of cirrhosis: 281 patients or 23.2%. This finding shows an increase in the prevalence of NASH of 100% compared with our report in 2004[21]. This increase in NASH prevalence corresponds to the current trends for liver cirrhosis worldwide. The recent obesity epidemic has contributed to the increase in the prevalence of NAFLD and its progressive form, NASH, which are becoming the leading causes of chronic liver disease in many countries[31]. Currently, the prevalence of NAFLD is very high in all regions, and the highest rates have been reported in South America (31%), the Middle East (32%), Asia (27%), the United States (24%), and Europe (23%). The current worldwide prevalence of NASH is 59.1%[32].

Although NAFLD has been considered a problem only in Western countries, several Asian studies have reported a growing prevalence of NAFLD in Asian countries[33,34]. The increasing prevalence of NAFLD in Asia is due to the growing trend of obesity in this country which is why it has been reported that the currently prevalence of NAFLD in Asia is around 25% to 30%[32,33,35]. Shanghai, Hong Kong and Central China are the cities with the highest prevalence rates of NAFLD; 38.17%[36], 28.8%[37] and 24.5%[38], respectively. These data are very alarming due to it is evident that obesity and its related diseases are becoming a serious problem worldwide.

In other Latin American countries such as Brazil, liver diseases are the eighth leading cause of death[39]. Cirrhosis related to alcohol consumption and to HBV and HCV infection represents 2.17% of disability-adjusted life years in Brazil[25,40]. In Brazil, the burden of liver disease is higher in young or middle-aged people[40]. By contrast, the age groups 61-70 and 51-60 years are the most affected in Mexico. This difference may reflect cultural differences because Mexicans normally do not seek medical attendance for cirrhosis until the disease has reached advanced stages. Brazilian studies have estimated that the prevalence of HCV infection in Brazilians is low (1.38%)[39,41]. However, in 2012, Gonçalves *et al*[27] reported that the main etiologies of liver cirrhosis were ALD (39.7%), HCV (14.5%), HBV (13.1%), and NASH (4.4%). Interestingly, ALD is currently one of the leading causes of mortality and hospital admissions in Brazil[39].

Similar to the trends in Mexico, ALD, viral hepatitis B and C, and metabolic syndrome related to overweight

Figure 2 Changes in the epidemiology of liver cirrhosis in different countries reflect differences in etiologies, such as alcohol abuse and hepatitis B virus and hepatitis C virus infection. However, non-alcoholic fatty liver disease and its progressive form nonalcoholic steatohepatitis are becoming the most frequent etiologies of liver cirrhosis in Western countries. ALD: Alcoholic liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Nonalcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease.

and obesity are the main underlying causes of liver cirrhosis in Europe and the United States. Alcohol is the strongest risk factor for chronic liver disease; alongside with NAFLD they represent 66% of liver diseases in the European population. The prevalence of NAFLD in this population is about 13%-44% which cause by itself the 13% of liver diseases and HCV with a prevalence of 0.13%-3.26% is related with 6% of liver disease. There is no percentage mentioned in European statistics about HBV (prevalence of 0.5%-0.7%) as cause of liver disease[8]. NAFLD affects around 51.7% of Americans followed by ALD (20.7%), HCV (8.6%), and HBV (3.1%)[6,42]. It is interesting to

mention that United Kingdom (UK) had a high increase of liver cirrhosis in the last 2 decades compared to other European countries[43]. Nowadays, it is estimated that 30000 people live with cirrhosis and at least 70000 new cases are diagnosed each year in UK[44]. Although ALD is the first cause of cirrhosis in UK (Figure 2), a recent study has reported that NAFLD is the most common etiology for asymptomatic altered liver biochemistry, accounting for 26.4% of cases in UK[45].

Despite the expectation that NAFLD will soon become the main cause of end-stage liver disease and need for liver transplantation, we expect that the prevalence of HCV-related cirrhosis will continue to increase in Mexico because of the improved methods for diagnosing HCV infection and the difficulties in receiving care for this disease. Similarly, Davis *et al*[46] have estimated that the percentage of patients with HCV-related cirrhosis will reach 45% by 2030 in the United States.

In conclusion, in the present study, HCV, ALD, and NASH were the main etiologies of liver cirrhosis. Interestingly, the epidemiology of liver cirrhosis in Mexico is similar to that presented in the United States and Europe. Despite the differences between human populations they share similar cultural factors related to alcohol, hepatitis infection and obesity. CLDs will continue to cause significant morbidity and mortality. Therefore, it is necessary to implement preventive measures, particularly those related to viral hepatitis infection, obesity, and alcohol consumption, to decrease the rates of liver cirrhosis.

ARTICLE HIGHLIGHTS

Research background

Liver cirrhosis is the fourth leading cause of death in Mexico. In our previous study, the main causes of liver cirrhosis were: alcoholic liver disease (ALD), hepatitis C virus (HCV) and nonalcoholic steatohepatitis (NASH). However, the rising prevalence of obesity and metabolic syndrome has probably modified the epidemiology of cirrhosis in Mexico.

Research motivation

It is of great clinical significance to explore the methods for early diagnosis of liver cirrhosis. Moreover, it is necessary to implement preventive measures, particularly those related to viral hepatitis infection, obesity, and alcohol consumption, in order to decrease the mortality of liver cirrhosis.

Research objectives

We aimed to investigate the main etiologies of liver cirrhosis in Mexicans in the last five years.

Research methods

In this retrospective study, the clinical data of 1210 patients with liver cirrhosis were collected. The inclusion criteria were a histological, clinical, biochemical, endoscopic, or imaging diagnosis of liver cirrhosis. Data were obtained during a 5-year period (January 2012–December 2017).

Research results

The most frequent causes of liver cirrhosis were HCV (36.2%), ALD (31.2%), and nonalcoholic steatohepatitis (23.2%). The least frequent etiologies were hepatitis B virus (1.1%), autoimmune disorders (7.3%), and other conditions (1.0%).

Research conclusions

HCV, ALD, and NASH were the main etiologies of liver cirrhosis in Mexico. However, further studies are needed to define the epidemiology and primary prevention of liver cirrhosis in Mexico.

Research perspectives

The identification of patients with risk factors for liver cirrhosis is an important point to reduce the mortality from this disease in our country.

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ORIGINAL ARTICLE

Retrospective Study

Retrograde intrarenal surgery *vs* miniaturized percutaneous nephrolithotomy to treat lower pole renal stones 1.5-2.5 cm in diameter

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Author contributions: All authors helped to perform the research; Li MM contributed to the data collection and manuscript writing; Yang HM contributed to the data analysis; Liu XM contributed to performing experiments and data analysis, Qi HG contributed to the data collection and statistical analysis; Weng GB contributed to the drafting conception and design.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Ningbo Urology and Nephrology Hospital.

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Abstract

AIM

To compare the outcomes of retrograde intrarenal surgery (RIRS) and miniaturized percutaneous nephrolithotomy (mini-PCNL) in treating lower pole (LP) renal stones with a diameter of 1.5-2.5 cm.

METHODS

A total of 216 patients who underwent mini-PCNL (n = 103) or RIRS n = 113) for LP stones with a diameter of 1.5-2.5 cm were enrolled between December 2015 and April 2017 at the Urology Department of Ningbo Urology and Nephrology Hospital.

RESULTS

Significant differences were found in the hospital stay (9.39 ± 4.01 *vs* 14.08 ± 5.26, P < 0.0001) and hospitalization costs (2624.5 ± 513.36 *vs* 3255.2 ± 976.5, P < 0.0001) between the RIRS and mini-PCNL groups. The mean operation time was not significantly different between the RIRS group (56.48 ± 24.77) and

the mini-PCNL group (60.04 ± 30.38, P = 0.345). The stone-free rates at the first postoperative day (RIRS *vs* mini-PCNL: 90.2% *vs* 93.2%, P = 0.822) and the second month postoperatively (RIRS *vs* mini-PCNL: 93.8% *vs* 95.1%, P = 0.986) were not significantly different.

CONCLUSION

RIRS and mini-PCNL are both safe and effective methods for treating LP stones with a diameter of 1.5-2.5 cm. RIRS can be considered as an alternative to PCNL for the treatment for LP stones of 1.5-2.5 cm.

Key words: Retrograde intrarenal surgery; Percutaneous nephrolithotripsy; Lower pole kidney stones; Miniaturized percutaneous nephrolithotomy

Core tip: This retrospective study aimed to compare the outcomes of retrograde intrarenal surgery (RIRS) and miniaturized percutaneous nephrolithotomy (mini-PCNL) in treating lower pole (LP) renal stones with a diameter of 1.5-2.5 cm. The results showed that the hospital stay (9.39 ± 4.01 *vs* 14.08 ± 5.26, P < 0.0001) and hospitalization costs (2624.5 ± 513.36 *vs* 3255.2 ± 976.5, P < 0.0001) in the RIRS patients were much lower than those of the mini-PCNL group. No significant differences were found in the mean operation time or stone-free rates between the RIRS and mini-PCNL groups. RIRS can be considered as an alternative to PCNL for the treatment of LP stones of 1.5-2.5 cm.

Li MM, Yang HM, Liu XM, Qi HG, Weng GB. Retrograde intrarenal surgery *vs* miniaturized percutaneous nephrolithotomy to treat lower pole renal stones 1.5-2.5 cm in diameter. *World J Clin Cases* 2018; 6(15): 931-935 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/931.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.931

INTRODUCTION

Retrograde intrarenal surgery (RIRS) is rapidly becoming an effective and safe treatment modality in the surgical treatment of urinary system stone disease[1]. Small kidney stones and upper urinary tract tumours can be effectively treated by RIRS using minimally invasive methods[2]. RIRS was first reported for the treatment of small kidney stones in 2002. In recent years, urologists also suggested using this approach to treat large stones, because of the fewer complications and reduced morbidity[3]. Indeed, the European Association of Urology (EAU) guidelines mentioned that RIRS is a valid choice of some surgeons for the treatment of larger stones[4].

Percutaneous nephrolithotomy (PCNL) is recommended for the treatment of larger stones, since it has a good success rate; however, the complication rates have been reported to be up to 25%[5]. With advancements in techniques and technologies, miniaturized PCNL (mini-PCNL), defined as a PCNL involving the use of smaller nephroscopes[6], can be performed effectively to manage kidney stones with high stone free rates and low complications[7]. The two surgical procedures have different advantages associated with the treatment of stones of different sizes affecting the urinary system[8-10]. However, few studies have compared the results of mini-PCNL to RIRS for the treatment of lower pole stones (LP stones) with a 1.5-2.5 cm diameter. In this study, we reviewed retrospectively 216 patients who underwent mini-PCNL (n = 103) or RIRS (n = 113) for LP stones with a 1.5-2.5 cm diameter between December 2015 and April 2017. Specifically, we compared the operation time, stone-free rate, complications, hospital stay, and hospitalization costs in patients treated by these two minimally invasive methods.

MATERIALS AND METHODS

Patients

We performed a retrospective analysis of 216 patients who underwent mini- PCNL (n = 103) or RIRS (n = 113) for LP stones with a 1.5-2.5 cm diameter by the same doctors between December 2015 and April 2017 at the Urology Department of Ningbo Urology and Nephrology Hospital. Patients were evaluated by plain radiography, intravenous urography, ultrasonography, and/or computed tomography (CT), urinalysis, urine culture, complete blood cell count, and coagulation tests before the procedure. Stone size was calculated according to the EAU guidelines. We determined the operation technique according to the LP pelvicalyceal anatomy, as well as the surgeon's and patient's choice. Patients with abnormal renal anatomy (horseshoe, pelvic, and malrotated kidneys, bifid pelvis, ectopic pelvic fusion anomaly), patients with non-opaque stones, and paediatric patients (< 18 years) were excluded from the study.

RIRS technique

All the patients undergoing the RIRS surgery were performed under general anaesthesia and were located at the lithotomy position. First, rigid ureteroscopy was used to passively dilate the ureter and to place a hydrophilic safety guidewire (0.038-inch) and advance to the renal pelvis by fluoroscopic assistance. Second, we used a ureteral access sheath (12/14 F) to traverse the guidewire through the ureteropelvic junction. We used a flexible ureterorenoscope (Flex-X2, Karl Storz, Tuttlingen, Germany) to insert into the renal pelvis within the ureteral access sheath. Kidney stones were fragmented using a Ho YAG laser (Dornier MedTech, Munich, Germany).

Mini-PCNL technique

All procedures were performed with the patient under general anaesthesia. At the beginning of the procedure,

Table 1 Stone characteristics and demographic data of patients

Characteristic	RIRS group	Mini-PCNL group	*P* value
Number	113	103	
Age (yr)	49.59 ± 12.66	49.89 ± 13.09	0.864
Man (%)	67 (59.3)	75 (72.8)	0.051
BMI (kg/m^2)	24.3 ± 3.21	23.24 ± 3.11	0.014
Side (right/left)	47/66	49/54	0.583
Stone size (mm)	18.27 ± 2.91	17.51 ± 5.29	0.218

Data presented are as means ± SD. BMI: Body mass index; PCNL: Percutaneous nephrolithotomy; RIRS: Retrograde intrarenal surgery.

placement of a 6 Fch ureteral catheter up to the renal pelvis was performed by means of rigid cystoscopy. Subsequently, patients were placed in the prone position, and percutaneous access was achieved by a urologist under ultrasonography guidance using an 18-gauge needle and guidewire. We used a 0.038-mm J-tipped guidewire to insert through the calyceal puncture into the renal pelvis. The first three Alkan dilators were used to dilate the tract (8F-14F-16F). Next, we inserted a 16-F sheath and introduced a rigid 10-F ureteroscope. The stone fragmentation was performed using a Ho:YAG laser (365-μm fibre; energy 2.5 Jd; frequency 20 Hz). A 16-F nephrostomy tube was inserted into the calyceal system at the end of the procedure. Three days after the surgery, the nephrostomy tube was removed. The double J ureteral stent was removed under local anaesthesia 2 wk later.

Assessment of outcomes

The outcomes including operative time, stone-free rate, complications, mean decrease in haemoglobin levels, hospital stay, and hospitalization costs for the patients who underwent these two minimally invasive methods were compared in this study.

Abdominal low-dose helical CT examination was performed before operation. Patients were re-evaluated using CT 2 mo after surgery to examine residual stone status. Residual stones size less than 2 mm in diameter were considered "clinically insignificant residues".

Statistical analysis

The chi-square test was applied to compare the proportions between two groups. Continuous variables are presented as means ± SD and were compared using the Student's *t*-test when the data followed a normal distribution. Where the distribution of the continuous variables was not normal, the Wilcoxon signed-rank test was used. The *P*-value was adjusted for gender and BMI. The adjusted calculation was performed using SPSS package with binary logistic regression. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) 17.0 (SPSS, Inc., Chicago, United States).

RESULTS

The characteristics of the study patients are provided in Table 1. A total of 103 patients who underwent mini-PCNL and 113 patients who underwent RIRS were enrolled in the study. The mean age of the patients was 49.66 ± 12.66 years (range 19-75 years) and the mean follow-up time was 8.7 ± 3.4 mo (range 4-16 mo). No significant differences were found between the two groups in terms of age, sex, BMI, onset position, or stone size ($P > 0.05$).

As shown in Table 2, significant differences between the RIRS and mini-PCNL groups were found in the duration of hospital stay (9.39 ± 4.01 *vs* 14.08 ± 5.26, $P < 0.0001$) and hospitalization costs (2624.5 ± 513.36 *vs* 3255.2 ± 976.5, $P < 0.0001$). The mean operative time was not significantly different between the RIRS group (56.48 ± 24.77) and the mini-PCNL group (60.04 ± 30.38, $P = 0.345$). The stone-free rates at the first postoperative day (RIRS *vs* mini-PCNL: 90.2% *vs* 93.2%, $P = 0.822$) and the second postoperative month (RIRS *vs* mini-PCNL: 93.8% *vs* 95.1%, $P = 0.986$) were not significantly different between the two groups. The complications and Hb levels were not different between the two groups ($P > 0.05$).

DISCUSSION

Urinary stones are a common condition in the Chinese population. PCNL is recommended as the first line of therapy for treating large kidney stones by the EAU[11]. Some studies of LP renal stones showed that there was a high success rate and a low complication rate for all stone sizes using PCNL[10,12]. PCNL has the advantage of a high stone-clearance rate[13]. Despite advances in technology, PCNL was an invasive surgery with the potential to cause many serious complications[14]. Although doctors have compared either PCNL or RIRS to shock wave lithotripsy to determine which is more suitable for patients with a diameter less than 2 cm, there are still relatively few studies comparing the results of mini-PCNL and RIRS in the treatment of LP renal stones[9]. In this study, we evaluated two of these treatment modalities in the management of LP renal stones. Such management option remains very controversial.

RIRS is considered an acceptable treatment for LP calculi but not a first-line treatment for calculi of 1.0-2.0 cm in diameter. Since the adoption of RIRS in the urological field, its success rate has been studied by many urologists. Grasso reported that[15] they treated LP renal calculi by retrograde ureteroscopy and the stone free rate was 82% for patients with stones 0.1-1.0 cm, 71% for patients with stones 1.1-2.0 cm, and 65% for patients with stones > 2.0 cm. Bozkurt *et al*[16] showed that the stone-free rate was 94.6% in patients who were treated (diameter 1.5-2.0 cm) using RIRS. In our study, the results suggested that both techniques were safe and equally effective, with stone-free rates following a single session at a 1-d follow-up being 93.2% in the mini-

Table 2 Intraoperative and postoperative parameters and surgical complications in study groups

Variable	RIRS group	Mini-PCNL group	*P* value
Operative time (min)	56.48 ± 24.77	60.04 ± 30.38	0.345
Stone-free rate (postoperative 1 d) (%)	102/113 (90.2)	96/103 (93.2)	0.822
Stone-free rate (postoperative 2 mo) (%)	106/113 (93.8)	98/103 (95.1)	0.986
Hospital stay (d)	9.39 ± 4.01	14.08 ± 5.26	< 0.0001
No. of Clavien complications			0.643
Grade 0	89	76	
Grade Ⅰ	18	19	
Grade Ⅱ	6	7	
Grade Ⅲ	0	1	
Grade Ⅳ/Ⅴ	0	0	
Preoperative Hb (g/dL)	137.12 ± 15.57	140.15 ± 16.04	0.161
Postoperative Hb (g/dL)	128.05 ± 16.87	125.34 ± 16.68	0.237
Hospitalization costs ($)	2624.5 ± 513.36	3255.2 ± 976.5	< 0.0001

Data are presented as mean ± SD. The *P*-value was adjusted by gender and BMI. Grade 0: No complication; Grade Ⅰ: Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic and radiographic interventions, and acceptable therapeutic regimens are drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy; Grade Ⅱ: Requiring pharmacologic treatment with drugs other than those allowed for grade Ⅰ complications, blood transfusions and total parenteral nutrition are also included; Grade Ⅲ: Requiring surgical, endoscopic, or radiographic intervention; Grade Ⅳ: Life-threatening complication requiring IC/ICU management; Grade Ⅴ: Death of a patient due to a complication. PCNL: Percutaneous nephrolithotomy; RIRS: Retrograde intrarenal surgery.

PCNL group and 90.2% in the RIRS group. Two months after the operation, the results showed that the efficacy of both techniques was similar. In the near future, with the improvement of lasers and the combination of less invasive anterograde-retrograde techniques, the residual rate will be further reduced. In this study, the hospitalization stay was longer for patients in the mini-PCNL group than in the RIRS group. This apparent delay may be attributed mainly to the nephrostomy tube placement for drainage. RIRS is typically an outpatient procedure. Our results showed that RIRS had a clear advantage in postoperative hospital stay compared with mini-PCNL. Patient recovery tends to be faster with RIRS, which was also supported by the studies of Bai *et al*[17] and Alazaby *et al*[18] The hospitalization cost was an important issue when comparing the different treatment modalities. RIRS surgery at our institution costs $2624 compared to $3255 for mini-PCNL technique, which translates into a savings of $631 per case. Pan *et al*[19] reported that the hospitalization cost of RIRS were much lower than that of mini-PCNL and suggested that RIRS was also a safe and reliable choice for patients with single renal stones 2.0-3.0 cm in diameter. Our study added another argument for making RIRS the optimal choice in an increasing number of stone cases. Our results showed that RIRS was an effective treatment option for LP calculi with a diameter of 1.5-2.5 cm.

This study has some limitations. First, X-rays and ultrasound were used to determine stone-free rates in the postoperative period although CT is a more specific and sensitive procedure. Second, the sample size was comparatively small. Third, there were potential differences in the preparation and management protocols of the patients in this retrospective study. Prospective studies controlling for such variables with large samples will allow a more robust evaluation of these phenomena.

In conclusion, out results suggest that both RIRS and mini-PCNL are safe and effective methods for treating LP stones with a diameter of 1.5-2.5 cm. RIRS can be considered as an alternative to PCNL for the treatment of LP stones of 1.5-2.5 cm.

ARTICLE HIGHLIGHTS

Research background

Retrograde intrarenal surgery (RIRS) is rapidly becoming an effective and safe treatment modality in the surgical treatment of urinary system stone disease.

Research motivation

The two surgical procedures have different advantages associated with the treatment of stones of different sizes affecting the urinary system. However, few studies have compared the results of miniaturized percutaneous nephrolithotomy (mini-PCNL) to RIRS for the treatment of lower pole stones (LP stones) with a 1.5-2.5 cm diameter.

Research objectives

This retrospective study aimed to compare the outcomes of RIRS and mini-PCNL in treating LP renal stones with a diameter of 1.5-2.5 cm.

Research methods

In this study, we reviewed retrospectively 216 patients who underwent mini-PCNL (n = 103) or RIRS (n = 113) for LP stones with a 1.5-2.5 cm diameter between December 2015 and April 2017. Specifically, we compared the operation time, stone-free rate, complications, hospital stay, and hospitalization costs in patients treated by these two minimally invasive methods.

Research results

Significant differences were found in the hospital stay (9.39 ± 4.01 *vs* 14.08 ± 5.26, P < 0.0001) and hospitalization costs (2624.5 ± 513.36 *vs* 3255.2 ± 976.5, P < 0.0001) between the RIRS and mini-PCNL groups. The mean operative time was not significantly different between the RIRS group (56.48 ± 24.77) and the mini-PCNL group (60.04 ± 30.38, P = 0.345). The stone-free rates at the first postoperative day (RIRS *vs* mini-PCNL: 90.2% *vs* 93.2%, P = 0.822) and the second month postoperatively (RIRS *vs* mini-PCNL: 93.8% *vs* 95.1%, P = 0.986) were not significantly different.

Research conclusions

Our results showed that both RIRS and mini-PCNL are safe and effective methods for treating LP stones with a diameter of 1.5-2.5 cm. RIRS can be considered as an alternative to PCNL for the treatment of LP stones of 1.5-2.5

cm. RIRS can be considered as an alternative to PCNL for the treatment of LP stones of 1.5-2.5 cm. Our study added another argument for making RIRS the optimal choice in an increasing number of stone cases.

Research perspectives

First, we used X-rays and ultrasound to determine stone-free rates in the postoperative period although CT is a more specific and sensitive procedure. Second, the sample size was comparatively small. Third, there were potential differences in the preparation and management protocols of the patients in this retrospective study. Prospective studies controlling for such variables with large samples will allow a more robust evaluation of these phenomena. RIRS can be considered as an alternative to PCNL for the treatment of LP stones of 1.5-2.5 cm. Future studies with larger sample sizes are required to replicate and extend these findings.

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ORIGINAL ARTICLE

Clinical Trials Study

Comparative study on operative trauma between microwave ablation and surgical treatment for papillary thyroid microcarcinoma

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Abstract

AIM

To compare the effect and postoperative trauma of ultrasound-guided percutaneous microwave ablation and surgical resection in the treatment of papillary thyroid microcarcinoma (PTMC).

METHODS

Eighty-seven patients with PTMC treated at Fudan University affiliated Shanghai Fifth People's Hospital were enrolled as subjects. The patients were divided into a microwave ablation group (41 cases) and a surgical group (46 cases). The operative time, intraoperative blood loss, length of hospital stay, serum C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), thyroid-related hormonal changes, and complications 7 d and 30 d after surgery were observed.

RESULTS

The operative time, intraoperative blood loss, and len-

gth of hospital stay in the surgical group were significantly higher than those in the microwave ablation group ($P < 0.05$). The levels of CRP, IL-6, and TNF-α in the surgical group were significantly higher than those in the microwave ablation group ($P < 0.05$). The free triiodothyronine (FT3) and free thyroxin (FT4) levels in the surgical group were significantly lower than those in the microwave ablation group ($P < 0.05$). However, the postoperative thyroid stimulating hormone (TSH) level was significantly higher than that in the microwave ablation group ($P < 0.05$). There were significant interactions between the FT3, FT4, and TSH 7 d and 30 d after operation and the treatment methods ($P < 0.05$). There was no significant difference in the complications between the two groups ($P > 0.05$).

CONCLUSION

Microwave ablation for papillary microcarcinoma of the thyroid gland has less trauma to the body, quicker recovery, and no scars. It can effectively shorten the length of hospital stay and improve the quality of life of patients.

Key words: Thyroidectomy; Body trauma; Ultrasound; Microwave ablation; Papillary thyroid microcarcinoma

Core tip: Although thyroidectomy is the standard treatment for papillary thyroid microcarcinoma (PTMC), it causes great trauma to the patient's body. In recent years, there have been reports on microwave ablation for patients with PTMC, but the efficacy is not certain. This study aimed to compare the efficacy and the impact on body trauma using ultrasound-guided percutaneous microwave ablation for PTMC and surgical resection. The results showed that microwave ablation for PTMC has less trauma, quicker recovery, and no scars, which can effectively shorten the hospitalization time and improve the quality of life.

Xu B, Zhou NM, Cao WT, Gu SY. Comparative study on operative trauma between microwave ablation and surgical treatment for papillary thyroid microcarcinoma. *World J Clin Cases* 2018; 6(15): 936-943 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/936.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.936

INTRODUCTION

With the popularization of thyroid ultrasonography and the wide application of ultrasound-guided fine needle aspiration, the detection rate of papillary thyroid microcarcinoma (PTMC) is increasing over time[1,2]. At present, thyroidectomy is still the standard treatment method. However, the patient's physical and psychological trauma caused by surgery is extremely high. Hemorrhage during the operation may easily damage the adjacent vital structures such as the parathyroid gland and the recurrent laryngeal nerve, causing complications such as hoarseness after surgery and leading to greater damage to the patient[3-5]. With the rapid development of minimal invasive techniques, ultrasound-guided microwave ablation has the advantages of small injury, short treatment time, effective curative effect, little effect on the surrounding structure and patient appearance, rapid recovery after ablation, no need for lifelong medication, *etc*. However, it is mainly used for treatment of thyroid benign nodules[6-8]. In recent years, microwave ablation has also been reported for some patients with PTMC and achieved good results[9-11]. However, the current clinical value of ultrasound-guided microwave ablation for PTMC has not yet reached a consensus and it cannot accurately judge whether this new treatment can replace traditional surgery. Therefore, the present study aimed to compare the impact of ultrasound-guided percutaneous microwave ablation of PTMC *vs* surgical resection on body trauma.

MATERIALS AND METHODS

General information

Totally 87 patients with PTMC diagnosed by ultrasound guided fine-needle aspiration biopsy (FNAB) at Fudan University Affiliated Shanghai Fifth People's Hospital from January 2012 to October 2017 were included. The maximum diameter of nodules was less than 1.0 cm. Microwave ablation or surgery was selected based on the patient's own condition and their wishes. The microwave ablation group consisted of 41 patients including 12 males and 29 females and aged from 24 to 65 years with an average age of 45.11 ± 7.28 years (Table 1). The inclusion criteria were: (1) Papillary microcarcinoma of the thyroid gland confirmed by FNAB; (2) Maximum tumor diameter $\leqslant$ 1.0 cm, not close to the capsule (distance > 2.0 mm), no obvious abnormality of the contralateral thyroid gland, and no large neck lymphadenopathy or metastatic lymph nodes; and (3) Ultrasound imaging had a clear needle path. Patients with severe heart or lung diseases or poor general condition which cannot tolerate surgery or those who rejected the surgery or were anxious about the disease for treatment were excluded.

Instrument

The GE Voluson E8 ultrasound diagnostic device with a line array probe (frequency from 5 to 10 MHz) was used. Microwave ablation was performed using Nanjing Kangyou KY-2000 microwave ablation instrument and the frequency was 2450 MHz with continuous adjustable output power from 10 to 100 W. Microwave ablation instrument is connected with a 16 G cold-cycle Thy-ablation microwave antenna through a low loss coaxial cable.

Table 1 General clinical data between the two groups of patients

Group	Case	Age (yr)	Gender		Maximum diameter of nodule (mm)
			Male	Female	
Surgery group	46	46.2 ± 11.5	16	30	8.13 ± 1.22
Microwave Ablation group	41	45.8 ± 10.2	12	29	8.87 ± 1.01
t/χ^2-value		0.171	0.302		-3.061
P-value		0.865	0.583		0.003

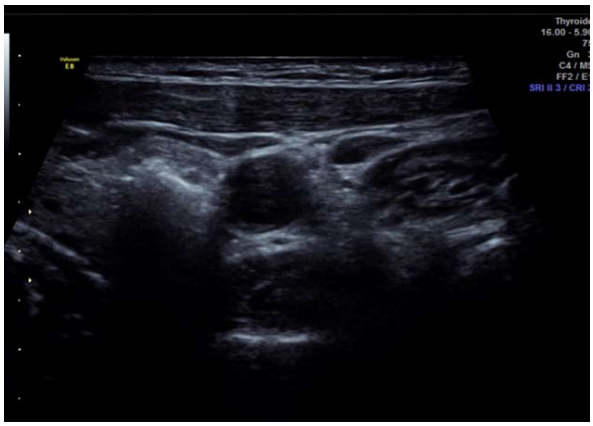

Figure 1 Ultrasound image of microwave ablation of thyroid tumors.

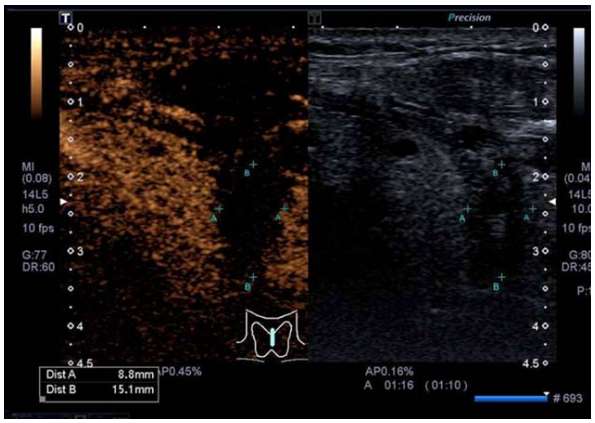

Figure 2 Two-dimensional and contrast-enhanced ultrasound images (no lesions intensified, completely ablated).

Surgical methods

Surgery group: A 5 cm long transverse incision was made 2 cm above the sternal fossa. Radical resection of the PTMC (the affected side of the thyroid and isthmus resection + lymph node dissection of the affected side VI) was adopted. Negative pressure drainage was performed after surgery.

Microwave ablation group: After the patient was intubated under general anesthesia, the patient was kept in a supine position. The saline was injected around the thyroid capsule according to the location of the tumor to form a "liquid barrier." After ultrasound guided percutaneous puncture, the microwave antenna was placed into the tumor (Figure 1). The ablation power was set at 50 W and the ablation time was set at 60-300 s. Extensive ablation of the tumor was performed. After the tumor was ablated, the ablation needle was slowly withdrawn to prevent the tumor cells from being transplanted along the needle path. Ultrasound angiography was used postoperatively to determine if ablation was complete (Figure 2).

Observation indicators

The operative time, intraoperative loss blood, length of hospital stay, serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) 24 h after operation, thyroid hormone-related changes, and complications 7 d and 30 d after operation were observed.

Statistical analysis

SPSS19.0 software was used for data analyses. Measured data are expressed as mean ± SD and the two groups were compared using the independent samples *t*-test. The number of cases or percentages of count data is expressed and comparison between the two groups was performed using the χ^2 test. Repeated measures analysis of variance was used to compare the levels of hormones [T3, T4, thyroid stimulating hormone (TSH)] preoperatively, 7 d after surgery, and 30 d after surgery. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical indicators

The surgical time, blood loss volume, and length of hospital stay in the surgical group were significantly higher than those in the microwave ablation group ($P < 0.05$) (Table 2).

Postoperative serum markers

The levels of CRP, IL-6, and TNF-α in the surgical group were significantly higher than those in the microwave ablation group ($P < 0.05$) (Table 3).

Thyroid hormone indexes before, 7 d after, and 30 d after operation

The hormone levels of the two groups (including the hormone levels of T3, T4, and TSH) were recorded before, 7 d after, and 30 d after surgery (Tables 4-6

Table 2 Clinical indicators between the two groups (mean ± SD)

Group	Case	Length of hospital stay (d)	Blood loss volume (mL)	Surgical time (min)
Surgery group	46	4.18 ± 0.55	33.12 ± 5.07	78.81 ± 12.19
Microwave	41	1.77 ± 0.71	10.32 ± 1.65	25.02 ± 4.14
Ablation group				
t-value		17.832	27.511	26.892
P-value		0	0	0

Table 3 Comparison of postoperative serum markers (mean ± SD)

Group	Case	CRP (mg/L)	IL-6 (ng/L)	TNF-α (ng/L)
Surgery group	46	12.05 ± 2.57	14.44 ± 4.61	51.39 ± 2.86
Microwave	41	0.71 ± 0.39	4.02 ± 1.78	43.55 ± 5.03
Ablation group				
t-value		27.951	13.591	9.059
P-value		0	0	0

CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

Table 4 Free triiodothyronine levels between the two groups before, 7 d after, and 30 d after treatment

FT3 (pmol/L)	Preoperative	7 d after surgery	30 d after surgery
Microwave ablation group	4.28 ± 0.49	4.25 ± 0.45	4.22 ± 0.53
Surgery group	4.33 ± 0.78	3.09 ± 0.64	2.78 ± 0.84

$F_{intra\text{-}group}$ = 6.435, $P_{intra\text{-}group}$ = 0.000; $F_{inter\text{-}group}$ = 8.546, $P_{inter\text{-}group}$ = 0.000; $F_{interaction}$ = 45.291, $P_{interaction}$ = 0.000. FT3: Free triiodothyronine.

Table 5 Comparison of free thyroxin levels before, 7 d after, and 30 d after treatment

FT4 (pmol/L)	Preoperative	7 d after surgery	30 d after surgery
Microwave ablation group	12.33 ± 1.51	12.87 ± 2.66	12.67 ± 2.83
Surgery group	12.72 ± 1.68	10.77 ± 2.25	9.45 ± 2.07

$F_{intra\text{-}group}$ = 0.866, $P_{intra\text{-}group}$ = 0.221; $F_{inter\text{-}group}$ = 9.257, $P_{inter\text{-}group}$ = 0.000; $F_{interaction}$ = 31.378, $P_{interaction}$ = 0.000. FT4: Free thyroxin.

Table 6 Thyroid stimulating hormone levels between the two groups before, 7 d after, and 30 d after treatment

TSH (mIU/L)	Preoperative	7 d after surgery	30 d after surgery
Microwave ablation group	2.11 ± 1.47	1.42 ± 0.91	1.08 ± 1.35
Surgery group	2.09 ± 1.01	13.44 ± 2.37	18.43 ± 2.67

$F_{intra\text{-}group}$ = 55.165, $P_{intra\text{-}group}$ = 0.221; $F_{inter\text{-}group}$ = 67.234, $P_{inter\text{-}group}$ = 0.000; $F_{interaction}$ = 75.443, $P_{interaction}$ = 0.000. TSH: Thyroid stimulating hormone.

and Figure 3). According to preoperative data analysis, there was no significant difference in thyroid hormone levels between the microwave ablation group and the surgery group ($P > 0.05$). Repeated measurement analysis of variance within the group found that free triiodothyronine (FT3) levels decreased significantly postoperatively compared with preoperative values ($P < 0.05$). In contrast, TSH levels increased significantly postoperatively compared with preoperative values ($P < 0.05$). Free thyroxin (FT4) levels had no significant changes after surgery ($P > 0.05$). Comparison between groups revealed that the FT3 and FT4 levels in the surgery group were significantly lower than those in the microwave ablation group ($P < 0.05$). The postoperative TSH level was significantly higher than that in the microwave ablation group ($P < 0.05$). There were significant interactions between the FT3, FT4, and TSH changes 7 and 30 d postoperatively and the treatment plan ($P < 0.05$).

Complications in patients

In the recovery process of the two groups, patients had different degrees of pharyngeal discomfort, hoarseness, pain, parathyroid injury, incision infection, or other complications. Those patients returned to normal after 3 mo. There were no significant difference in the compli-

Table 7 Postoperative complications in patients

Group	Microwave ablation group (n = 41)	Surgery group (n = 46)	χ^2	P
Pharyngeal discomfort	0	1	1.508	0.219
Hoarseness	1	2		
Pain	0	1		
parathyroid injury	0	0		
Incision infection	0	1		
Cough after drinking water	1	2		
Incidence of complications	4.9%	15.2%		

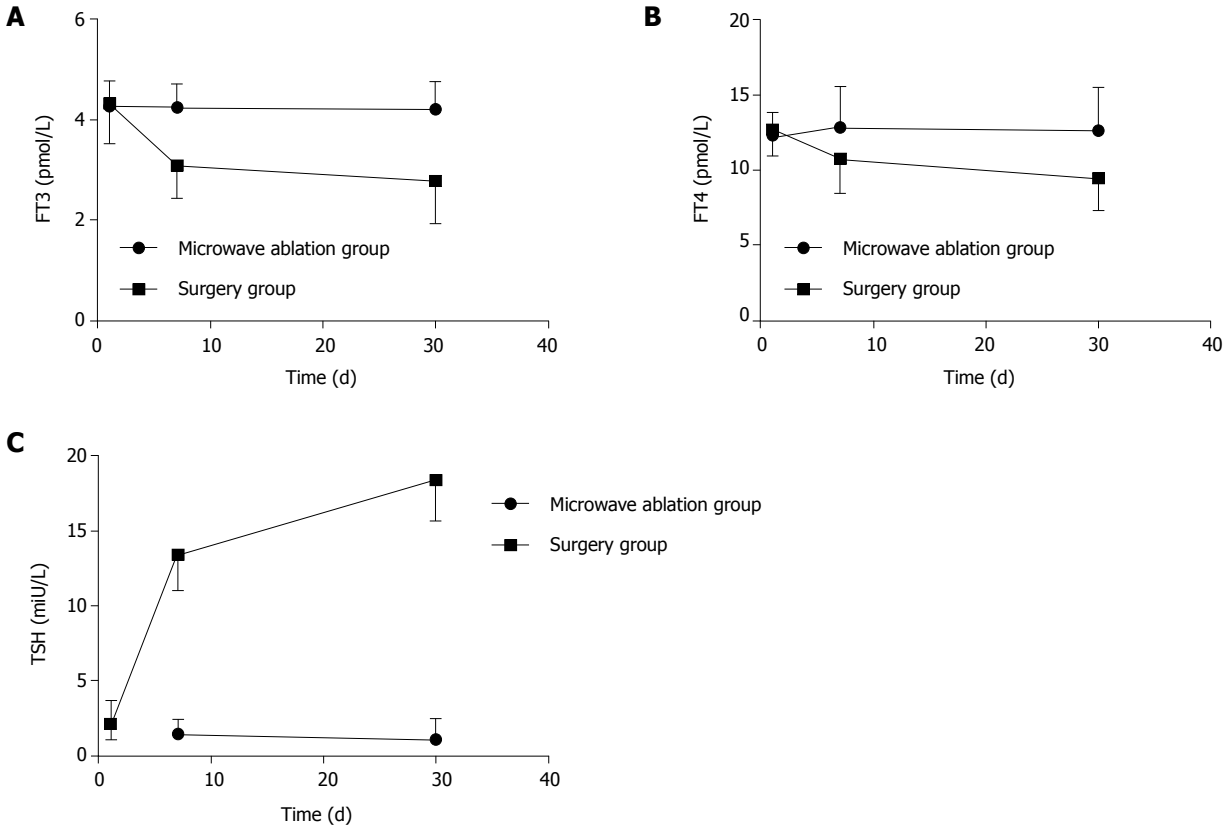

Figure 3 Trend of free triiodothyronine (A), free thyroxin (B), and thyroid stimulating hormone levels before, 7 d after, and 30 d after treatment. FT3: Free triiodothyronine; FT4: Free thyroxin; TSH: Thyroid stimulating hormone.

cations between the two groups (P > 0.05) (Table 7).

DISCUSSION

The direction of modern surgical development is minimally invasive treatment that is to achieve the purpose of treatment with minimal surgical trauma and to minimize the impact of surgical trauma on the body. At present, the standard treatment for single PTMC is still surgical lobectomy, which is unacceptable to some patients because of its disadvantages such as large trauma, long recovery time, and medication for life[12-15]. Given that papillary thyroid cancer has "moderate" biological behavior, it is slow-growing and some patients carry no progression during their lifetime. Therefore, it is particularly necessary to find a therapeutic method that is effective, safe, minimally invasive, and more aesthetically pleasing. Microwave ablation is guided by ultrasound to make the microwave ablation electrode enter into the target tissue and ablate it through rapid hyperthermia coagulation necrosis, necrotic tissue will be absorbed by the body over time and ultimately achieve the purpose of treatment with the advantages of minimal trauma, rapid recovery, easy to use, *etc*[16-19]. This study compared the impact of ultrasound-guided percutaneous microwave ablation and surgical resection of PTMC on body trauma in order to explore the clinical value of ultrasound-guided microwave ablation of PTMC.

The surgical time, intraoperative blood loss, and length of hospital stay in the surgery group were significantly higher than those in the microwave ablation group (P < 0.05), indicating that microwave ablation of PTMC can significantly reduce the trauma to the patient. It is known that microwave ablation and surgical trauma

as external environmental stimuli can both cause the body's non-infectious stress response. The size and duration of stress response after surgery reflect the severity of surgical trauma[20,21]. Therefore, lower trauma during surgery can reduce the body's stress response. In terms of reflecting the stress response of the body, it is known that CRP is synthesized by the liver and can be significantly elevated under stress conditions. The more severe the trauma, the more obvious the increase of CRP[22,23]. IL-6 is a multi-functional cytokine that is mainly produced by monocytes/macrophages and T cells and is extremely low in normal human plasma. Many pathological factors can affect the production of IL-6. Surgical trauma is one of the important factors. IL-6 is now considered to be a sensitive index of reactive tissue damage[24,25]. Similarly, TNF-α can be used as a marker to analyze the secretion of cytokines and is a sensitive marker for early trauma in tissues[26,27]. In this study, the level of stress response of postoperative patients was more accurately measured by measuring the levels of these three indicators in postoperative patients. The results revealed that the levels of CRP, IL-6, and TNF-α in the surgical group were significantly higher than those in the microwave ablation group at 24 h after operation ($P < 0.05$). The stress response of the patients in the surgery group was even stronger, and the microwave ablation significantly reduced the patient's body trauma. This is because ultrasound-guided microwave ablation is guided by ultrasound under real-time guidance and avoids major organs such as large blood vessels in the puncture path. The microwave ablation electrode is rapidly and accurately implanted in the thyroid tumor lesions for ablation. It has the advantages of simpler operation, shorter time, less intraoperative blood loss, and less traumatic emergency response[28,29]. Those advantages can prompt the recovery of the patient's health as soon as possible, shorten the patient's hospitalization time, and improve the patient's quality of life.

During surgical treatment of PTMC, changes in the thyroid function of the patient should cause extra attention. In this study, thyroid hormone levels were measured before, 7 d after, and 30 d after surgery in patients with microwave ablation and surgery. Thyroid function was dynamically monitored in each patient to better reflect postoperative dynamic changes of the thyroid function. Repeated-measures analysis of variance revealed that the FT3 and FT4 levels in the surgical group had a significant decrease after surgery, and the TSH increased significantly. Considering that most of the thyroid tissue was removed by surgery, the patients lost some of the endogenous thyroid function. The patients revealed a more obvious performance of hypothyroidism. In the microwave ablation group, the level of TSH slightly decreased after surgery, but the change was not obvious and there was no significant increase after surgery for a long time. This indicates that microwave ablation can better protect normal thyroid tissue than surgical resection, which is similar to the study of Baek *et al*[30]. It is worth noting that there was no significant change in the FT3 and FT4 levels at the 7th and 30th days after surgery in the microwave ablation group compared with the surgical group. This indicates that microwave ablation is relatively infrequent in the thyroid. Thyroid function was still maintained at a certain level after surgery and no significant reduction in thyroid function occurred. This has important implications for patients in the clinic. If the patient's thyroid function remains stable after surgery, long-term use of thyroid hormone drugs can be avoided and the quality of life of patients can be improved.

The incidence of postoperative complications was observed in the study. The results revealed that postoperative complications occurred in 2 out of 41 patients who underwent microwave ablation. The overall incidence of complications was 4.9% in the microwave ablation group. The overall incidence of complications in the surgery group was 15.2%. There was no significant difference between the two groups ($P > 0.05$). Considering that the sample size was small in this study, the difference was not obvious and large sample data are needed. Long-term efficacy and complications should be further observed.

In summary, the use of microwave ablation for the treatment of PTMC has little risk of traumatic stress and safety. This technology can effectively shorten the length of hospital stay and improve the quality of life of patients. Due to the small damage caused by microwave ablation, the postoperative thyroid function is not significantly affected, which has a high clinical value.

ARTICLE HIGHLIGHTS

Research background

The detection rate of papillary thyroid microcarcinoma (PTMC) has increased over time. Because thyroidectomy is prone to various complications, it can cause physical and mental harm to the patient. With the rapid development of minimally invasive techniques, microwave ablation is the main method of minimally invasive thyroid treatment, and is often used for the treatment of benign thyroid nodules. However, whether this method is indicated for the treatment of patients with PTMC is still controversial.

Research motivation

In this study, microwave ablation was used to treat patients with PTMC. It is hoped that microwave ablation can achieve the same effect as thyroid surgery, and can reduce the complications caused by thyroid surgery.

Research objectives

The aim of this study was to compare the efficacy of thyroidectomy and microwave ablation in the treatment of PTMC and their trauma to the patient's body, to find a more appropriate treatment for patients.

Research methods

Eighty-seven patients diagnosed with papillary thyroid carcinoma were enrolled. There were 46 cases in the surgical group and 41 cases in the microwave ablation group. Microwave ablation and thyroidectomy were performed in each group. The operative time, intraoperative blood loss, hospitalization time, serum C-reactive protein (CPR), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were observed in the two groups. The changes of thyroid-related hormones and the postoperative complications of the two groups were observed 7 d and 30 d after surgery.

Research results

The operative time, intraoperative blood loss, hospitalization time, CPR, IL-6, and TNF-α in the surgical group were significantly higher than those in the microwave ablation group. The free triiodothyronine (FT3) and free thyroxin (FT4) levels in the surgical group were significantly lower than those in the microwave ablation group, while thyroid stimulating hormone (TSH) was significantly higher than that in the microwave ablation group. The complications of the two groups were similar.

Research conclusions

Microwave ablation for the treatment of PTMC has less stress response and higher safety. It can effectively shorten the hospitalization time of patients and improve the life quality. The thyroid function of patients after operation is not affected, so microwave ablation treatment of PTMC has a high clinical value.

Research perspectives

With the development of minimally invasive treatment, minimally invasive treatment methods are increasingly applied to various diseases, so that patients can achieve therapeutic goals with minimal surgical trauma, and minimize the impact of surgical trauma on the body. Minimally invasive surgery is a new technological innovation that still requires large sample and multi-center clinical research support to evaluate long-term safety and efficacy.

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ORIGINAL ARTICLE

Observational Study

Association between functional abdominal pain disorders and asthma in adolescents: A cross-sectional study

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Abstract

AIM

To find the association between asthma and different types of functional abdominal pain disorders (FAPDs) among teenagers.

METHOD

A cross-sectional study was conducted among 13 to 15-year-old children from six randomly selected schools in Anuradhapura district of Sri Lanka. Data were collected using translated and validated self-administered questionnaires (Rome Ⅲ questionnaire, International Study on Asthma and Allergies in Child-

hood questionnaire, and Pediatric Quality of Life Inventory 4.0) and administered under an examination setting after obtaining parental consent and assent.

RESULTS

Of the 1101 children included in the analysis, 157 (14.3%) had asthma and 101 (9.2%) had at least one FAPDs. Of children with asthma, 19.1% had at least one type of FAPDs. Prevalence rates of functional abdominal pain (FAP) (8.9% *vs* 3.3% in non-asthmatics), functional dyspepsia (FD) (2.5% *vs* 0.7%), and abdominal migraine (AM) (3.2% *vs* 0.4%) were higher in those with asthma ($P < 0.05$, multiple logistic regression analysis), but not in those with irritable bowel syndrome (4.5% *vs* 3.1%, $P = 0.2$). Severe abdominal pain (10.8% *vs* 4.6%), bloating (16.6% *vs* 9.6%), nausea (6.4% *vs* 2.9%), and anorexia (24.2% *vs* 16.2%) were more prevalent among asthmatics ($P < 0.05$). Lower gastrointestinal symptoms did not show a significant difference. Scores obtained for health related quality of life (HRQoL) were lower in those with asthma and FAPDs ($P < 0.05$, unpaired *t*-test).

CONCLUSION

Asthma is associated with three different types of FAPDs, namely, FD, AM, and FAP. HRQoL is significantly impaired in teenagers with asthma and FAPDs.

Key words: Health related quality of life; Functional gastrointestinal disorders; Abdominal pain; Asthma; Children

Core tip: A cross-sectional study was conducted to assess the association between asthma and functional abdominal pain disorders (FAPDs) in teenagers. We observed a strong, independent association between asthma and three types of FAPDs, namely, functional abdominal pain, functional dyspepsia, and abdominal migraine, indicating possibility of common underlying pathophysiology. However, no association was observed with irritable bowel syndrome. Most upper gastrointestinal symptoms were more common among asthmatics than in non-asthmatics, but lower gastrointestinal disorders showed no difference. Health related quality of life was significantly decreased in both asthma and FAPDs, indicating the significant impact of both disorders.

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INTRODUCTION

Functional abdominal pain disorders (FAPDs) are a group of disorders characterized by recurrent episodes of abdominal pain with no identifiable organic pathology. There are four recognized types of FAPDs in children, namely, functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain (FAP)[1]. It is estimated that 13.5% of children worldwide suffer from FAPDs[2]. The complex patho-physiology of FAPDs involves gastrointestinal dysmotility, visceral hypersensitivity, dysregulation of mucosal immune system, altered gut microbiota, and complex bidirectional interactions in the brain-gut axis[3].

Asthma is a chronic inflammatory disorder of airways with airway hyper- responsiveness and airflow limitation. It is a major public health problem affecting 300 million people worldwide. In children, the global prevalence of asthma ranges from 0.8% to 32.6%[4]. Patho-physiology of asthma involves complex immunological reactions, environmental triggers, smooth muscle dysfunction, and psychological factors[5,6].

Both FAPDs and asthma are known to have significant repercussion on child health and overwhelming effects on their health related quality of life (HRQoL)[7,8]. These lead to high healthcare expenditure taxing a significant proportion of health budgets[9,10]. The association between asthma and FAPDs has been previously assessed only in IBS[11-13], but not in other types (FD, AM, and FAP). Furthermore, this association has not been previously studied in paediatric age groups. Exact reason for association between FAPDs and asthma is not clear. However, smooth muscle dysfunction[14,15] and altered immune reactions[16-18] are possible shared patho-physiological mechanisms for both disorders. Therefore, the main objective of this study was to evaluate the association between asthma and different types of FAPDs in the paediatric population and the effects of these disorders on their HRQoL.

MATERIALS AND METHODS

Study population

A cross-sectional survey was conducted in the largest district of Sri Lanka, Anuradhapura. A list of schools in the Anuradhapura district was obtained from the Provincial Educational Department, North Central province, Sri Lanka. Multi-stage sampling technique was used to select the study population. There are four types of schools recognized by the Ministry of Education, Sri Lanka. They are Type 1AB, 1C, Type 2, and Type 3. This categorization is mainly based on the number of academic grades available in a school. In the first stage, all the schools from Type 1AB, 1C, and Type 2 in the district were selected, representing adolescents aged

Table 1 Prevalence of functional abdominal pain disorders according to asthma (*n* = 1101) *n* (%)

Disease category	Asthmatics	Non-asthmatics	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*P*-value
BS	7 (4.5)	29 (3.1)	1.6 (0.7-3.8)	1.7 (0.7-4.0)	0.2
FD	4 (2.5)	7 (0.7)	3.9 (1.1-13.6)	3.9 (1.1-13.5)	0.03
AM	5 (3.2)	4 (0.4)	8.5 (2.2-32.4)	10.2 (2.6-39.5)	0.001
FAP	14 (8.9)	31 (3.3)	3.1 (1.6-5.9)	3.1 (1.6-6.0)	0.001
With any type of FAPDs	30 (19.1)	71 (7.5)	2.9 (1.8-4.6)	2.9 (1.8-4.7)	< 0.0001

IBS: Irritable bowel syndrome; FD: Functional dyspepsia; AM: Abdominal migraine; FAP: Functional abdominal pain; FAPDs: Functional abdominal pain disorders.

13-15 years. In the second stage, two schools from each type were randomly selected, representing all five educational zones in the Anuradhapura district. In the final stage, from every selected school, six classes were randomly selected. All the students aged 13 to 15 years present in a selected class on the day of the survey were included.

Data collection

Consent was obtained from the school administration, parents, and the children themselves. Previously translated and validated Rome Ⅲ questionnaire (self-reported form for children above 10 years)[7,19] and International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire[20,21] were used to diagnose FAPDs and asthma, respectively. HRQoL was evaluated using translated and pretested Pediatric Quality of Life Inventory 4.0 (PedsQL - Generic Core Scales) self-report form for teens[7,22]. All parts of the questionnaire were distributed among students in an examination setting, to ensure confidentiality and privacy. The principal investigator and trained research assistants were present and explanations were given while filling the questionnaire.

Identification of children with FAPDs or asthma

Types of FAPDs (IBS, FD, AM, and FAP) were categorized using Rome Ⅲ criteria[1]. Severity of abdominal pain was coded using a 4-point scale (no pain, mild, moderate, and severe). Students reporting to have both physician diagnosed asthma and wheezing during the previous 12 mo[20] were categorized as current asthma.

Computation of HRQoL

The PedsQL inventory assessed 23 items, including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). A 5-point response scale was applied to assess the responses (0 = never a problem; 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, and 4 = almost always a problem). Items were reverse scored and linearly transformed to a 0 to 100 scales (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0) final HRQoL scores were computed out of 100 so that higher scores indicate better HRQoL.

Statistical methods

The sample size was calculated based on an expected prevalence of 20%, absolute precision of 5%, and standard normal deviation of 1.96 for a confidence level of 95%. The minimum sample size required for determining the prevalence of FAPDs and prevalence of asthma was 672.

Data from all schools were pooled for the initial analysis. A logistic regression model was used to evaluate an independent association between asthma and FAPDs. The association between asthma and severity of abdominal pain was assessed using binary logistic regression. The chi-square statistic and odds ratios with 95%CI were calculated to compare the prevalence of upper and lower gastrointestinal symptoms between asthmatics and non-asthmatics. One-way ANOVA was used with Bonferroni correction to compare HRQoL scores between groups. $P < 0.05$ was considered significant. PSPP statistical software version 1.0.1 was used in all calculations. Statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 1113 questionnaires were distributed and all of them were returned. Of them, properly filled 1101 (98.9%) questionnaires were included in the final analysis. The study population consisted of 509 boys (46.2%) with a mean age of 14.03 years (range 13-15 years, SD of 0.8 years). In this study, the prevalence of current asthma was 14.3%. One hundred and one adolescents had at least one type of FAPD (9.2%). According to Rome Ⅲ criteria, FAP was identified in 45 (4.1%), 36 (3.3%) had IBS, 11 (1%) had FD, and 9 (0.8%) had AM.

Association between asthma and FAPDs

Of children with asthma, 19.1% had at least one type of FAPD. Logistic regression analysis showed a strong, independent association between asthma and FAP, FD, and AM after adjusting for age and sex (Table 1). There was also a significant association between asthma and severity of abdominal pain (Table 2).

Gastrointestinal symptoms among asthmatics

Upper gastrointestinal symptoms which showed a

Table 2 Severity of abdominal pain according to asthma (*n* = 1101) *n* (%)

Abdominal pain severity	Asthmatics	Non-asthmatics	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*P*-value
Mild	38 (24.2)	225 (23.8)	1.1 (0.7-1.8)	1.1 (0.7-1.7)	0.49
Moderate	36 (22.9)	217 (23.0)	1.1 (0.7-1.7)	1.1 (0.7-1.8)	0.48
Severe	17 (10.8)	43 (4.6)	2.7 (1.4-5.1)	2.8 (1.5-5.3)	0.001

Table 3 Prevalence of gastrointestinal symptoms among asthmatics (*n* = 1101) *n* (%)

	Asthmatics	Non asthmatics	Odds ratio (95%CI)	*P*-value
Upper gastrointestinal symptom				
Abdominal pain	33 (21)	109 (11.5)	2.0 (1.3-3.1)	0.002
Bloating	26 (16.6)	91 (9.6)	1.8 (1.1-2.9)	0.01
Loss of appetite	38 (24.2)	153 (16.2)	1.6 (1.1-2.4)	0.02
Nausea	10 (6.4)	27 (2.9)	2.3 (1.0-4.8)	0.04
Vomiting	7 (4.5)	54 (5.7)	0.7 (0.3-1.7)	0.6
Early satiety	15 (9.6)	119 (12.6)	0.7 (0.4-1.2)	0.3
Lower gastrointestinal symptom				
Increased frequency of defecation	17 (10.8)	82 (8.7)	1.2 (0.7-2.2)	0.3
Decreased frequency of defecation	14 (8.9)	70 (7.4)	1.2 (0.6-2.2)	0.5
Frequency of passage of hard stool	10 (6.4)	76 (8.1)	0.7 (0.3-1.5)	0.4
Frequency of passage of loose stool	18 (11.5)	92 (9.7)	1.1 (0.7-2.0)	0.5

Table 4 Health related quality of life scores in children with each disease category and controls (*n* = 1101)

Quality of life domain	Children with FAPDs only mean (SD) *n* = 70	Children with asthma only mean (SD) *n* = 129	Children with both asthma and FAPDs mean (SD) *n* = 30	Controls mean (SD) *n* = 872
Physical functioning	77.0 (14.5)[b]	80.8 (14.0)[b]	72.7 (13.6)[b,c]	88.4 (10.5)
Emotional functioning	69.0 (20.2)[b]	75.3 (16.8)	69.8 (14.4)[a]	78.1 (16.0)
Social functioning	78.6 (19.1)[b,c]	85.6 (14.3)[a]	83.3 (15.2)	88.9 (12.0)
School functioning	74.7 (17.8)[a]	77.2 (15.7)[a]	68.5 (16.4)[b,c]	81.1 (14.1)
Total HRQoL score	75.1 (14.0)[b,c]	79.9 (11.1)[b]	73.4 (11.0)[b,c]	84.7 (10.1)

HRQoL: Health related quality of life; FAPDs: Functional abdominal pain disorders. [a]$P < 0.05$ *vs* controls, [b]$P < 0.0001$ *vs* controls, [c]$P < 0.05$ *vs* asthmatics.

significant association with bronchial asthma were abdominal pain, bloating, nausea, and loss of appetite. However, lower gastrointestinal symptoms were not associated with asthma (Table 3).

HRQoL among affected adolescents

Children with both diseases had lower overall HRQoL scores compared to controls (Table 4). Children with both FAPDs and asthma had significantly lower quality of life than those with asthma alone. Furthermore, children having FAPDs only had a higher impairment of the quality of life, compared to those with asthma alone, but there was no significant difference between children with FAPDs only and those with both diseases.

DISCUSSION

For perhaps the first time in the paediatric literature, we found a strong, independent association between asthma and three different types of FAPDs, namely, FAP, FD, and AM. Furthermore, the severity of abdominal pain in FAPDs was an independent predictive factor of having asthma. In contrast to previous studies among adults, we did not note a significant association between IBS and asthma. This finding is probably not surprising as most of the studies have specifically studied the association between asthma and patients with IBS only[11,12,23]. One study using data from General Practice has shown a weak association between IBS and asthma. However, when adjusted to age, gender, and psychological co-morbidities, the association became insignificant[24]. In their study, the clinical diagnosis of FAPDs was made by a general practitioner and not conforming exactly to standard Rome criteria, which made comparisons difficult. Olén *et al*[25] studied a birth cohort of 2610 children at the age of 12 years in Sweden. They found that the presence of asthma during the first 2 years was significantly associated with abdominal pain of functional origin at 12 years. They looked at the association between asthma and non-specific abdominal pain, but did not attempt to look at the exact association with specific FAPDs.

In our study, the gastrointestinal symptoms independently associated with asthma were abdominal pain, bloating, nausea, and loss of appetite. Our finding was supported by a case-control study that reported that abdominal pain and vomiting were significantly more prevalent in asthmatic children than in controls[26].

In contrast to our study, they showed that lower gastrointestinal symptoms were also significantly more prevalent. Another study among adolescents showed a significant association between allergic wheeze and abdominal pain[27]. Further studies found higher prevalence of gastrointestinal symptoms in patients with allergic rhinitis and wheeze[28,29].

In our study, the prevalence of FAPDs (9.3%) among teenagers was less than the study that had reported 16.5% of prevalence among Sri Lankan adolescents aged 13-18 years[7]. In contrast, a recent meta-analysis has shown a worldwide pooled prevalence of FGIDs of 13.5% in children[2]. Regional differences in the dietary patterns, life styles, differences in survey methods, inclusion of different age groups, and changing diagnostic criteria would have contributed to these differences. The prevalence of asthma in this study is more than that previously reported by Danansuriya *et al*[21] (10.7%) in Sri Lankan adolescents aged 12-14 years. However, the prevalence rate of asthma reported in this study is within the range reported by the ISAAC studies carried out throughout the world, which ranged between 0.8% to 32.6% among adolescents aged 13 to 14 years[4]. Different prevalence rates can be explained by selected age group, sample selection, and case definition used.

We observed that adolescents with only asthma or FAPDs together with adolescents suffering from both disease conditions had significantly lower HRQoL compared to controls. To our knowledge, this is the first study which reported the impact of asthma on quality of life among Sri Lankan adolescents. An Australian study found that asthma caused mild to moderate quality of life impairment among adolescents[8]. A Brazilian study observed a significant impairment of quality of life among adolescents with severe asthma[30]. Another study reported that asthma impairs quality of life not only among asthmatic children but also among their primary caregivers[31].

Pain predominant FGIDs showed lower scores for all four domains of HRQoL in affected adolescents. Similarly, several previous studies have reported lower HRQoL in children with FAPDs[7,32]. We found that adolescents with both diseases (FAPDs and asthma) had lower HRQoL than children with asthma alone. This can be explained by the dual disease burden among these adolescents. Interestingly, in our study, children having only FAPDs had a lower total HRQoL score than adolescents with asthma alone. Although asthma is a chronic condition similar to FAPDs, the impact of FAPDs on quality of life appears to be greater than that of asthma. Youssef *et al*[32] showed that children with FAPDs had lower HRQoL, compared to those with inflammatory bowel disease and gastro-oesophageal reflux disease. We could possibly conclude that FAPDs have a more devastating impact on HRQoL than other chronic diseases which have at least reasonable therapeutic options. In fact, FAPDs have minimal therapeutic options despite decades of research. This could also contribute to the lower HRQoL in adolescents with FAPDs only.

Why asthma and FAPDs, two different disorders involving two different systems, are associated with each other? One hypothesis is that the generalized smooth muscle dysfunction in both gastrointestinal and respiratory systems gives rise to symptoms simultaneously. Gastric motility is maintained by gastric smooth muscle, and disturbance in gastric motility is well reported in children with all types of FAPDs[33,34]. A study assessing gastric motility in adult asthmatics noted a significant delay in gastric emptying rate and lower antral motility index compared to controls[14]. Similarly, disturbance in airway resistance has been demonstrated in patients with IBS[12,15]. Amra *et al*[15] studied IBS patients with no respiratory symptoms and reported that forced expiratory volume in the first second (FEV_1) was significantly lower and the airway resistance at 5 Hz was significantly higher in them compared to healthy subjects. It supports the evidence of a subclinical increase in airway resistance and airway smooth muscle dysfunction in patients with IBS, indicating a possible association between these two entities.

An immunological link between the lung and gut, and therefore, disordered immune response common to both biological systems, can play a role in the association between FAPDs and asthma. In asthma, airway inflammation results in increased numbers of activated eosinophils, mast cells, and T lymphocytes in the airway mucosa[35]. The same immunological reactions have been detected in small bowel biopsy specimens of asthmatics[16]. Similar cellular immune responses have been shown in the gut of patients with FGIDs. Friesen *et al*[17] found that 71% of children evaluated for FD have significant eosinophil infiltration in the duodenal mucosa including intraepithelial eosinophils. Another study showed increased mast cell infiltration in the small and large intestine of patients with IBS, compared to healthy controls[36]. Infiltrated mast cells in gut mucosa spontaneously release mediators like histamine in close proximity to visceral sensory nerves and these substances in turn may lower the sensory threshold for pain, inducing visceral hypersensitivity[18]. Several studies conducted in patients with IBS have found a correlation between the number of activated mast cells present in the gut mucosa and increased severity of abdominal pain and bloating[37,38]. On the other hand, mast cells in airways release the same immune mediators like histamine which have a profound effect on airway smooth muscle cells inducing bronchial hyper responsiveness[39]. Further, TH_2 related immune activation is also known to be associated with both of these disorders[6,40]. These studies indicate the possibility of FAPDs and asthma sharing the same immunological mechanisms and perhaps similar underlying pathophysiology.

The present study has several strengths. Large sample size and multistage sampling technique have increased the validity of our results. Further, we used standard questionnaires (Rome Ⅲ questionnaire for

children and ISAAC tool to diagnose asthma in children) in data collection, which were translated and validated for Sri Lanka. Limitations of this study include not conducting a physical examination and investigations of these children to confirm the diagnosis of asthma and FAPDs. We could not perform lung function testing and bronchodilator reversibility test to confirm the diagnosis of asthma and basic investigation to exclude organic pathologies causing abdominal pain due to this large sample size. In addition, by the time this study was conducted, Rome Ⅳ criteria were not released and therefore we used Rome Ⅲ criteria for diagnosis of FAPDs. However, the pathophysiological mechanisms are unlikely to be affected by the use of older criteria and therefore, unlikely to have a significant effect on our conclusions.

Identifying the association between FAPDs and asthma has several implications. Both these disorders are very common in paediatric practice and considered as emerging global health problems in children. Further, it is quite possible that the association between these two conditions would reduce the HRQoL and increase healthcare expenditure in children possibly in an additive manner than either disease alone. Therefore, clinicians need to be aware of the association between these two disorders as well as the association between asthma and upper gastrointestinal symptoms to provide holistic clinical care to the affected children. Finally, our findings would suggest the possibility of a common patho-physiological mechanism for both disorders.

In conclusion, this is the first report of a strong independent association between asthma and three different types of FAPDs, namely, FAP, FD, and AM in the pediatric literature. Upper gastrointestinal symptoms are significantly more common among children with asthma than in non-asthmatics. Our findings suggest the possibility of a common underlying patho-physiological mechanism for both disorders. Furthermore, the lower HRQoL of children with FAPDs compared to those with other diseases demands novel and innovative therapeutic modalities to manage children with this disorder.

ARTICLE HIGHLIGHTS

Research background

Both functional abdominal pain disorders (FAPDs) and asthma are highly prevalent diseases among children and have a significant individual and public health impact. Chronic recurrent nature of both diseases is known to impair the health related quality of life (HRQoL) of affected individuals and drain a large amount of public funds in treating exacerbations and long-term follow-up.

Research motivation

Studies among adults have shown a potential association between irritable bowel syndrome and bronchial asthma and suggested the possibility of common patho-physiology for both disorders. However, no studies have attempted to evaluate the association between these two highly prevalent diseases in children.

Research objectives

The main objective of our study is to explore the association between FAPDs and asthma in children and their impact on HRQoL.

Research methods

A cross-sectional survey was conducted among school children aged 13-15 years. Multi-stage sampling technique was used to select the study population. We used validated Rome III questionnaire and International Study on Asthma and Allergies in Childhood questionnaire to assess gastrointestinal and respiratory symptoms. Pediatric quality of life inventory (PedsQL Generic Core Scale) was used to assess HRQoL. Rome III criteria were used to diagnose FAPDs. Students reporting to have both physician diagnosed asthma and wheezing during the previous year were categorized as having asthma. HRQoL was computed using the standard protocol.

Research results

A total of 1101 questionnaires were included in the final analysis. We found asthma in 14.3% of children and at least one type of FAPD in 9.2% of children. The logistic regression analysis model showed an independent association between asthma and functional abdominal pain (FAP), functional dyspepsia (FD), and abdominal migraine (AM). Upper gastrointestinal symptoms such as abdominal pain, bloating, nausea, and loss of appetite were significantly associated with asthma. Quality of life scores in both children with asthma and those with FAPDs were lower when compared to normal children.

Research conclusions

We found a clear association between asthma and three FAPDs, namely, FAP, FD, and AM, suggesting the possibility of asthma and FAPDs sharing same pathophysiological mechanisms. Generalized smooth muscle dysfunction in both gastrointestinal and respiratory tracts could be triggered simultaneously through autonomic dysfunction, which could have been one potential pathophysiological mechanism to explain this association. Furthermore, it is also possible that common immunological phenomena such as mast cell dysfunction and altered TH2 response could drive the pathophysiology of both disorders.

Research perspectives

In this study we highlighted the potential association between two common pediatric disorders (asthma and FAPDs). Future studies should be directed to explore underlying pathophysiological basis for this association, especially focusing on smooth muscle dysfunction and immune dysregulation of both gastrointestinal and respiratory systems.

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ORIGINAL ARTICLE

Prospective Study

Evaluating mucosal healing using colon capsule endoscopy predicts outcome in patients with ulcerative colitis in clinical remission

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Abstract

AIM

To examine whether second generation of colon capsule endoscopy (CCE-2) is acceptable for assessing the severity of mucosal inflammation and evaluating mucosal healing using CCE-2 is able to predict outcome in ulcerative colitis (UC) patients, especially in clinical remission.

METHODS

A total of 30 consecutive UC patients in clinical remission were enrolled to undergo CCE-2. Clinical remission was defined as clinical activity index (CAI) $\leqslant$ 4 according to Rachmilewitz index. The rate of total colon observation and colon cleansing level were evaluated. Severity of mucosal inflammation in UC was assessed according to the Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Relapse-free survival was assessed. Acceptability of CCE-2 was assessed using a questionnaire survey.

RESULTS

The rate of total colon observation within its battery life was 93.3%. The proportion of "excellent" plus "good" cleansing level was 73.3%. The rate of mucosal healing (MES 0, 1) assessed by CCE-2 was 77.0%. The relapse-free survival rate was significantly higher in MES 0, 1 than in MES 2, 3 (P = 0.0435), and in UCEIS 0-3 than in UCEIS 4-8 (P = 0.0211), whereas there was no significant difference between CAI 0 and CAI 1-4 groups. A questionnaire survey revealed an overall acceptability of CCE.

CONCLUSION

CCE-2 is acceptable for assessing the severity of mucosal inflammation in UC patients, especially in clinical remission. Evaluating mucosal healing using CCE-2 was able to predict outcome.

Key words: Colon capsule endoscopy; Ulcerative colitis; Mucosal healing; Mayo endoscopic subscore; Ulcerative Colitis Endoscopic Index of Severity

Core tip: Although mucosal healing is a newly established therapeutic goal in ulcerative colitis (UC), it remains unclear whether evaluating endoscopic activity using colon capsule endoscopy (CCE-2) is able to predict outcome. The present study was a prospective study to evaluate the usefulness of CCE-2 in patients with UC, especially in clinical remission. We revealed that our reduced-volume preparation regimen for CCE-2 could attain a high rate of total colon observation and high acceptability, and that assessment of endoscopic activity by CCE-2 using Mayo endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity can predict outcome.

Takano R, Osawa S, Uotani T, Tani S, Ishida N, Tamura S, Yamade M, Iwaizumi M, Hamaya Y, Furuta T, Miyajima H, Sugimoto K. Evaluating mucosal healing using colon capsule endoscopy predicts outcome in patients with ulcerative colitis in clinical remission. *World J Clin Cases* 2018; 6(15): 952-960 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/952.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.952

INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease with a relapsing and remitting course, and is associated with impaired quality of life[1]. Conventional colonoscopy (CS) plays a major role in the diagnosis and assessment of disease severity and extent as well as surveillance for dysplasia in patients with UC[2-4]. In recent years, besides symptom control, mucosal healing has been established as a new therapeutic goal. It predicts clinical remission and the requirement for hospitalization and surgery[5-8]. However, conventional CS has several limitations, including adverse events, low patient compliance and has manpower restrictions[9,10]. Therefore, an alternative approach that can overcome these limitations is required.

In 2009, the second generation of colon capsule endoscopy (CCE-2) was released, providing a larger number of images per second and a broader viewing angle[11]. CCE-2 has several benefits for patients with UC in assessing mucosal inflammation as the procedure is relatively non-invasive without direct trauma to the mucosa or air insufflation[12,13]. Therefore, it has a high level of patient acceptance without anaesthesia. To date, the accuracy of CCE-2 for assessment of mucosal inflammation in UC appears to be comparable with that of CS[14-16]. However, there have been a limited number of studies. It remains unclear which UC patients may benefit from the use of CCE-2.

The Mayo endoscopic subscore (MES) is widely used in clinical trials to describe the degree of endoscopic activity in patients with UC. In clinical trials as well as in practise, a MES of 0 or 1 is a commonly accepted criterion for mucosal healing and predicts a better outcome[17-19]. More recently, another score index, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), was validated to measure endoscopic severity in UC[20,21]. UCEIS is more sensitive in detecting mucosal inflammation and is superior to other scoring systems in detecting treatment response and predicting disease outcomes[22,23]. However, it is not yet confirmed whether assessment of mucosal inflammation by CCE-2 using

Table 1 Schedule of bowel preparation

Day		Procedure
Previous day	Diet	Low-fibre diet
	After dinner	Magnesium citrate 50 g/180 mL + Sennoside 48 mg
Examination	09:00	Mosapride citrate 20 mg
		Swallowing of CCE-2 capsule
	Booster (1)	1 L of low-volume PEG (MoviPrep) + 0.5 L water
	Booster (2)	1 L of low-volume PEG (MoviPrep) + 0.5 L water
	Booster (3)	Magnesium Citrate 50 g/180 mL

Booster (1): start after capsule moves into small intestine; Booster (2): start 1 h after booster (1); Booster (3): 3 h after booster (1) if capsule is not exhausted. CCE-2: Second generation of colon capsule endoscopy; PEG: Polyethylene glycol.

MES or UCEIS is able to predict outcome in clinical practise.

Conventional bowel preparations may be excessive for patients with severe or fulminant UC, leading to increased diarrhea and bleeding. Therefore, the preparation should be tailored to the patient in such cases. In the present study, we developed a novel reduced-volume regimen for CCE-2 examination in patients with UC, especially those in clinical remission, and assessed the feasibility of evaluating the severity of mucosal inflammation. Furthermore, we examined whether evaluation of endoscopic activity by CCE-2 using MES and UCEIS was able to predict outcome.

MATERIALS AND METHODS

Study design

This was a single-center, prospective study conducted in UC patients with clinical remission, carried out in accordance with the Declaration of Helsinki. Approval for the study was obtained from the ethics committee of Hamamatsu University School of Medicine, Japan. Written informed consent for participation in the study was obtained from all patients. This study was registered with the University Hospital Medical Information Network (UMIN), UMIN000030539.

Enrolment of patients aged 16 to 80 years began in October 2015 and was completed in December 2017. Eligible patients had a histologically confirmed diagnosis of UC with clinical remission (Rachmilewitz index $\leqslant$ 4)[24]. Patients with the following criteria were excluded: dysphagia; pregnant or possibly pregnant women; a pacemaker or other implanted electromedical device; presence or history of small and large bowel obstruction; a contraindication to bowel preparation (congestive heart failure, renal insufficiency, life-threatening condition); allergic to polyethylene glycol (PEG), magnesium citrate, sennoside, metoclopramide or mosapride citrate; those undergoing magnetic resonance imaging 2 wk after CCE-2; and inappropriate for this study by other reasons judged by the investigators.

CCE-2 procedure

The present study used a CCE-2 known as PillCam COLON 2 (Medtronic Japan Co., Ltd., Tokyo, Japan). A modified regimen of bowel preparation was developed to improve patient's acceptability by reducing the volume and shortening the time of examination using low-volume PEG (MoviPrep, EA Pharma, Tokyo, Japan). Details of the CCE-2 procedure are presented in Table 1. On the day before the capsule procedure, patients ate a low-fiber diet and drank 50 g of magnesium citrate mixed with 180 mL of water and received 48 mg oral sennosides after dinner. On the procedure day, patients swallowed a colon capsule with 20 mg mosapride citrate at 9:00 am. If the capsule had moved out from the stomach to the duodenum, 1 L of low-volume PEG plus 0.5 L of water was administered as a first booster. After 1 h, 1 L of low-volume PEG plus 0.5 L of water was administered again as a second booster. Three hours later, if the capsule was not excreted outside the body, 50 g of magnesium citrate mixed with 180 mL of water was administrated as a third booster. Optional use of bisacodyl suppository was allowed only if the capsule was not excreted outside the body after a third booster. Recording was continued until the battery ran down or the capsule was excreted.

CCE-2 evaluation

The rate of CCE-2 excretion was calculated, and the transit time for each part of the gastrointestinal tract was recorded. The level of colonic cleansing was scored according to a four-point grading scale, as previously reported[25]. The hepatic flexure and splenic flexure which had been automatically determined by the software were reconfirmed and used as markers to separate the segment in the colon. Each segment was scored as cecum, ascending colon, transverse colon, proximal left-sided colon and distal left-sided colon. Representative images are shown in Figure 1A. Adverse effects were also recorded. CCE-2 images were reviewed independently by two experts of capsule endoscopy (Osawa S and Takano R). One (Osawa S) had eight years of clinical experience in capsule endoscopy and the other (Takano R) had four years of clinical experience, and both had read more than 200 capsule endoscopy videos. The final reports involving endoscopic activity score and cleansing effectiveness were prospectively made based on a consensus bet-

Table 2 Patients' characteristics *n* (%)

Numbers of patients	30
Gender (male/female)	18/12
Age [mean ± SD (range), yr]	48.6 ± 13.3 (24-67)
Disease duration [mean ± SD (range), yr]	13.9 ± 9.5 (1-32)
Inpatient/outpatient	0/30
History of abdominal surgery	2 (6.7)
Type of disease	
Total colitis	19 (63.3)
Left-sided	10 (33.3)
Proctitis	1 (3.3)
Disease activity (Rachmilewitz index)	
CAI = 0	19 (63.3)
CAI = 1	4 (13.3)
CAI = 2	4 (13.3)
CAI = 3	2 (6.7)
CAI = 4	1 (3.3)
Serum albumin (mean ± SD, g/dL)	4.2 ± 0.5
Serum CRP (mean ± SD, mg/dL)	0.11 ± 0.15
Medications	
5-ASA	24 (80.0)
Steroid	4 (13.3)
Thiopurines	12 (40.0)
Anti-TNF-Ab	1 (3.3)
No medication	1 (3.3)
Observation period after CCE; median (range)	20.5 (5-27)

CAI: Clinical activity index; 5-ASA: 5-aminosalicylic acid; SD: Standard deviation; CRP: C-reactive protein; CCE: Colon capsule endoscopy.

Table 3 Performance of second generation of colon capsule endoscopy procedure

Total colon observation[1], %	93.3% (28/30)
Excretion within 8 h, %	90.0% (27/30)
Capsule retention rate, %	0% (0/30)
Mean transit time ± SD (range), min	
Stomach	27.2 ± 15.4 (4-63)
Small intestine	72.7 ± 34.3 (23-155)
Colon[2]	163.9 ± 211.0 (9-775)
Cecum and ascending colon	50.4 ± 84.2 (1-386)
Transverse colon	11.7 ± 17.6 (5-80)
Left-side colon[2]	101.9 ± 186.3 (5-751)
Total time[2]	263.8 ± 228.2 (54-952)
Total liquid volume of the examination day	2329 ± 854 (500-3180)

[1]Excretion before the battery ran down; [2]Involving the end point of battery time without excretion.

ween the two experts.

Clinical efficacy evaluation

Patients were evaluated using the clinical activity index (CAI) according to Rachmilewitz[24]. Clinical remission was defined as CAI $\leqslant$ 4. Relapse was defined as an increase in the CAI score, CAI > 4, after achieving clinical remission. Exacerbation was defined as any additional treatment for clinical symptoms.

Endoscopic activity evaluation

The endoscopic activity of UC was evaluated by MES and UCEIS. MES is a four-point scale (0-3). The UCEIS is a nine-point scale (0-8) of three descriptors, calculated as a simple sum: vascular pattern (0-2), bleeding (0-3) and erosions and ulcers (0-3)[20]. The highest score among segments was determined as the overall score.

Acceptability of CCE-2

A questionnaire survey was conducted to evaluate the acceptability of the CCE-2 procedure, asking patients about following five items: physical pain, mental distress, bowel preparation, next examination and overall acceptability. Each question comprised five-grade evaluations.

Statistical analysis

Statistical analysis was carried out using SPSS (SPSS 17.0; SPSS Inc., Chicago, Illinois, United States). Results were expressed as mean ± SD with minimum and maximum values, and categorical data were expressed as percentage. Pearson's Chi-square test was used to compare distribution of the activity score assessed by CCE. Kaplan-Meier plots with log-rank test were used to compare between two groups in relapse-free and exacerbation-free survival.

RESULTS

Patient characteristics

A total of 30 patients were enrolled in the study. Patients' demographics are shown in Table 2. The mean age was 48.6 ± 13.3 years; 18 subjects were male and 12 were female. The mean disease duration was 13.9 ± 9.5 years, and the clinical UC activity of the enrolled patients assessed by Rachmilewitz index was 0.73 ± 1.14 (63.3% in CAI = 0 and 36.7% in CAI = 1-4). Regarding types of disease, 19 patients (63.3%) had total colitis, 10 (33.3%) had left-sided colitis and one (3.3%) had proctitis. Most of the patients were treated with 5-aminosalicylate drugs. The median observational period was 20.5 mo (range 5-27 mo).

Performance of CCE-2

CCE-2 performance is shown in Table 3. The rate of total colon observation within its battery life in UC patients were 93.3% and 27 patients (90.0%) excreted the CCE-2 within 8 h. The mean total transit time was 263.8 ± 228.2 min (range 54-952 min). The mean colonic and small intestinal transit times were 163.9 ± 211.0 min (range 9-775 min) and 72.7 ± 34.3 min (range 23-155 min), respectively. The total liquid volume on the examination day was 2329 ± 854 mL (range 500-3180 mL). No severe adverse events were observed in this study.

The effectiveness of cleansing using our bowel preparation regimen is shown in Figure 1B. The percentages of "excellent" plus "good" were 40% in the cecum, 57% in the ascending colon, 80% in the transverse colon, 77% in the proximal left-sided colon and 70% in the distal left-sided colon. As a whole, the proportion of

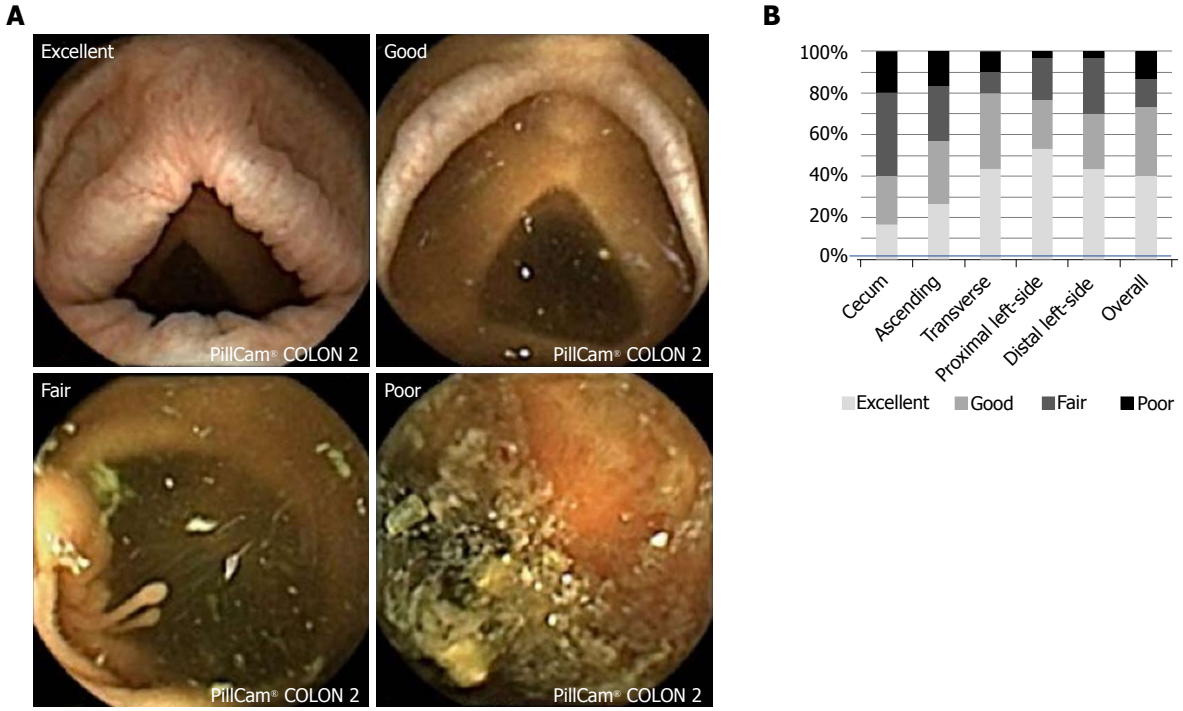


Figure 1 Effectiveness of cleansing at each site in the colon. A: Level of colonic cleansing was scored according to a four-point grading scale: excellent, good, fair and poor; B: Each site in the colon was scored: cecum, ascending colon, transverse colon, proximal left-sided colon and distal left-sided colon. The overall proportion of "excellent" plus "good" cleansing level was 73.3%.

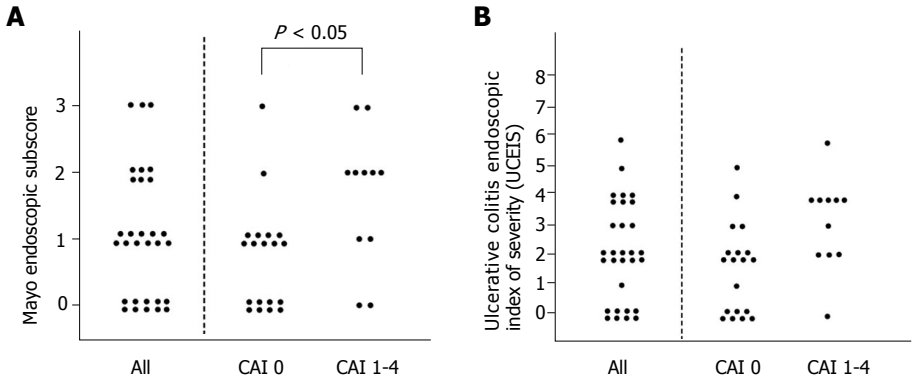


Figure 2 Distribution of the activity score assessed by second generation of colon capsule endoscopy. A: Distribution of the Mayo endoscopic subscore (MES) assessed by second generation of colon capsule endoscopy (CCE-2); B: Distribution of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) assessed by CCE-2. We examined whether there was a difference in the distribution of each endoscopic activity score by CCE-2 in clinical activity index (CAI) 0 or CAI 1-4 groups using a test of independence. The distribution of MES by CCE-2 was statistically different between CAI 0 and CAI 1-4 groups, whereas that of UCEIS was not. Statistical analysis was performed by Pearson's chi-square test. CAI: Clinical activity index.

"excellent" plus "good" cleansing level was 73.3%.

Distribution of the endoscopic activity score assessed by CCE-2

We examined the distribution of endoscopic activity score assessed by CCE-2 in clinical remission. As shown in Figure 2A, the rate of mucosal healing (MES 0, 1) assessed by CCE-2 was 77.0%. When we evaluated the distribution of endoscopic activity score in between CAI 0 and CAI 1-4 groups, statistical difference was observed in the distribution of MES, whereas distribution of UCEIS by CCE-2 was not statistically different in between CAI 0 and CAI 1-4 groups (Figure 2B).

Assessment of endoscopic scoring by CCE-2 and outcome

Based on the Kaplan–Meier survival estimator graphs (Figure 3), the overall cumulative relapse-free and exacerbation-free survival rates at 12 mo were 85.2% and 71.2%, respectively. The relapse-free survival rate was significantly higher in MES 0, 1 than in MES 2, 3 ($P < 0.05$; log-rank test), and in UCEIS 0-3 than in UCEIS 4-8 ($P < 0.05$; log-rank test). Furthermore, the exacerbation-free survival rate was significantly

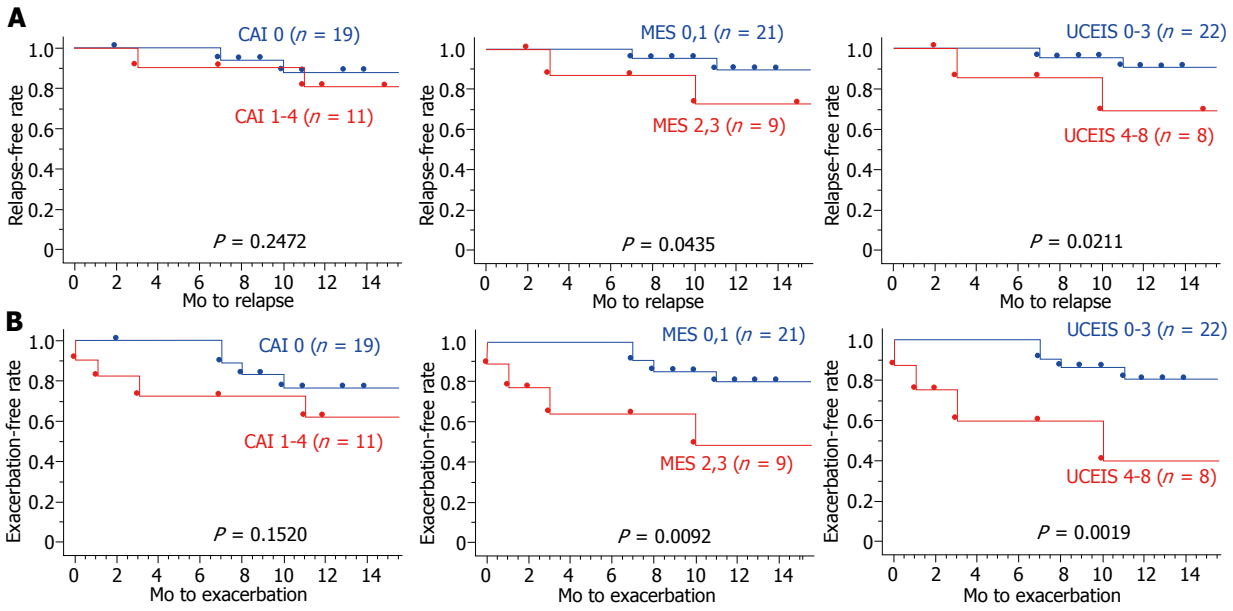
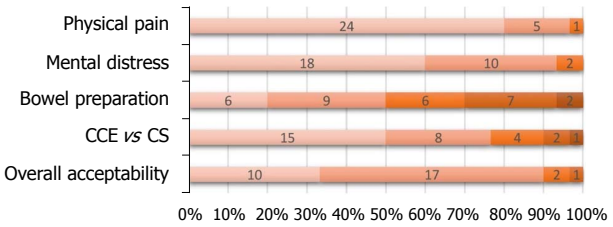


Figure 3 Kaplan–Meier plots for relapse-free survival and exacerbation-free survival. A: Kaplan–Meier plots for relapse-free survival; B: Kaplan–Meier plots for exacerbation-free survival. The relapse-free survival rate was significantly higher in Mayo endoscopic subscore (MES) 0, 1 than in MES 2, 3 ($P < 0.05$; log-rank test), and in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) 0-3 than in UCEIS 4-8 ($P < 0.05$; log-rank test). Furthermore, the exacerbation-free survival rate was significantly higher in MES 0, 1 than in MES 2, 3 ($P < 0.01$; log-rank test), and in UCEIS 0-3 than in UCEIS 4-8 ($P < 0.01$; log-rank test). However, there was no significant difference between clinical activity index (CAI) 0 and CAI 1-4 groups for both survival rates. MES: Mayo endoscopic subscore; CAI: Clinical activity index; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.



	Physical pain	Mental distress	Bowel preparation	CCE *vs* CS next examination	Overall acceptability
	not at all	not at all	easy	CCE	excellent
	almost not	almost not	relatively easy	CCE > CS	good
	a little	a little	tolerable	CCE = CS	tolerable
	painful	hard	hard	CCE < CS	fair
	intolerable	intolerable	intolerable	CS	intolerable

Figure 4 Questionnaire survey about the acceptability of the second generation of colon capsule endoscopy. A questionnaire survey was carried out by all of the patients about the following five items: physical pain, mental distress, bowel preparation, next examination and overall acceptability. Each question comprised five-grade evaluations. CCE: Colon capsule endoscopy; CS: Colonoscopy.

higher in MES 0, 1 than in MES 2, 3 ($P < 0.01$; log-rank test), and in UCEIS 0-3 than in UCEIS 4-8 ($P < 0.01$; log-rank test). However, in both survival rates, there was no significant difference between CAI 0 and CAI 1-4 groups. These results indicated that indices for predicting UC relapse risk are endoscopic scores rather than clinical scores.

Satisfactory survey

To evaluate the acceptability of the CCE-2 procedure, we conducted a questionnaire survey about the following five items: Physical pain, mental distress, bowel preparation, next examination and overall acceptability. The results are shown in Figure 4. For overall acceptability, the proportion of "excellent" plus "good" was 90%. For physical pain and mental distress, most patients felt almost nothing or nothing at all. In the pre-treatment, patients' opinion varied regarding the tolerance of bowel preparation. The questionnaire survey showed that 77% of patients would choose CCE-2 rather than CS for future scheduled endoscopies.

DISCUSSION

The present study was a prospective study to evaluate the usefulness of CCE-2 in patients with UC, especially in clinical remission, and revealed the following novel findings: (1) our reduced-volume preparation regimen for CCE-2 could attain a high rate of total colon observation, and high acceptability; and (2) assessment of endoscopic activity by CCE-2 using MES and UCEIS can predict outcome. These results suggested that CCE-2 could be an alternative to endoscopic examination for follow-up of UC, especially in clinical remission.

The current European Society of Gastrointestinal Endoscopy recommendation for CCE preparation is use of 4 L of PEG solution administered as a split-dose (2 L the day before the examination and 2 L before capsule ingestion) combined with oral use of prokinetics, low-

volume sodium phosphate (NaP) boosters[26]. However, most Japanese patients are not able to tolerate it in clinical practise because of the high volume. Although reduced-volume regimens have been reported for UC patients previously[14,27], there was still room for improvement in terms of cleansing level and rate of total colon observation, Usui *et al*[27] reported that the proportion of "excellent" plus "good" cleansing was approximately 60%. They discussed that a fair level of colonic cleansing was adequate for the evaluation of UC mucosal severity, whereas it is not sufficient for surveying colon polyps. In this study, we developed a novel reduced-volume regimen of bowel preparation for CCE-2 examination in patients with UC, especially in clinical remission expecting receptive improvement without bowel preparation before swallowing a capsule endoscopy on the examination day. As a result, a shortened transit time through the stomach and colon, and high rates of total colon observation with adequate cleansing could be obtained. More recently, Okabayashi *et al*[28] reported a simple 1-d CCE-2 procedure using castor oil added to the booster without dietary restrictions, which successfully achieved a high excretion rate of 93.9% (31/33) and high acceptance. It is attractive regimen enabled the volume of bowel preparation to be reduced to 1.45 ± 0.07 L whereas the cleansing level was lower than our procedure.

In this study, the rate of mucosal healing assessed by CCE-2 seemed to be equivalent to that of CS. First-generation CCE (CCE-1) displayed a sensitivity and specificity of 89% and 75%, respectively, for the diagnosis of active UC. Although the procedure was safe, the usefulness of CCE-1 for evaluation of UC activity was controversial among studies because of its low specificity[14,29-32]. CCE-2 equipped with an accelerated frame rate and larger angle of view has improved the accuracy for detecting intraluminal abnormality. Oliva *et al*[15] investigated the performance of CCE-2 in 29 paediatric UC patients, and reported that the sensitivity, specificity, positive predictive value and negative predictive value for inflammation detection were 95%, 100%, 100% and 85%, respectively. A recent prospective study in 150 patients revealed that CCE-2 had a sensitivity of 97% and 94% to detect mucosal inflammation (MES ⩾ 1) and moderate to severe inflammation (MES ⩾ 2), respectively. To detect moderate-to-severe mucosal inflammation, the negative predictive value was improved substantially from 65% with the first-generation capsule to 96% with CCE-2[16]. These studies using CCE-2 support our findings of high detectability using CCE-2.

Until now, there has not been an established scoring system of CCE used worldwide for evaluating endoscopic activity of UC[12]. Recently, the largest-scale study consisting of 150 patients using CCE-2 showed substantial agreement between CCE-2 and CS for either MES [intraclass correlation coefficient (ICC) 0.69; 95% confidence interval (CI), 0.46–0.81] or UCEIS (ICC 0.64; 95%CI: 0.38-0.78) with almost perfect (ICC > 0.80) intra- and inter-observer agreement[16]. However, there have been no studies evaluating whether score of capsule endoscopic activity contributes to the prediction of the clinical course in patients with UC. In our study, assessing mucosal healing by CCE-2 using MES, which is most frequently used in clinical trials and practice, was able to predict outcome in the same way as CS. That is, so-called mucosal healing of MES 0-1 was significantly associated with low relapse-free survival rate and exacerbation rate. Furthermore, we also revealed that UCEIS, which has been validated to be more sensitive in detecting mucosal inflammation, was able to predict outcome in the same way as CS. In this score the threshold for mucosal healing has yet to be determined. Remission is defined as UCEIS 0-1 in some studies[22,33,34]. According to our analysis, MES 0-1 by CCE-2 was equivalent to UCEIS 0-3.

There were several limitations to this study. First, since this study was designed as a preliminary study, a small number of patients were enrolled. Second, this study was conducted in a single center setting that might have involved some bias for selecting patients and the details of the CCE-2 procedure. Third, as all of the enrolled patients were Japanese, it is not confirmed whether bowel preparation regimen of this study is suitable for patients with UC worldwide. Fourth, there was no direct comparison between CCE-2 and CS findings in our study, by which the value of this study would be further increased. Finally, although endoscopic surveillance for colitis-associated cancer is another important issue in the management of UC, the end points of this study did not involve this as it requires tissue sampling for histology.

Nevertheless, despite the limitations and disadvantages of tissue sampling for histology, our study strongly suggests, even in small sample size, that CCE-2 with our regimen of bowel preparation showed high acceptability in UC patients and endoscopic activity by CCE-2 using MES and UCEIS was significantly associated with outcome in clinical remission. This painless, much less invasive tool may be routinely used instead of CS in the near future to monitor inflammation in UC patients, especially those in clinical remission.

ARTICLE HIGHLIGHTS

Research background

Mucosal healing is a newly established therapeutic goal in ulcerative colitis (UC). The accuracy of the second generation of colon capsule endoscopy (CCE-2) for assessment of mucosal inflammation in UC appears to be comparable with that of colonoscopy (CS). It remains unclear which UC patients may benefit from the use of CCE-2, and whether evaluating endoscopic activity using CCE-2 is able to predict outcome. Further, a standard preparation regimen validated for UC patients in clinical remission has not been established.

Research motivation

Conventional CS has several limitations, such as adverse events and low patient compliance. To clarify the usefulness of less-invasive CCE-2 would

provide a new option in clinical practice in UC patients.

Research objectives

To assess the feasibility of CCE-2 with a novel reduced-volume regimen in patients with UC in clinical remission, and to examine whether evaluation of endoscopic activity by CCE-2 is able to predict outcome.

Research methods

The study was conducted as single-center, prospective setting. A total of 30 consecutive patients were enrolled. CCE-2 performance was evaluated, and acceptability was assessed using a questionnaire survey. Endoscopic activity was assessed according to both Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS).

Research results

The rate of total colon observation was 93.3% and the proportion of "excellent" plus "good" cleansing level was 73.3% with the reduced-volume regimen. The relapse-free survival rate was significantly correlated with MES and UCEIS, whereas it was not correlated with clinical activity index. A questionnaire survey revealed an overall acceptability of CCE-2.

Research conclusions

CCE-2 was acceptable for UC patients in clinical remission. Evaluating mucosal healing using CCE-2 was able to predict outcome.

Research perspectives

Despite the small sample size, this study certainly suggested the usefulness of CCE-2 in UC patients in clinical remission. CCE-2 could serve as an alternative modality to CS for follow up of UC. Further extensive study with a larger sample size is expected to be conducted to spread this novel modality widely.

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META-ANALYSIS

Probiotic Medilac-S® for the induction of clinical remission in a Chinese population with ulcerative colitis: A systematic review and meta-analysis

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Author contributions: Sohail G and Xu X contributed to acquisition of data, interpretation of data, drafting and revising the article; Christman MC contributed to analysis and interpretation of the data, drafting and revising the article; Tompkins TA contributed to study concept, data evaluation, critical revisions; final manuscript as submitted was reviewed and approved by all authors.

Conflict-of-interest statement: Sohail G, Xu X and Tompkins TA declare that they are paid employees of Lallemand Health Solutions Inc. (Montreal, QC), a company that studies, manufactures and sells probiotics globally, business-to-business, but not to consumers.

PRISMA 2009 Checklist statement: This systematic review with meta-analysis was prepared and revised according to the PRISMA 2009 guidelines and checklist.

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Abstract

AIM

To assess the effects of probiotic Medilac-S® as adjunctive therapy for the induction of remission of ulcerative colitis (UC) in a Chinese population through a systematic review and meta-analysis.

METHODS

A systematic literature search was conducted to find randomized, controlled trials in a Chinese population with at least two study arms - a control arm which receives a conventional, oral aminosalicylate drug, and a treatment arm, which administers the same conventional drug in conjunction with the probiotic Medilac-S® *per os*. Both English and Chinese databases were searched, including PubMed, EMBASE, Google Scholar, Chinese National Knowledge Infrastructure, Wanfang Data, and VIP Search, and study data was extracted onto standardized abstraction sheets. Meta-analyses were conducted for primary and secondary outcomes of interest using a fixed or random effects model. The primary outcome was the induction of clinical remission and the secondary outcomes included changes in Sutherland index, endoscopic and histological scores, proportion of reported clinical symptoms and adverse events (AEs). For outcomes with sufficient data, the type of conventional

drug therapy was also assessed to determine if the effects of combination therapy with Medilac-S® was influenced by drug type. All tests were conducted using a type Ⅰ error rate of 0.05 and all confidence intervals (CI) were based on a 95% confidence level. Review protocol was uploaded to PROSPERO (CRD42018085658 upon completion).

RESULTS

Fifty-three clinical trials with a total of 3984 participants were identified and included in the review. Medilac-S® adjunctive therapy significantly improved induction of clinical remission (RR = 1.21; 95%CI: 1.18-1.24; $P < 0.0001$) with the estimated likelihood of effective treatment, on average, 21% higher for those consuming the probiotic. Sutherland index scores showed the control mean was on average 3.10 (CI: 2.41-3.78; $P = 0.0428$) units greater than the treatment mean, thereby demonstrating significant improvement in participants taking the probiotic. Similarly, a significant difference was seen between the overall reduction of endoscopic and histological scores of control and treatment arm participants, with score decreases in the control groups 0.71 (CI: 0.3537-1.0742) and 1.1 (CI: 0.9189-1.2300) units smaller than treatment group score decreases. The proportion of participants reporting clinical symptoms, (abdominal pain, tenesmus, blood and mucous in stool, and diarrhea) was significantly reduced after combination therapy with Medilac-S® ($P < 0.0001$) and estimated to be on average 44% (RR = 0.44, CI: 0.32-0.59), 53% (RR = 0.53, CI: 0.38-74), 40% (RR = 0.40, CI: 0.28-0.58) and 47% (RR = 0.47 CI: 0.36-0.42) respectively, of the proportion of individuals reporting the aforementioned symptoms after conventional therapy alone. The risk of AEs was also significantly reduced with adjunctive Medilac-S® therapy. The proportion of individuals in the treatment groups reporting AEs was an estimated 72% of the proportion of individuals in the control groups reporting AEs (RR = 0.72, CI: 0.55-0.94, $P = 0.0175$). Upon comparing effect means for different drug types in conjunction with Medilac-S®, evidence of significant variability ($P < 0.0001$) was observed, and sulfasalazine was found to be the most effective drug in both primary and secondary outcomes.

CONCLUSION

Evidence suggests Medilac-S® adjunctive therapy should be considered standard care for UC in a Chinese population because it aids in the induction of clinical remission, improves symptoms of the gastrointestinal tract and reduces risk of AEs.

Key words: Clinical remission; Systematic review; Meta-analysis; Mesalazine; Sulfasalazine; Ulcerative colitis; Medilac-S®

Core tip: Growing evidence demonstrates the important role of probiotics in the treatment of ulcerative colitis (UC), however past reviews evaluating the efficacy of probiotics as UC treatment often demonstrate significant heterogeneity, making it difficult to interpret results accurately. In this systematic review and meta-analysis, only one disease state, one probiotic and one population are reviewed and a focused analysis is conducted on the effects of the probiotic Medilac-S® in conjunction with conventional drug therapy to improve symptoms of UC and induce clinical remission within a Chinese population.

Sohail G, Xu X, Christman MC, Tompkins TA. Probiotic Medilac-S® for the induction of clinical remission in a Chinese population with ulcerative colitis: A systematic review and meta-analysis. *World J Clin Cases* 2018; 6(15): 961-984 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/961.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.961

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) of the colonic gastrointestinal (GI) tract, characterized by chronic, recurring inflammation, irritation and the formation of ulcers on the inner lining of the large intestine[1]. While the etiology of UC remains unknown, growing evidence suggests a connection between UC pathogenesis and host-specific microbial composition changes within the colonic environment[2].

The average human GI tract contains an estimated 1000 bacterial species[3], which form the microbial communities involved in regulating various aspects of normal host physiology, including host nutrition and metabolism, protection against pathogens and immunomodulation[4]. Recent studies show the enteric microbiota play a fundamental role in the onset of GI disorders, including IBD, as a result of overly aggressive immune responses to the natural microflora in genetically predisposed individuals[1,2]. The immune response may result in loss of the natural balance of intestinal microbiota, commonly known as gut dysbiosis[5].

Traditionally, IBD has been categorized as a disease of the western and developed world[6]. However, incidence rates are increasing across the globe, particularly in Asian countries, such as China, where rapid industrialization and urbanization are also thought to be contributing factors in growing UC onset[7].

Several pharmacological anti-inflammatory therapies, such as corticosteroids and aminosalicylates, have been at the forefront of UC therapy for a number of decades[8]. However, evidence for the critical role of intestinal microflora in UC pathogenesis[2,9] has led researchers to suggest the development and use of alternative therapies, such as probiotics, for the management and treatment of UC[10].

Probiotics are defined by the WHO as live microorganisms which confer health benefits to the host when administered in adequate amounts[11]. In clinical

and pre-clinical studies, probiotics have been shown to stimulate anti-inflammatory effects by influencing inflammatory cytokine levels and aiding in the production of mediators involved in gut permeability regulation[12,13]. As such, probiotics may be used to modify the gut microbiota towards a more remedial composition to control mucosal inflammation and decrease symptoms of UC[12,13].

Several systematic reviews and meta-analyses have shown specific probiotics can improve rates of symptom remission and maintenance in patients with UC[14-17]. A meta-analysis completed in 2013[15], and another in 2017[18], revealed that the use of the probiotic VSL #3 significantly improved remission rate in UC patients. An older study completed in 2004 found the probiotic preparation of *Escherichia coli* Nissle 1917 to be as effective as the 5-aminosalicylic acid (5-ASA) mesalazine in maintaining remission in patients with UC[18].

A number of clinical studies completed in China have also provided evidence for probiotics as effective agents in the induction and maintenance of UC symptoms; however the primary focus has been on the probiotic formulation Medilac-S®. Medilac-S® is sold by Hanmi Pharmaceuticals in Asia, primarily China and South Korea, where it is registered as a pharmaceutical. It is composed of two probiotic bacteria, *Enterococcus faecium* R0026 and *Bacillus subtilis* R0179, at a ratio of 90:10 respectively. This product has also been used in other applications, such as the management of symptoms of irritable bowel syndrome, acute gastritis, liver cirrhosis and improving outcomes associated with *Helicobacter pylori* therapy[19].

These Chinese clinical studies were conducted in accordance with guidelines from the Chinese Society of Gastroenterology[20-23] and demonstrate unique uniformity amongst trial designs and populations. The level of homogeneity allows for more accurate comparisons and data analysis of pooled study results, however the studies are rarely published in international or English journals, making it more difficult for the global research community to gain further insight.

Only one systematic review and meta-analysis, published in a Chinese journal by Hu *et al*[24], has, to date, discussed the efficacy of the probiotic Medilac-S® on the induction and maintenance of remission in UC patients. The review includes 24 randomized, controlled trials (RCTs), which compare conventional therapy, such as pharmacological or herbal Chinese interventions, to combination therapy with Medilac-S® and the same conventional therapy used as a control. Studies showed significant improvements in the induction and maintenance of remission in participants treated with Medilac-S® combination therapy. Since the review's publication, a large number of new studies have been published and remain to be evaluated in a meta-analytic setting. Results presented in the past review, although promising, had a limited bias analysis, poorly defined meta-analytic procedures and grouped together studies using various concomitant treatments (orally and rectally administered). Therefore, in this study, our primary aim was to conduct an up-to-date systematic review and meta-analysis, taking into account the totality of the published evidence, to assess the efficacy of Medilac-S® as an adjunctive to conventional oral aminosalicylates for the induction of UC symptom remission within a Chinese population. We focused on the use of oral pharmaceuticals as concomitant therapies, as opposed to herbal remedies or enemas, due to ease of practical use and global clinical application. In addition, we wished to present our findings in an English-speaking journal which is more readily accessible by the international community. Analysis was limited to induction of remission and improvement of physician assessed and patient reported symptoms, as evaluated by scoring indices and patient reports.

MATERIALS AND METHODS

The review protocol for this systematic review with meta-analysis was run according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[25] and registered in PROSPERO (CRD42018085658). It can be accessed at the following web address: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID = 85658.

Search strategy

Using combinations of the key words and terms described below, the following online databases were searched for RCTs (2000–2017): Google Scholar (last searched - July 17th 2017; https://scholar.google.ca/) PubMed (last searched - August 5th 2017; https://www.ncbi.nlm.nih.gov/pubmed/); EMBASE (last searched - August 18th 2017; https://www.elsevier.com/solutions/embase-biomedical-research) and the Cochrane Database of Systematic Reviews (last searched-August 18th 2017; http://onlinelibrary.wiley.com/cochranelibrary/search/).

Similarly, combinations of English and Chinese search terms were used for the following Chinese databases: China National Knowledge Infrastructure (last searched - July 22nd 2017; http://oversea.cnki.net/) VIP Search (last searched - October 27th 2017; http://en.cqvip.com/index.html); Wanfang Data (last searched - October 27th 2017; http://www.wanfangdata.com/); Chinese Biomedical Database (last searched - October 27th 2017; http://www.imicams.ac.cn), and the Chinese Clinical Trial Registry (last searched October 27th 2017; http://www.chictr.org.cn/enIndex.aspx).

English search terms included any of the following: Ulcerative colitis, Medilac-S®, probiotics, mesalazine, sulfasalazine, olsalazine, MeiChangAn, microecological preparation, *Bacillus subtilis*, *Enterococcus faecium*, randomized and controlled.

The following Chinese search terms were also used: Probiotic, microecological preparation, *Bacillus subtilis*, *Enterococcus faecium*, ulcerative colitis, random, control,

MeiChangAn, mesalazine, olsalazine, sulfasalazine.

Selection criteria

Study selection was independently performed by two authors (Ghania Sohail and Xiaoyu Xu) using a pre-specified selection criterion for published or unpublished RCTs completed in China between 2000-2017, which evaluate the efficacy of the probiotic Medilac-S® in reducing symptoms of mild, moderate or severe UC in Chinese patients. No language or study size restrictions were made.

Titles and abstracts of the literature were first reviewed to exclude all irrelevant studies, and after obtaining the full text of any remaining studies, a finalized list was identified and cross-examined with the inclusion/exclusion criteria. Discrepancies between the selection of studies were resolved through discussion between the two authors. If resolution was not possible, a third reviewer (TT) was consulted.

No age or gender restrictions were placed on participants within the trials and no trials exclusively conducted on infants or children were included. All included studies had at least two comparable study arms - a control arm which received only conventional oral medication (aminosalicylates), and a treatment arm which administered the same conventional medication used in the control in combination with the probiotic Medilac-S® *per os*. No restrictions were placed on the dose of conventional medication or probiotic given to participants.

Additionally, articles were included if they provided at least one study outcome measurement as follows: Clinical remission, changes in patient-reported clinical symptoms, maintenance of remission and relapse rate, Sutherland index, adverse events (AEs), endoscopic assessment, and/or histological assessment.

RCTs which described only concurrent therapy with traditional Chinese medicines or different probiotics in all study arms were excluded. Studies reporting only unconventional primary endpoints inappropriate for assessment of UC disease activity, such as microflora counts, or which did not provide sufficient details on patient selection or study outcomes were also excluded.

Data extraction

Independent data extraction was performed by two review authors (Ghania Sohail and Xiaoyu Xu) using a standardized Microsoft Excel file. The original extraction file included the following: Authors and journal details, start and end dates, study design, probiotic and comparator with route of administration, probiotic dose with regime and duration, participant enrollment, gender by study arm, primary objective, follow-up, study outcome measurement types, study results, AEs, and diagnostic criteria assessment guidelines used.

Study outcome measurement data were independently extracted by the two review authors (Ghania Sohail and Xiaoyu Xu) on separate Microsoft Excel sheets. For each outcome, extraction sheets varied to reflect the specific types of data presented. An attempt was made to contact study authors to collect any possible missing data. Discrepancies between the extracted data were resolved through discussion between the two authors. If resolution was not possible, a third reviewer (TT) was consulted.

Outcome assessments

Primary outcome: The primary outcome of this systematic review and meta-analysis is an evaluation of the induction of remission in patients with UC within a Chinese population. Studies adhere to the definitions of clinical efficacy stated in the guidelines from the Chinese Society of Gastroenterology[20-23] which evaluate changes in clinical symptoms, changes to mucosal inflammation identified through colonoscopy, and, in some instances, the number of stools per day and blood in stool.

Secondary outcomes: The effects of the probiotic Medilac-S® in combination therapy with conventional oral medication was also assessed for the following secondary outcomes: Sutherland Index score, physical changes in the GI tract through endoscopic and histological assessments, the proportion of patient-reported clinical symptoms of UC, including abdominal pain, diarrhea, tenesmus and mucous and/or blood in stool, and the evaluation of AEs in treatment and control groups.

Assessment of study quality and risk of bias

To adhere to the PRISMA guidelines, studies were independently reviewed by two review authors (Ghania Sohail and Xiaoyu Xu) for risk of bias using the approaches for assessing and assigning risk described in the Cochrane Handbook[26]. Bias due to systematic differences among treatment groups was assessed using review of the following categories: (1) Random Sequence Generation - the randomization scheme for assigning subjects to treatments; (2) Allocation Concealment - the randomization scheme for assigning treatments to the subjects; (3) Performance Bias - blinding of study subjects to the actual interventions; (4) Detection Bias - blinding of study personnel and data analysts to the actual interventions; (5) Attrition Bias - whether loss of data due to attrition of subjects is due to a missing completely at random mechanism or is non-ignorable; (6) Reporting Bias - whether results of the outcomes were pre-specified and reported fully; and (7) Other - whether any other possible sources of bias exist within studies.

Studies were assigned an overall level of risk of bias (low, high, unclear) for each outcome of interest based on a subjective review by the investigators (Ghania Sohail and Xiaoyu Xu). Discrepancies between the assessment of risk were resolved through discussion between the two reviewers, and if resolution was not possible a third reviewer (TT) was consulted.

Publication bias

Publication bias, such as bias in the meta-analysis results due to unreported data, was assessed with a funnel plot showing the relationship of the effect size [log(RR)] and its standard error (SE) among studies. Kendall's tau, a rank correlation test, was used to test for a correlation between the effect size and SE. Additionally, the trim and fill method of Duval and Tweedie[27,28] was used to estimate the number of studies missing from the meta-analysis due to possible suppression of more extreme results. This method augments the observed data so that the funnel plot is more symmetric and identifies the likely number of missing studies that would symmetrize the funnel plot. The method can only be applied to models without moderators and was therefore run on the simple fixed effects model.

Data synthesis and statistical analysis

Meta-analyses were conducted for each outcome of interest, using a random effects model if heterogeneity was found to be significant, or a fixed effects model if no heterogeneity was observed among the studies. Heterogeneity was tested using the standard measure of inconsistency, I^2, and a review of the *P*-value of the chi-square test for the random effect of study. For outcomes with sufficient data, a moderator variable for the type of conventional therapy (drug type) was added to the meta-analytic model to determine whether the difference in effect size between the control and treatment groups depended on the type of drug used in combination with Medilac-S®.

Outcomes of interest were either binary categorical variables (*e.g.,* clinical remission) which were analyzed using risk ratios (RRs), or continuous variables (*e.g.,* histology scores) for which the mean difference was used. The RRs were natural logarithm transformed before analysis and results are reported as back-transformed RRs. For some outcomes (*e.g.,* clinical symptoms) data at baseline as well as after intervention were reported, so a meta-analysis for baseline differences in the outcome was first assessed. If the treatment group effect size at baseline was not statistically significantly different, the meta-analysis for mean differences was performed for outcomes reported at the end of the intervention period. If the test for the treatment group effect size at baseline was statistically significant, then the difference in effect size from baseline was compared between the two treatment groups (the difference of differences).

All tests were conducted using a type I error rate of 0.05 and all confidence intervals (CIs) are based on a 95% confidence level. All analyses were conducted using the Metafor package[29] in R: A Language and Environment for Statistical Computing[30]. The statistical methods of this study were conducted and reviewed by Dr. Mary Christman from MCC Statistical Consulting.

RESULTS

Study selection

A flow diagram, in adherence with PRISMA guidelines, summarizing the screening of studies can be found in Figure 1. A total of 404 studies were identified from a literature search completed using both English and Chinese databases. After screening study titles and abstracts against basic eligibility criteria and searching for duplicates, 325 studies were discarded and 79 studies remained. Further screening of the study titles, abstracts and obtaining of the full study text eliminated 19 additional studies. After review of the full study texts of 60 articles, seven were eliminated and 53 RCTs were identified as eligible for the review[31-83]. The remaining 26 articles were excluded for various reasons. The rationale for exclusion of the 26 studies is found in Supplementary Table 1.

Study characteristics

The 53 Chinese RCTs included 3984 participants in our review, with 1985 and 1999 participants in control and treatment arms respectively. All studies contained a control arm, providing only conventional oral medication (aminosalicylates), and a treatment arm providing the same conventional medication with Medilac-S®. Treatment periods ranged from 4 to 96 wk. Twelve studies included a third study arm[35,47,55,60-62,66,70,72,77,82,83] which was not incorporated into the study analysis as a comparator because it incorporated the use of a different probiotic product, an herbal remedy and/or an enema. Nine studies included a post-treatment follow-up period of 8, 26 or 52 wk to track the maintenance of symptom remission[32,39,44,48,53,57,63,68,74] and one study, by Wang *et al*[66] 2016 evaluated the maintenance of remission alone. Most studies[31,33-37,40,41,43-48,51,53-57,59-62,65-67,69,71-77,79-83] included participants with mild-to-moderate UC symptoms (75.4%; 40/53), one study included participants with severe UC[49] and the remaining studies[32,38,39,42,50,52,58,63,64,68,70,78] did not describe the severity of all participants, however the levels of severity between control and treatment groups at baseline were stated as not significantly different. Study characteristics and outcomes are presented in Table 1.

Risk of bias in included studies

Results of the risk of bias analysis are presented in Figure 2. Although all included trials are RCTs, most fail to report the method used for randomization, resulting in unclear risk of bias in 77.4% (41/53) of studies[31-34,36,38,40-44,46-52,54,55,57-59,62-71,73,74,76,77,80-83]. The twelve remaining studies report appropriate methods to randomize participants, such as random number tables, and are ranked as low risk of bias for random sequence generation[35,37,39,45,53,56,60,61,72,75,78,79].

Only 7.55% (4/53) of studies report the implemented levels of blinding[40,56,60,61]. These four studies reported a blind assessment of participant samples, thereby receiving a low risk of detection bias rating. No other forms of blinding for participants, personnel or assessors were reported, nor was allocation concealment reported in any studies, resulting in unclear levels of bias for allocation concealment and detection bias amongst all studies.

Table 1 Characteristics of included studies

Trial reference	Participants evaluated	Medication	Probiotic dose	Treatment duration	Follow-up period	Outcomes analyzed
Bu *et al*[31] 2017	68	Mesalazine	3.0×10^9 cfu/d	16 wk	NR	1, 6
Chen[32] 2007	47	SASP	3.0×10^9 cfu/d	12 wk	26 wk	1, 4, 5, 6
Chen[33] 2014	100	Mesalazine	3.0×10^9 cfu/d	6 wk	NR	1, 4
Chen *et al*[34] 2017	68	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	1, 6, 7
Duan *et al*[35] 2015	64	SASP	3.0×10^9 cfu/d	4 wk	NR	2, 3, 6, 7
Gu[36] 2012	62	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Guo and Sun[37] 2009	92	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
He *et al*[38] 2016	52	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Jiang[39] 2013	110	Mesalazine	3.0×10^9 cfu/d	16 wk	52 wk	1, 5, 6
Jin *et al*[40] 2014	226	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Li[41] 2011	62	Mesalazine	60 mg/d	12 wk	NR	1
Li[42] 2013	124	SASP	3.0×10^9 cfu/d	12 wk	NR	1, 6
Li[43] 2014	147	SASP	3.0×10^9 cfu/d	4 wk	NR	1
Li *et al*[44] 2006	50	SASP	3.0×10^9 cfu/d	12 wk	26 wk	1, 5
Li *et al*[45] 2016	100	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	1, 4, 6
Liang *et al*[46] 2016	92	Mesalazine	3.0×10^9 cfu/d	16 wk	NR	1
Liu[47] 2014	62	SASP	3.0×10^9 cfu/d	4 wk	NR	1, 2, 3
Liu and Yao[48] 2012	139	Mesalazine	3.0×10^9 cfu/d	unknown	unknown	1, 5
Liu *et al*[49] 2009	43	SASP	3.0×10^9 cfu/d	8 wk	NR	1, 6
Liu and Li[50] 2014	101	Mesalazine	3.0×10^9 cfu/d	6 wk	NR	1, 2, 4
Luo[51] 2016	56	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	1, 4, 6
Lu and Lei[52] 2011	132	Olsalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Miao[53] 2014	72	Mesalazine	3.0×10^9 cfu/d	8 wk	26 wk	1, 5, 6
Meng[54] 2012	90	SASP	3.0×10^9 cfu/d	8 wk	NR	1, 2
Qin[55] 2015	56	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	4
Qin *et al*[56] 2010	20	SASP	3.0×10^9 cfu/d	4 wk	NR	3, 7
Qin *et al*[57] 2010	64	Mesalazine	3.0×10^9 cfu/d	8 wk	26 wk	5, 6
Shen[58] 2014	96	Mesalazine	3.0×10^9 cfu/d	6 wk	NR	1, 4, 6
Su[59] 2015	120	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Tan *et al*[60] 2008	20	SASP	3.0×10^9 cfu/d	4 wk	NR	2, 3, 6, 7
Tan *et al*[61] 2014	20	SASP	3.0×10^9 cfu/d	4 wk	NR	2, 3, 6, 7
Tang[62] 2008	104	SASP	3.0×10^9 cfu/d	4 wk	NR	1
Wang[63] 2013	84	Mesalazine	3.0×10^9 cfu/d	16 wk	52 wk	1, 5
Wang and Liu[64] 2007	36	SASP	3.0×10^9 cfu/d	4 wk	NR	1, 6
Wang and Li[65] 2014	100	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	1, 2
Wang *et al*[66] 2016	65	Mesalazine	3.0×10^9 cfu/d	26 wk	NR	5, 6
Xiang and Feng[67] 2006	46	SASP	3.0×10^9 cfu/d	4 wk	NR	1, 4, 6
Xiao[68] 2014	63	SASP	3.0×10^9 cfu/d	8 wk	8 wk	5, 6
Xu[69] 2014	60	Balsalazide	3.0×10^9 cfu/d	12 wk	NR	1, 4, 6
Xu and Cui[70] 2009	56	Mesalazine	3.0×10^9 cfu/d	4 wk	NR	1
Yang[71] 2014	80	Mesalazine	3.0×10^9 cfu/d	Unknown	NR	1
Yang *et al*[72] 2008	52	SASP	3.0×10^9 cfu/d	4 wk	NR	1
Yuan *et al*[73] 2008	40	SASP	3.0×10^9 cfu/d	12 wk	26 wk	1, 4, 6
Zeng[74] 2008	49	SASP	3.0×10^9 cfu/d	12 wk	NR	1, 5
Zhang[75] 2013	78	SASP	3.0×10^9 cfu/d	4 wk	NR	1, 4, 6
Zhang[76] 2013	68	Olsalazine	3.0×10^9 cfu/d	12 wk	NR	1, 6
Zhang *et al*[77] 2010	54	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1
Zhang *et al*[78] 2016	70	Mesalazine	60 mg/d	12 wk	NR	1
Zhang *et al*[79] 2016	60	Mesalazine	3.0×10^9 cfu/d	12 wk	NR	1
Zhao and Zhang[80] 2016	62	Mesalazine	3.0×10^9 cfu/d	24 wk	NR	1
Zheng *et al*[81] 2016	118	Mesalazine	3.0×10^9 cfu/d	4 wk	NR	1, 6
Zhu *et al*[82] 2013	44	Olsalazine	3.0×10^9 cfu/d	96 wk	NR	2, 3
Zhuo *et al*[83] 2016	40	Mesalazine	3.0×10^9 cfu/d	8 wk	NR	1, 3, 6

Outcomes analyzed: (1) Clinical Efficacy; (2) Histological Assessment; (3) Endoscopy Assessment; (4) Clinical Symptoms; (5) Maintenance of Remission; (6) Adverse Events; (7) Sutherland Index. NR: Not reported.

After evaluating for incomplete outcome data and selective reporting, 83.0% (44/53) of studies[31-41,44-49,51-55,62-65,67-81,83] were ranked as low risk of attrition bias and 81% (43/53) of studies[32,34-47,49-51,55,56,58-62,64,66-82] were ranked as low risk of reporting bias. Three trials[42,43,50] were rated as high risk of attrition bias because of inconsistencies in subject reporting and the remaining six studies[56,57,60,61,66,82] were rated as unclear risk of attrition bias due to missing information regarding possible participant withdrawal. The ten studies[31,33,48,52-54,57,63,65,83] which were not ranked as low risk of reporting bias were rated as high risk of reporting bias because results were either reported without pre-specification or expected outcomes failed to be included.

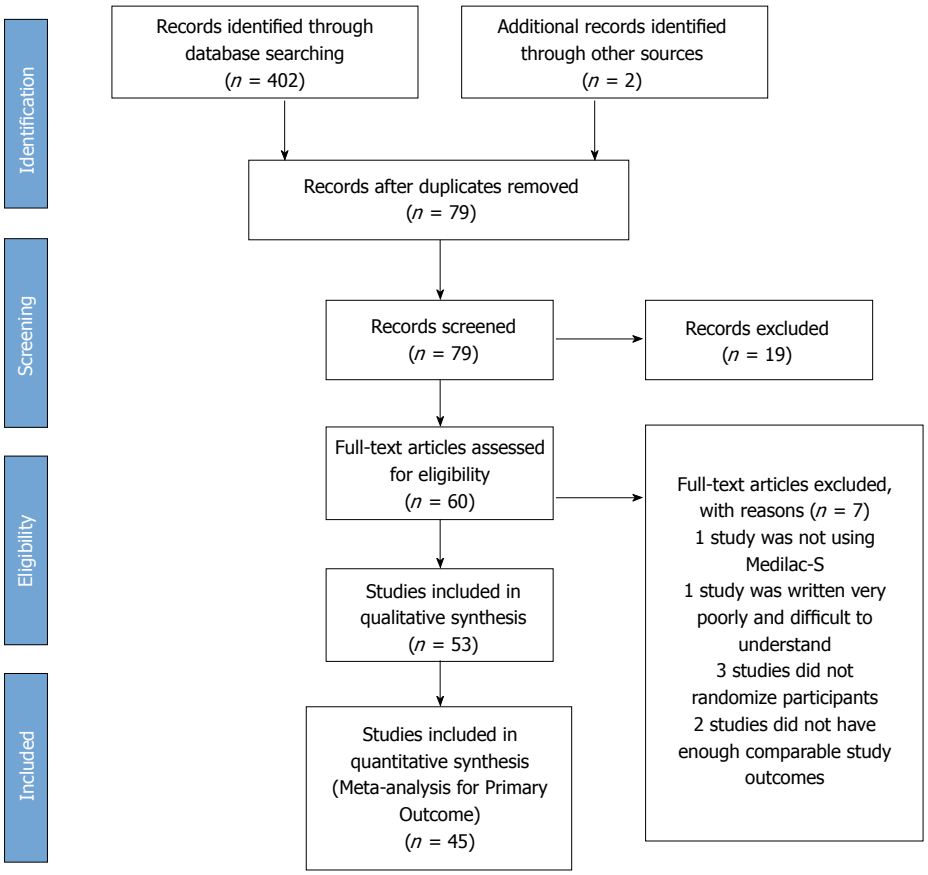


Figure 1 Study selection flow diagram.

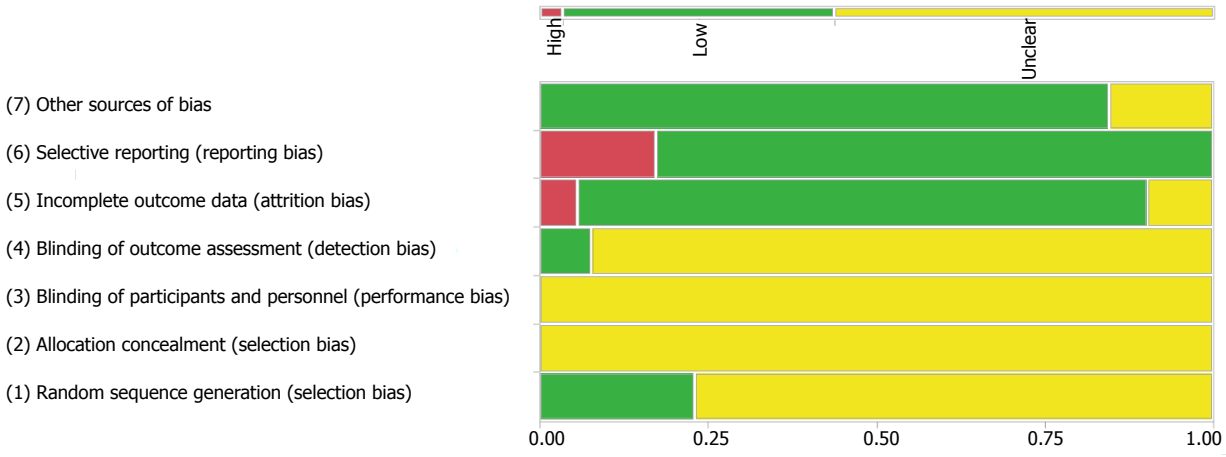


Figure 2 Risk of bias mosaic plot showing proportion of studies deemed to be at high (red), unclear (yellow) or low (green) risk in each bias category.

Other potential sources of bias included an evaluation of the characteristic similarity and prognostic indicators of disease at baseline in study groups. In trials of UC, it is important for studies to limit significant differences between disease severity of participants at baseline because the medication and dosage differ for those suffering from varying stages of disease, ranging from mild and moderate to severe. Most studies[31-43,45-49,52,54-56,58,59,61,63-71,75-83] (83.0%; 44/53) highlighted no significant differences between the control and treatment groups at baseline, thereby being labelled as low risk bias. The nine remaining studies not ranked as low risk of bias[44,51,55,57,60,62,72-74] had insufficient information to determine the presence of other types of bias and therefore are ranked as unclear risk. Overall, studies were better ranked in their provision of study results and participant withdrawals, and were ranked more poorly in their explanation of randomization techniques blinding.

Effects of intervention - primary outcome

Clinical remission: Forty-six studies reported clinical

remission as a primary outcome, however, only 45 studies[31-34,36-55,58,59,62-65,67,69-81,83] were included in the meta-analysis because one study[57] failed to report enough data. Studies included 3624 participants, with 1808 in the control group and 1816 in the treatment group. The proportion of subjects for which the treatment was effective was analyzed, with "effective" defined as any response not considered "ineffective"-including participants with "completely effective", "very effective" or "somewhat effective" responses. Further analysis was then conducted by comparing induction of clinical remission using specific drug-probiotic combinations to assess the most effective combination. One study used balsalazide as the conventional drug[69], two studies used olsalazine[52,76], 14 studies used SASP[32,42,43,45,47,49,54,62,64,67,72-75] and 28 studies used mesalazine[31,33-41,44,46,48,50,51,53,55-61,63,65,66,68,70,71,77-84].

The first analysis with the 45 studies was conducted using a fixed effects model since the test for heterogeneity was not significant (P = 0.8102). Results showed a positive effect of Medilac-S® treatment (RR = 1.21, CI: 1.18-1.24, P < 0.0001) with the "risk" of treatment being effective estimated to be, on average, 21% higher for those on combination Medilac-S® therapy, than conventional drug therapy alone.

Upon comparing effect means for different drug types, evidence of significant variability (P < 0.0001) was seen. In the balsalazide study the predicted mean RR was the same as in the study, RR = 1.21 (CI: 1.00-1.46). In studies using olsalazine, the estimated mean was RR = 1.25 (CI: 1.10-1.42). Finally, the estimated mean RR for SASP drug therapy was RR = 1.26 (CI: 1.19-1.33) and the mean RR for mesalazine was RR = 1.19 (CI: 1.15-1.23) (Figure 3). Since there were sufficient numbers of studies using mesalazine and SASP, further comparison of the mean effect sizes was performed, and a significant difference between mean effect sizes of studies using mesalazine and SASP was observed (P < 0.0001), with SASP outperforming mesalazine.

Publication bias: A funnel plot was constructed based on the results of the fixed effects model with drug type moderator (Figure 4). A rank correlation test, Kendall's tau, tested for asymmetry in the plot by evaluating whether the observed effect sizes and the corresponding sampling errors are correlated. Kendall's tau was 0.5366 (P < 0.0001), providing strong evidence of publication bias. The funnel plot suggests a few studies with smaller sample size present larger SEs for Medilac-S® consumption with greater RR values than studies with larger sample sizes.

In addition, the number of missing studies from the meta-analysis due to the suppression of the more extreme results to one side of the funnel plot, were estimated using the trim and fill method of Duval and Tweedie[27,28]. Results indicate that the funnel plot would be made symmetric with the addition of 18 (SE = 4.0663) studies on the left side of the plot. With the addition of the studies, the average log(RR) would decrease to approximately 0.16 (SE = 0.0128; estimated RR = 1.17), which still indicates a positive impact of adding Medilac-S® to conventional drug therapy.

Effects of intervention - secondary outcomes

Sutherland index: A mixed effects meta-analysis was completed on six studies[34,35,47,57,60,61] to evaluate changes in the Sutherland index score, comprised of three clinical symptom scores (stool frequency, rectal bleeding and mucosal appearance) and a physician's global rating of disease. Analysis was also conducted with a moderator variable for drug type to determine which drug-probiotic combination is most effective in improving the Sutherland index score. Studies included 254 participants, with 127 participants in both control and treatment groups. One study used mesalazine as concomitant medication[34] and five studies used SASP[35,433,56,60,61].

The effect size analyzed is the difference in means between treatment and control groups at the end of the intervention period because no differences were found between groups at baseline using the random effects model without the moderator variable for conventional drug type (P = 0.9999). Differences were seen using a random effects model run on the post-intervention treatment group means, both with the moderator variable (P = 0.0428) and without (P = 0.0032).

Results indicate a positive effect of Medilac-S® treatment on the Sutherland Index. Without the moderator variable for conventional drug therapy, the mean difference between the control and treatment at the end of the intervention period was 3.10 (95%CI: 2.41, 3.78), indicating that the control mean is, on average, 3.10 units greater than the treatment arm. With the moderator variable, results suggest that the effect size may be drug-type dependent (P < 0.0001), with SASP outperforming mesalazine. The mean difference in the index between treatment and control arms was 3.33 (CI: 2.63-4.03) for the drug SASP and 2.25 (CI: 0.95-3.55) for mesalazine (Figure 5).

Endoscopy scores: Seven clinical studies[35,43,56,60,61,82,83] with 270 participants, 135 in both control and treatment arms, were included in a meta-analysis to evaluate changes in the endoscopic scores assessed using a Chinese version of the Modified Baron Score evaluating mucosal friability, hyperemia, granulation, spontaneous bleeding and ulceration[21,22,84]. Reporting was done as the average of the change in score. The effect size analyzed is the difference between treatment and control arms of the change in mean scores between final and baseline measurements. As the test for heterogeneity was significant (P = 0.0001), a random effects model was used for the analysis. Further analysis to determine if the results are dependent on concomitant drug therapy was not conducted due to

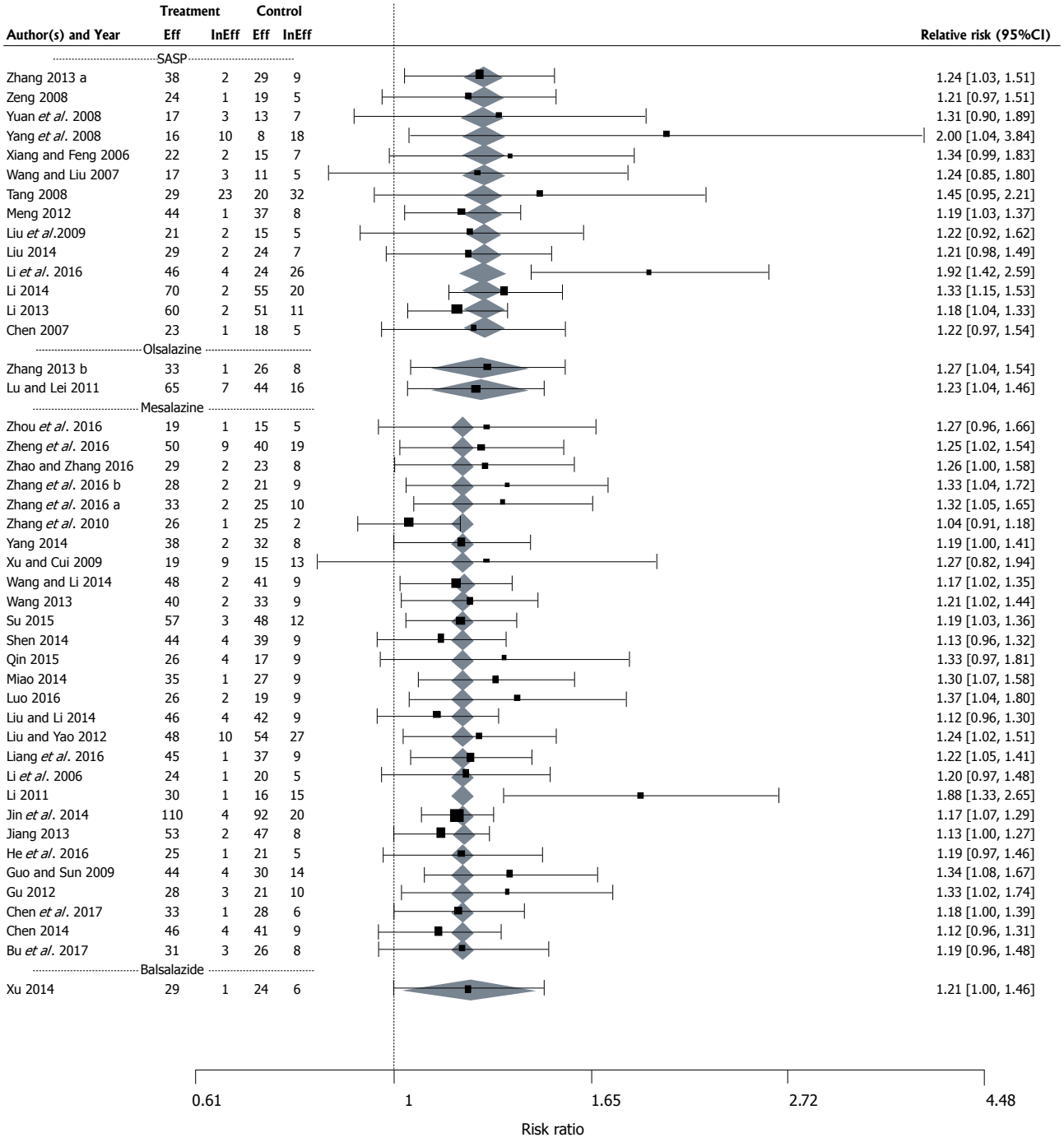


Figure 3 Forest plot of the results of a fixed effects meta-analysis with a moderator for concomitant drug therapy with 45 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on clinical efficacy. "Eff" is the number of subjects in the study for which the treatment was effective and "InEff" is the number of subjects in the study for which the treatment was ineffective. The relative risk (RR) and its 95%CI for each study are listed on the right hand side of the graph. The 95%CI for the estimated mean RR for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints and the location of the maximum width of the diamond being at the estimated mean RR for that drug type. The vertical dashed line at 1 indicates a RR of 1 which occurs when there is no observed difference between the treatment and the control.

insufficient data.

Results present a positive effect of Medilac-S® treatment for the improvement of the endoscopic score (P = 0.0001). The difference from baseline in the control and treatment arms was 0.7139 (95%CI: 0.3537-1.0742), indicating that the average decrease of endoscopy scores for the control arm was 0.71 units smaller than the average decrease of endoscopy scores for the treatment arm (Figure 6). The mean drop in scores for those in the control arm was approximately 1.01, while the mean drop for those on combination therapy was approximately 1.72.

Histological scores: Eight clinical studies[35,43,50,54,60,61,65,82] included 501 participants, with 251 in the control arm and 250 in the treatment arm, in a meta-analysis

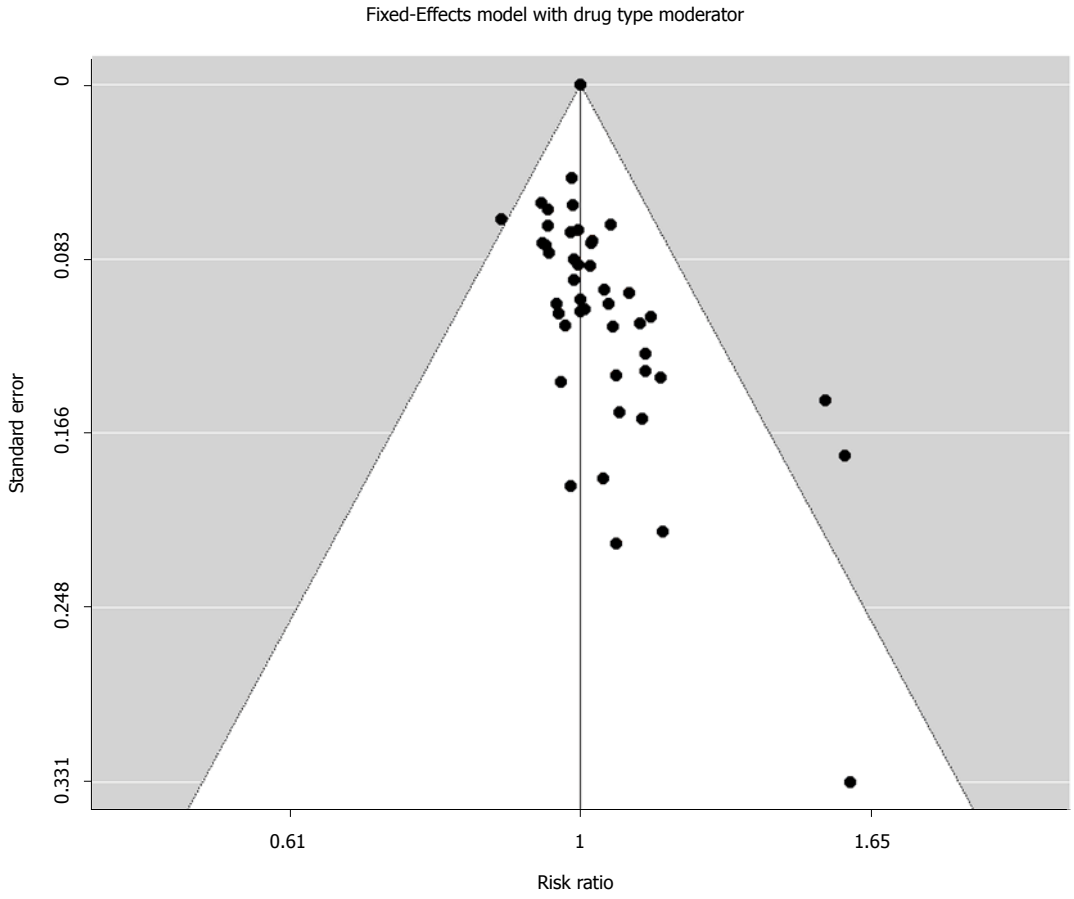


Figure 4 Funnel plot showing the relationship between the relative risk and its standard error for each of 45 studies used in a fixed effects meta-analysis with a moderator for concomitant drug therapy evaluating the effect of Medilac-S® in combination with conventional drug therapy on clinical efficacy.

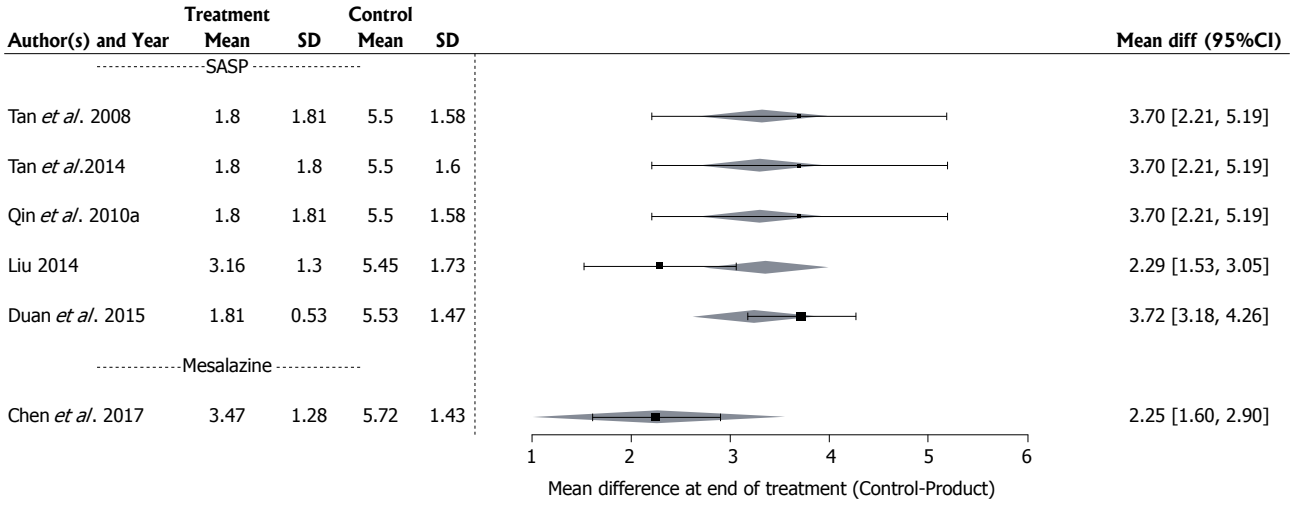


Figure 5 Forest plot of the results of a mixed effects meta-analysis with a moderator for concomitant drug therapy, with 6 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on the change in mean Sutherland index score evaluating three clinical symptoms and a global physician's assessment. "Mean" is the mean index and "SD" is the standard deviation for each study; the difference between the treatment and control of the mean indices at the end of the study and its 95%CI is listed on the right hand side of the graph; the 95%CI for the estimated mean difference for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints and the location of the maximum width of the diamond being at the estimated mean difference for that drug type.

to evaluate changes in the histological scores assessed using a Chinese version of the Truelove and Richards Index evaluating colonic histological specimens for inflammation and crypt distortion[21-22,85]. Reporting was done as the average of the change in score. The effect size used in the analysis is the difference between

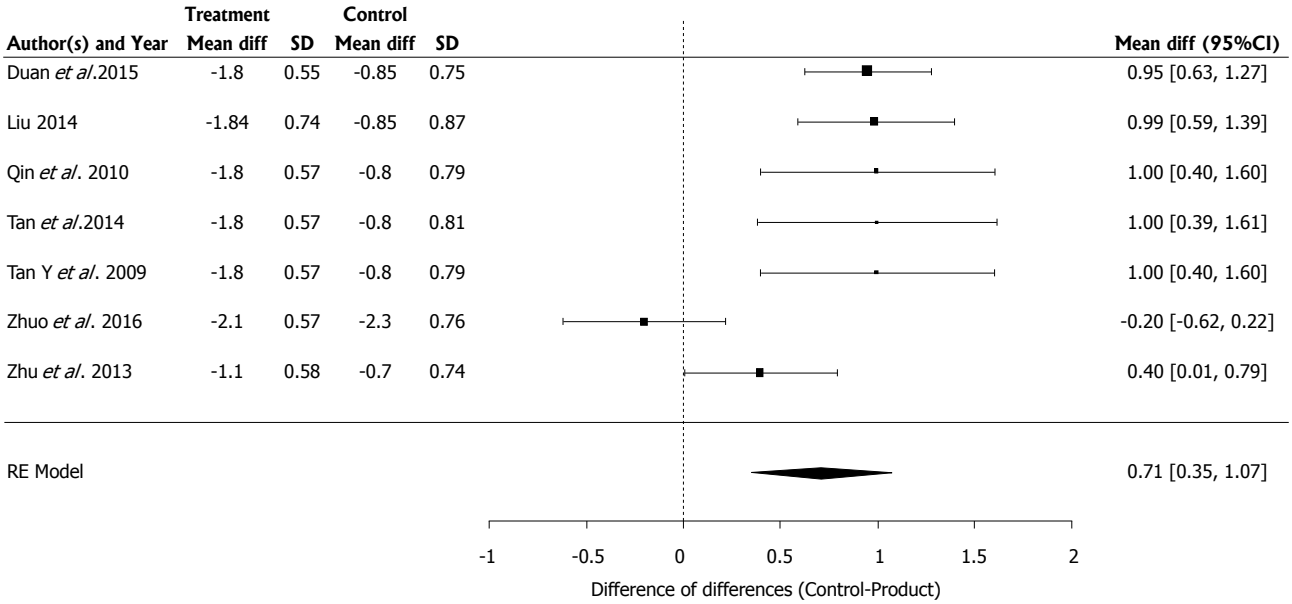


Figure 6 Forest plot of the results of a random effects meta-analysis with 7 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on the change in mean endoscopic score evaluating mucosal friability, hyperemia, granulation, spontaneous bleeding and ulceration. "Mean Diff" is the change of the treatment mean score from the baseline mean score and "SD" is the standard deviation of the mean change; the difference between the treatment and control of the change in the mean score and its 95%CI for each study is listed on the right hand side of the graph; the 95%CI for the estimated mean difference in the change from baseline for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints and the location of the maximum width of the diamond being at the estimated mean difference for that drug type; the vertical dashed line at 0 indicates a difference of 0 which occurs when there is no observed difference between the change from baseline for the treatment and the control.

treatment and control of the change in mean scores between final and baseline measurements. The test for heterogeneity was not significant (P = 0.8427) and so a fixed effects model was used for the analysis. Further analysis to determine if the results are dependent on concomitant drug therapy was not conducted due to insufficient data.

The test for difference between the change from baseline for treatment and control arms was significant (P < 0.0001) and favors results of Medilac-S® treatment. The difference in the change from baseline of the control and treatment arms was 1.07 (95%CI: 0.9189-1.2300) indicating that the average decrease in histology scores between baseline and final measurements for the control arm was approximately 1.1 units smaller than the average decrease between baseline and final measurements for the treatment arm (Figure 7). The mean drop in histology scores for those in the control arm was approximately 0.9 while the mean drop for those on treatment was approximately 1.9.

Clinical symptoms: A meta-analysis of 11 studies[32,33,45,50,51,55,58,67,69,73,75] was conducted to evaluate changes in any of the following patient-reported symptoms: Abdominal pain, tenesmus, blood and mucous in stool, and/or diarrhea. Analysis was also conducted with a moderator variable for drug type to determine which drug-probiotic combination was most effective in reducing clinical symptoms. Studies included 780 participants, with 386 participants in the control arm and 394 participants in the treatment arm.

The effect size is the ratio of the proportion of individuals reporting symptoms in the treatment group as compared to the proportion of individuals reporting symptoms in the control group. Values less than one for the RR or less than zero for log (RR) indicate that subjects receiving combination therapy with Medilac-S® have a lower probability of reporting clinical symptoms relative to subjects receiving drug therapy alone.

Using the random effects model, no significant differences were reported at baseline between control and treatment groups for any of the clinical symptoms and no significant evidence for heterogeneity was seen in the proportion of individuals reporting symptoms between treatment arms. Consequently, fixed effects models were used to identify variability in mean RRs after intervention.

Results of the fixed effects meta-analyses demonstrate a significant decrease (P < 0.0001) in the proportion of individuals reporting abdominal pain (RR = 0.44, CI: 0.32-0.59), tenesmus (RR = 0.53, CI: 0.38-74), blood and mucous in stool (RR = 0.40, CI: 0.28-0.58) and diarrhea (RR = 0.47, CI: 0.36-0.42) post-intervention after using combination therapy. Hence, the proportions of individuals who received combination therapy are 44%, 53%, 40% and 47% respectively of the proportion of individuals in the control group reporting the same symptoms.

When the moderator variable is applied, significant differences (P < 0.0001) are indicated for at least one pair of mean RRs among drug types for every clinical symptom. One study[69] used balsalazide, five studies[33,50,51,55,58]

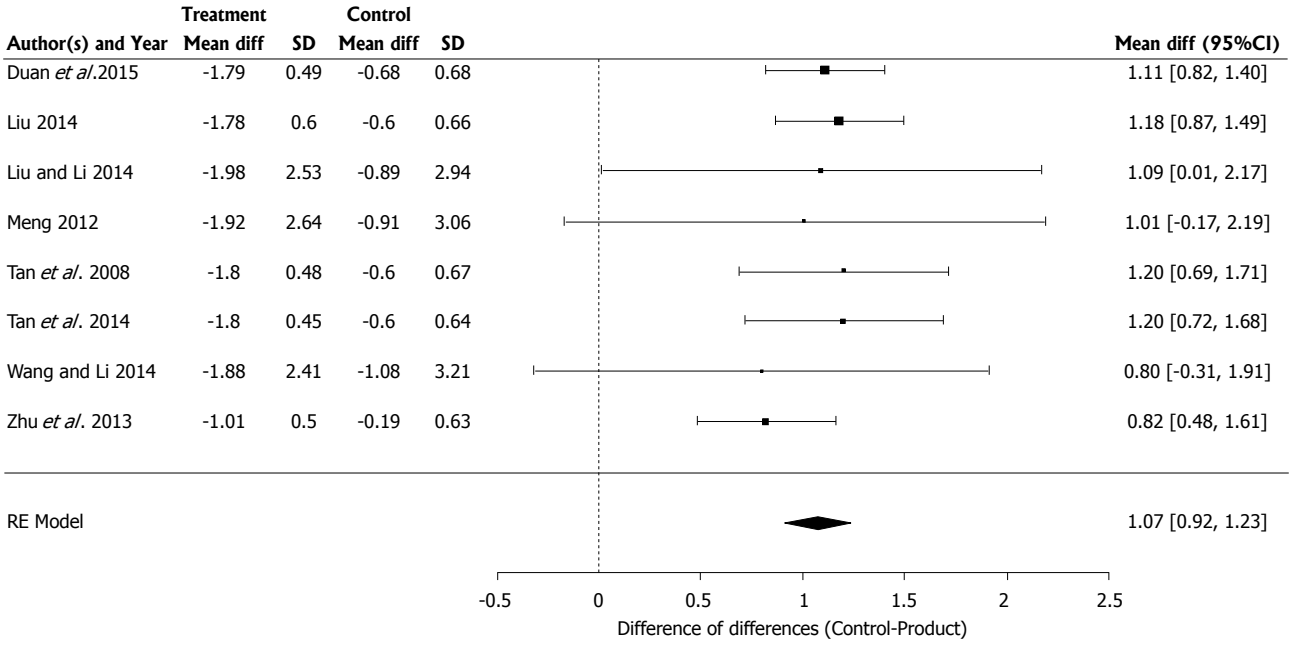
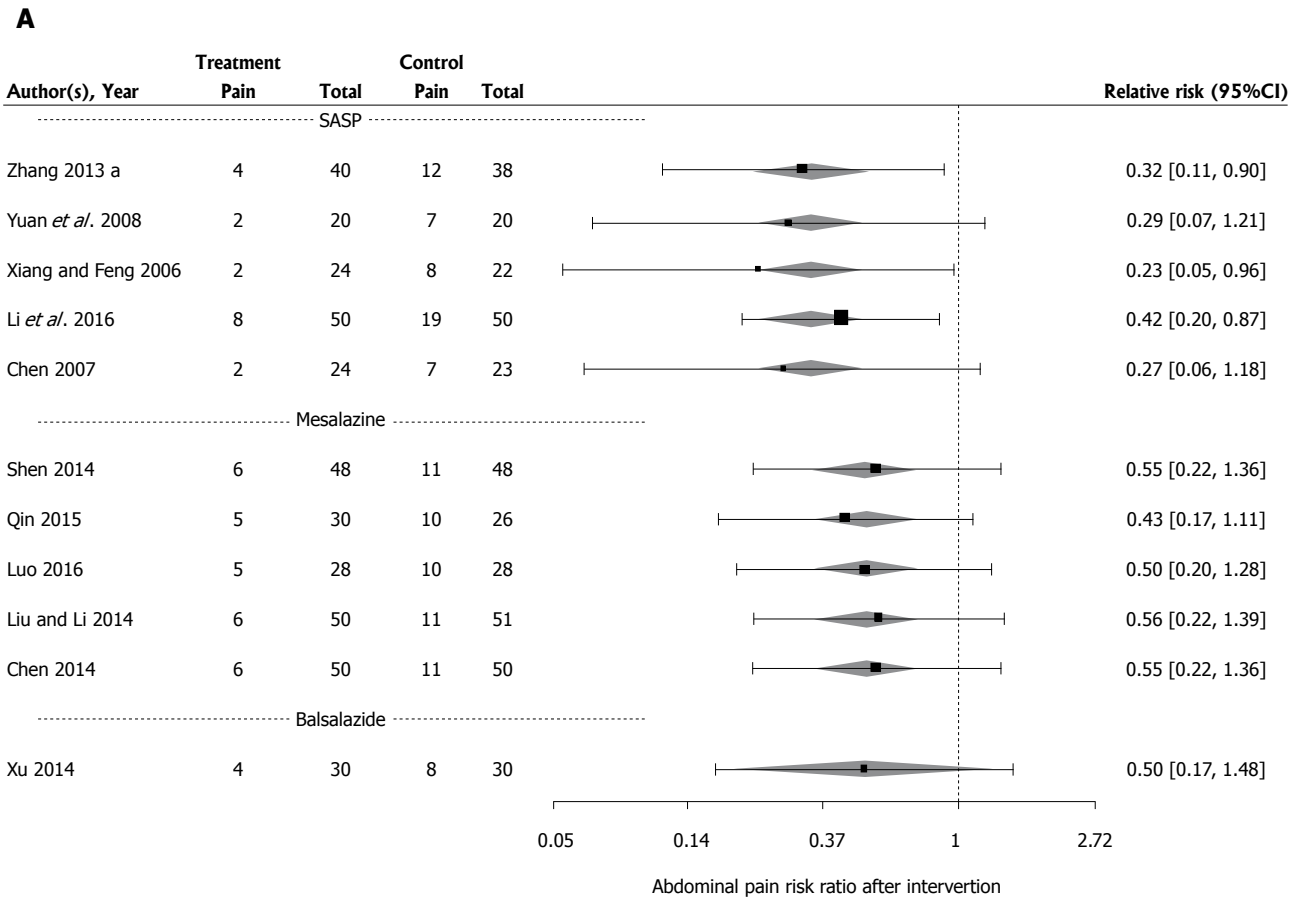


Figure 7 Forest plot of the results of a random effects meta-analysis with 8 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on the change in mean histological score, evaluating colonic histological specimens for inflammation and crypt distortion. "Mean Diff" is the change of the treatment mean score from the baseline mean score and "SD" is the standard deviation of the mean change; the difference between the treatment and control of the change in the mean score and its 95%CI for each study is listed on the right hand side of the graph; the 95%CI for the estimated mean difference in the change from baseline for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints and the location of the maximum width of the diamond being at the estimated mean difference for that drug type; the vertical dashed line at 0 indicates a difference of 0 which occurs when there is no observed difference between the change from baseline for the treatment and the control.



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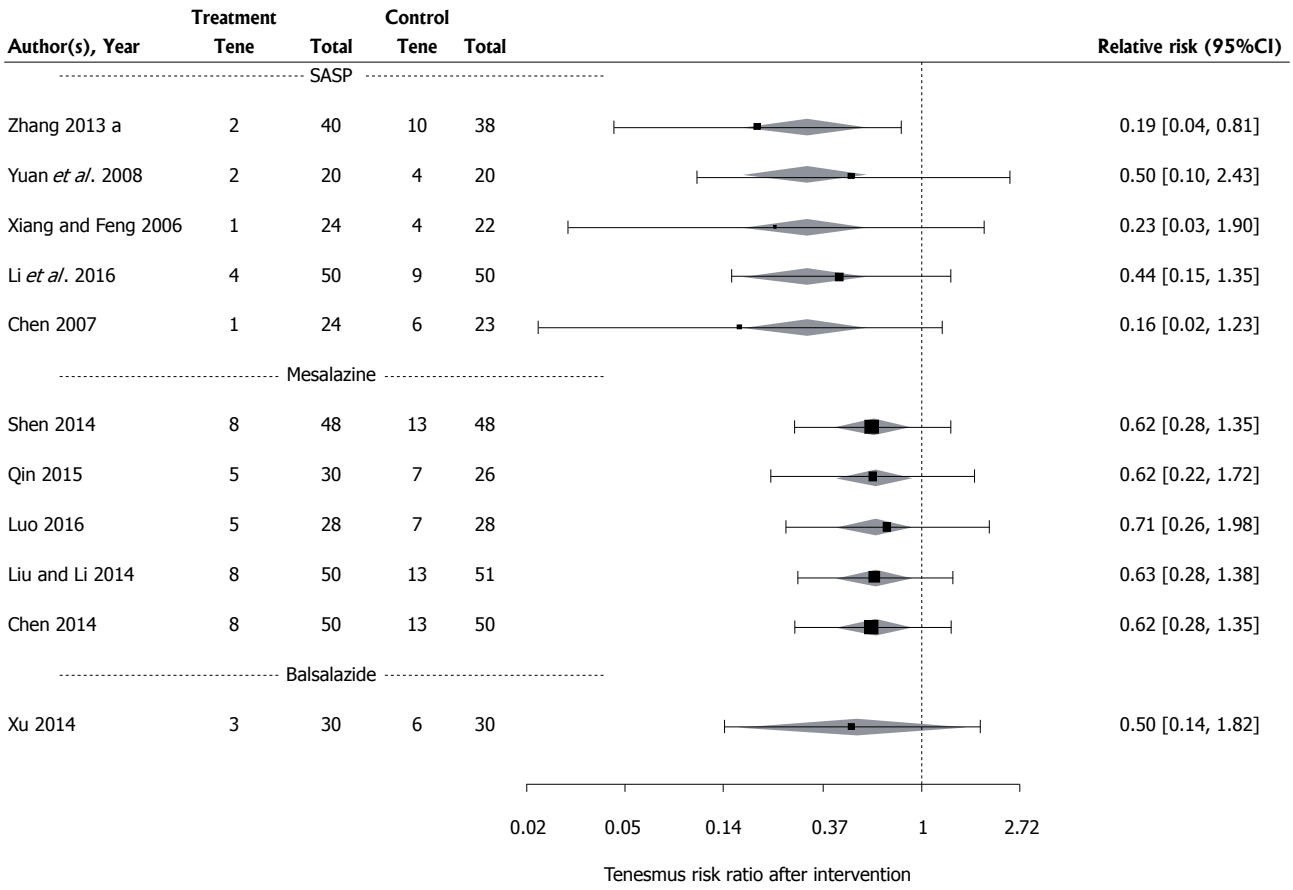
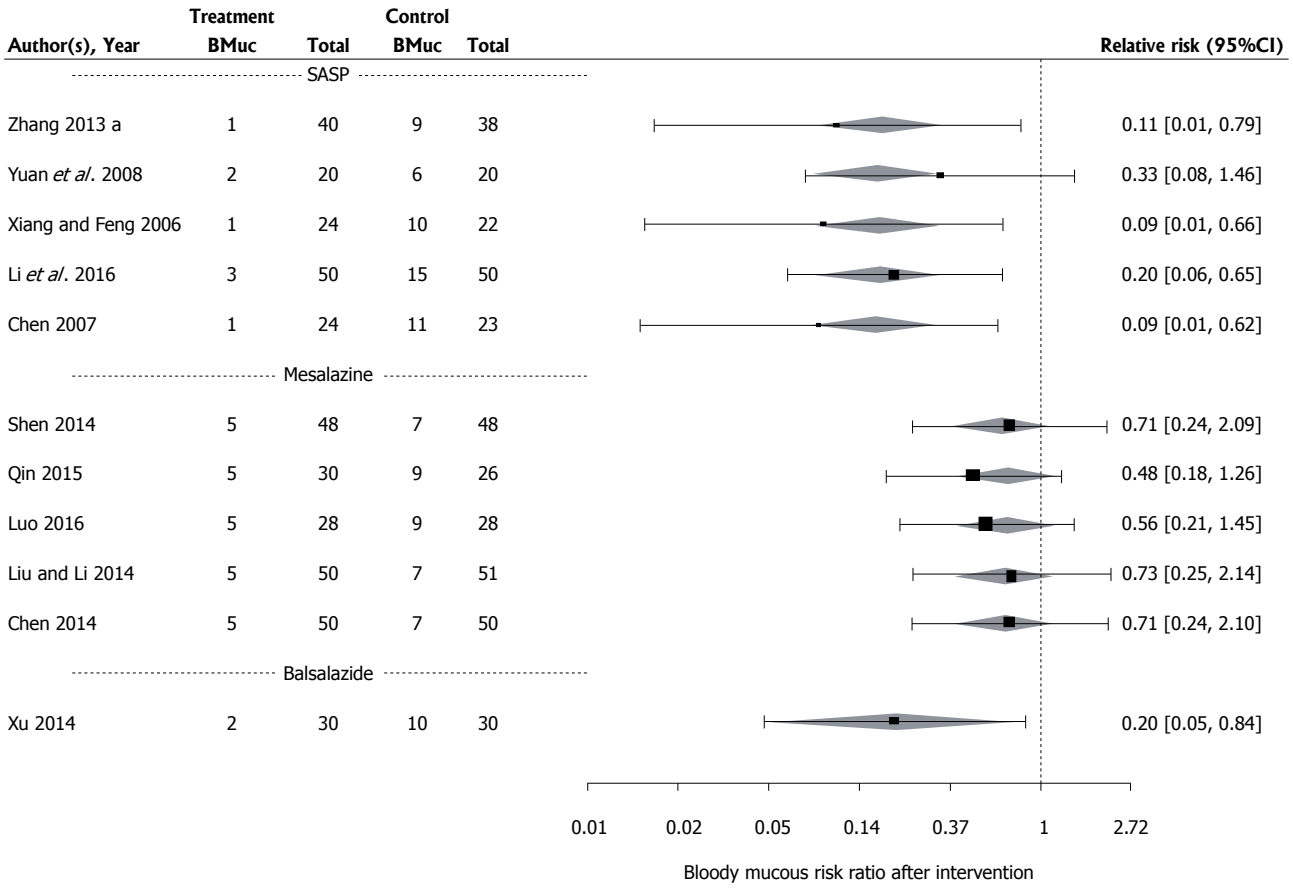

Treatment
Control
Author(s), Year
Tene
Total
Tene
Total
Relative risk (95%CI)
SASP
Zhang 2013 a 2 40 10 38 0.19 [0.04, 0.81]
Yuan et al. 2008 2 20 4 20 0.50 [0.10, 2.43]
Xiang and Feng 2006 1 24 4 22 0.23 [0.03, 1.90]
Li et al. 2016 4 50 9 50 0.44 [0.15, 1.35]
Chen 2007 1 24 6 23 0.16 [0.02, 1.23]
Mesalazine
Shen 2014 8 48 13 48 0.62 [0.28, 1.35]
Qin 2015 5 30 7 26 0.62 [0.22, 1.72]
Luo 2016 5 28 7 28 0.71 [0.26, 1.98]
Liu and Li 2014 8 50 13 51 0.63 [0.28, 1.38]
Chen 2014 8 50 13 50 0.62 [0.28, 1.35]
Balsalazide
Xu 2014 3 30 6 30 0.50 [0.14, 1.82]
0.02
0.05
0.14
0.37
1
2.72
Tenesmus risk ratio after intervention

C


Treatment
Control
Author(s), Year
BMuc
Total
BMuc
Total
Relative risk (95%CI)
SASP
Zhang 2013 a 1 40 9 38 0.11 [0.01, 0.79]
Yuan et al. 2008 2 20 6 20 0.33 [0.08, 1.46]
Xiang and Feng 2006 1 24 10 22 0.09 [0.01, 0.66]
Li et al. 2016 3 50 15 50 0.20 [0.06, 0.65]
Chen 2007 1 24 11 23 0.09 [0.01, 0.62]
Mesalazine
Shen 2014 5 48 7 48 0.71 [0.24, 2.09]
Qin 2015 5 30 9 26 0.48 [0.18, 1.26]
Luo 2016 5 28 9 28 0.56 [0.21, 1.45]
Liu and Li 2014 5 50 7 51 0.73 [0.25, 2.14]
Chen 2014 5 50 7 50 0.71 [0.24, 2.10]
Balsalazide
Xu 2014 2 30 10 30 0.20 [0.05, 0.84]
0.01
0.02
0.05
0.14
0.37
1
2.72
Bloody mucous risk ratio after intervention

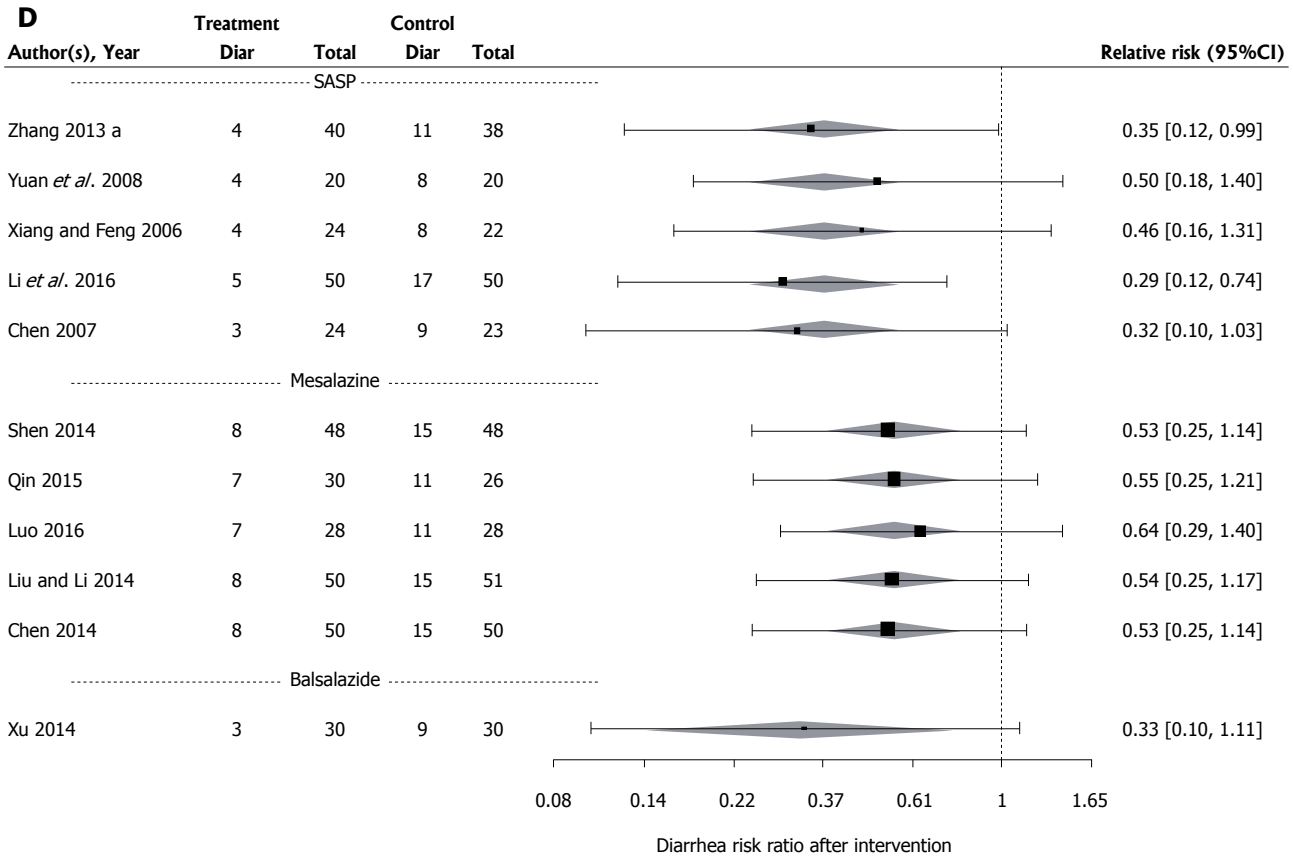


Figure 8 Forest plots of the results of fixed effects meta-analysis with a moderator for concomitant drug therapy for 11 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on number of participants reporting clinical symptoms including: (A) abdominal pain; (B) tenesmus; (C) blood and mucous in stool; and (D) diarrhea. "Pain" is the number of participants reporting abdominal pain in each study, "Tene" is the number of participants reporting tenesmus in each study, "BMuc" is the number of participants reporting blood and mucous in stool in each study, "Diar" is the number of participants reporting diarrhea in each study, and "Total" is the total number of participants in each study. The relative risk (RR) and its 95%CI for each study is listed on the right hand side of the graph. The 95%CI for the estimated mean RR for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints and the location of the maximum width of the diamond being at the estimated mean RR for that drug type. The vertical dashed line at 1 indicates a RR of 1 which occurs when there is no observed difference between the treatment and the control.

used mesalazine and five studies[32,45,67,73,75] used SASP as the concomitant medications with Medilac-S®.

The calculated predicted mean RRs for combination therapy with balsalazide drug include: RR = 0.5 (95%CI: 0.17-1.48) for abdominal pain, RR = 0.53 (CI: 0.14-0.82) for tenesmus, RR = 0.2 (CI: 0.05-0.84) for blood and mucous in stool, and RR = 0.33 (CI: 0.10-1.11) for diarrhea. The estimated mean RRs calculated for SASP drug include: RR = 0.34 (CI: 0.21-0.55) for abdominal pain, RR = 0.31 (CI: 0.16-0.62) for tenesmus, RR = 0.17 (CI: 0.08-0.34) for blood and mucous in stool, and RR = 0.37 (CI: 0.23-0.59) for diarrhea. The estimated mean RR for mesalazine drug therapy include: RR = 0.51 (CI: 0.34-0.78) for abdominal pain, RR = 0.63 (CI: 0.43-0.93) for tenesmus, RR = 0.62 (CI: 0.39-0.98) for blood and mucous in stool, and RR = 0.56 (CI: 0.39-0.79) for diarrhea. Results of RRs and CIs are presented in Figure 8A-D. Because of the greater number of studies using SASP and mesalazine, tests for differences in mean RRs for SASP and mesalazine were also performed for each clinical symptom. A significant difference was seen between the effects of the two medications ($P < 0.0001$) for all clinical symptoms with SASP outperforming mesalazine.

Maintenance of clinical remission: Ten studies[32,39,44,48,53,57,63,65,68,74] enrolled 379 patients in the control group and 364 in the treatment group for a total of 743 participants, excluding any participants in a third arm. These studies evaluated the ability of Medilac-S® treatment, in conjunction with conventional medication, mesalazine or SASP, to maintain clinical remission of UC symptoms. A meta-analysis was not conducted for these ten studies as there was insufficient data to evaluate relapse rate as a function of follow-up time.

Nine studies first aimed to induce UC remission in patients and included a follow-up period to observe symptom recurrence. Of the nine studies, one had a follow-up period of 8 wk[68], five studies[32,44,53,57,74] had a 26 wk follow-up period, two studies[39,63] had a 52-wk follow-up period and one study had a follow-up period of unknown length[48]. One study by Wang *et al*[66] did not aim to induce UC remission as only patients in remission were recruited. The study evaluated a

maintenance of remission for a period of 26 wk.

In 80% (8/10) of studies the symptom recurrence rate for participants receiving conventional therapy with Medilac-S® was significantly lower ($P < 0.05$) than participants taking conventional medication alone. In contrast, one study, by Qin *et al*[56] 2010, showed a greater number of participants in the treatment group experiencing symptom recurrence, with 17.2% (5/29) experiencing symptom recurrence during post-treatment evaluation at 26 wk and only 15.8% (3/19) in the control group. However, the study reports no significant difference between the two recurrence rates. The study by Wang *et al*[66] also reported no significant difference ($P = 0.753$) between the recurrence rates of the control and treatment group at 26 wk, however, the treatment group experienced less symptom recurrence than the control group, at 9.09% and 12.5% respectively.

AEs: A meta-analysis of 30 RCTs reporting AEs which included 2430 participants, with 1195 in the control group and 1235 in the treatment group, was completed. As the test for heterogeneity was not significant ($P = 0.9914$) analysis was conducted with a fixed effects model[31,32,34-40,42,45,49,51-53,57-61,64,66-69,73,75,76,81,83]. As shown on Figure 9, on average, the proportion of individuals in the treatment arm reporting an AE is estimated to be 72% of the proportion of individuals reporting an AE in the control arm (RR = 0.72, 95%CI: 0.55-0.94, $P = 0.0175$).

Publication bias for secondary outcomes

Publication bias for the secondary outcomes was included in the meta-analyses. In studies reporting the endoscopy scores, histology scores, and AEs, no evidence of publication bias was seen [Kendall's tau -0.30 ($P = 0.3567$)], which may be related to the very small sample sizes (Figure 10A-C).

For the clinical symptoms, outcome results indicate some evidence of publication bias. Kendall's tau was significant for two clinical symptom outcomes -abdominal pain [-0.4909 ($P = 0.0405$)] and tenesmus [-0.45273 ($P = 0.0264$)] (Figure 11A and B). The trim and fill method of Duval and Tweedie[27,28] suggests the funnel plot for studies reporting abdominal pain would be made symmetric with the addition of two studies on the left side of the plot (SE = 2.308). The same method suggests that one study be added on the right side of the plot for studies reporting tenesmus (SE = 2.2944). The average log(RR) would be reduced to -0.78 (SE = 0.1478; RR = 0.46) for abdominal pain and -0.60 (SE = 0.1634; RR = 0.55) for tenesmus, which still indicates a positive impact of adding Medilac-S® to conventional drug therapy.

DISCUSSION

Currently available therapies for UC, such as pharmaceutical anti-inflammatories, elicit high response rates, however, due to the potential for high-risk side effects, costs and non-adherence, alternative treatments such as probiotics are being considered[10]. Growing evidence illustrates the pivotal role of gut microflora in UC pathogenesis[2,9], and studies have also shown the influence of the gut microflora on drug pharmacokinetics[86,87], particularly drugs consumed *per os*. Thus, identifying specific probiotics which mediate symptoms of UC may improve responses to, and decrease potential side effects of, currently available therapies.

The present systematic review and meta-analysis evaluates 53 RCTs to assess the efficacy of the probiotic Medilac-S® in combination with aminosalicylates to induce UC clinical remission within a Chinese population. Results show that combination therapy improves clinical remission rates, reduces symptom severity within the GI tract, and decreases incidence of UC symptoms and AEs. A review of studies evaluating maintenance of remission rates also shows reduced symptom recurrence of participants in the probiotic combination therapy groups as compared to conventional therapy alone. Prior studies have demonstrated similar positive effects of probiotics in UC patients through probiotic combination therapy[15,88] or probiotic therapy alone[89]. However, some studies show limited evidence of probiotics as clinically beneficial for the induction and maintenance of UC remission[90,91]. Consequently, it would appear that not all probiotic products will be effective and each product must be uniquely evaluated in the target population.

Some concerns with several prior systematic reviews and meta-analyses are the relatively small numbers of pooled participants analyzed and significant heterogeneity amongst studies due to pooling of data from mixed populations (*i.e.,* adults and children), various probiotic combinations, and the use of different concomitant therapies, which makes it difficult to interpret results accurately. Additionally, many of these reviews fail to incorporate studies outside of North America and Europe, where different probiotics are routinely used and accepted in combination with standard care. For example, many Asian countries have readily accepted probiotics as dietary supplements and pharmaceuticals for a number of years[19]. This results in very few alternative probiotic therapies highlighted amongst systematic reviews assessing probiotics and IBD, which may be misleading.

This systematic review and meta-analysis is distinctive because it focuses on one disease state, one product and one population type, thereby allowing for a more focused analysis. In the past, only one other review has been completed to evaluate the efficacy of Medilac-S® on symptoms of UC[24]. However, due to the unconventional methodology and the abundance of new evidence, it was important to reconstruct the process using stricter review guidelines and improved sub-

Author(s) and Year	Treatment AE	Treatment N	Control AE	Control N	Relative risk (95%CI)
Bu *et al*. 2017	3	34	8	34	0.43 [0.12, 1.49]
Chen 2007	2	24	1	23	1.85 [0.18, 19.08]
Chen *et al*. 2017	4	34	2	34	1.89 [0.37, 9.72]
Duan *et al*. 2015	4	32	4	32	1.00 [0.27, 3.69]
Gu 2012	3	31	7	31	0.48 [0.13, 1.71]
Guo and Sun 2009	4	48	4	44	0.92 [0.24, 3.49]
He *et al*. 2016	2	26	2	26	1.00 [0.15, 6.61]
Jiang 2013	10	55	11	55	0.92 [0.42, 2.02]
Jin *et al*. 2014	8	114	12	112	0.68 [0.29, 1.60]
Li 2013	3	62	3	62	1.00 [0.21, 4.77]
Li *et al*. 2016	4	50	6	50	0.69 [0.21, 2.32]
Liu *et al*. 2009	2	23	2	20	0.88 [0.14, 5.73]
Luo 2016	0	28	0	28	1.00 [0.02, 48.72]
Lu and Lei 2011	3	72	3	60	0.84 [0.18, 4.02]
Miao 2014	2	36	2	36	1.00 [0.15, 6.74]
Qin *et al*. 2010 b	0	34	1	30	0.30 [0.01, 7.22]
Shen 2014	1	48	2	48	0.51 [0.05, 5.45]
Su 2015	3	60	15	60	0.24 [0.07, 0.79]
Tan *et al*. 2008	1	10	1	10	1.00 [0.07, 14.05]
Tan *et al*.2014	1	10	1	10	1.00 [0.07, 14.05]
Wang and Liu 2007	6	20	4	16	1.15 [0.38, 3.55]
Wang *et al*. 2016	0	33	5	32	0.10 [0.01, 1.77]
Xiang and Feng 2006	1	24	2	22	0.48 [0.05, 4.95]
Xiao 2014	4	32	5	31	0.80 [0.23, 2.74]
Xu 2014	0	30	1	30	0.34 [0.01, 8.13]
Yuan *et al*. 2008	0	20	0	20	1.00 [0.02, 48.09]
Zhang 2013 a	1	40	9	38	0.13 [0.02, 0.96]
Zhang 2013 b	3	34	3	34	1.00 [0.22, 4.64]
Zheng *et al*. 2016	0	59	0	59	1.00 [0.02, 49.58]
Zhuo *et al*. 2016	7	20	11	20	0.73 [0.33, 1.62]
FE Model					0.72 [0.55, 0.94]

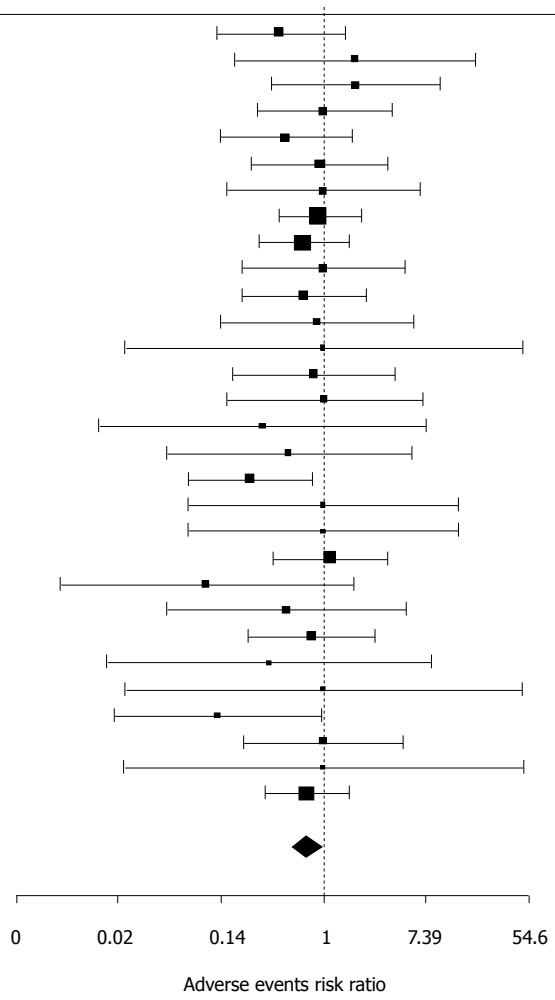
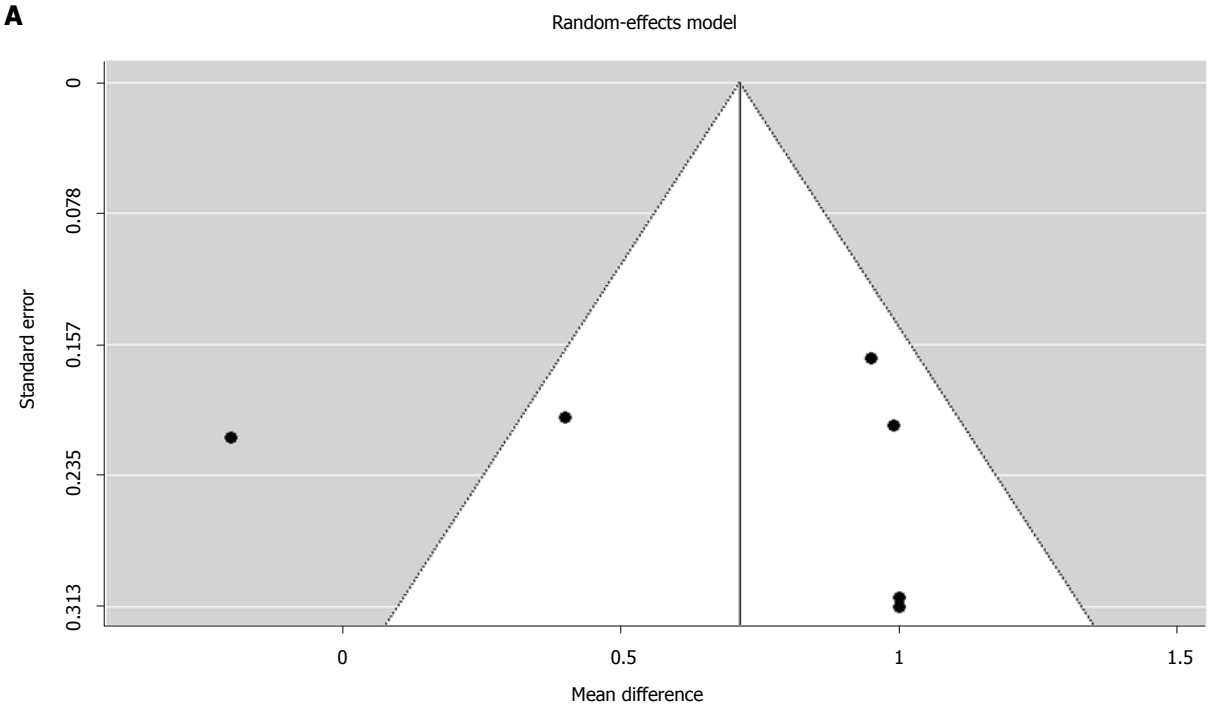


Figure 9 Forest plots of the results of fixed effects meta-analysis with 30 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on number of participants reporting adverse events. "AE" is the number of participants reporting adverse events within a study and "N" is the total number of participants within the study. The relative risk (RR) and its 95%CI for each study are listed on the right hand side of the graph. The 95%CI for the estimated mean RR for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints. The vertical dashed line at 1 indicates a RR of 1 which occurs when there is no observed difference between the treatment and the control.



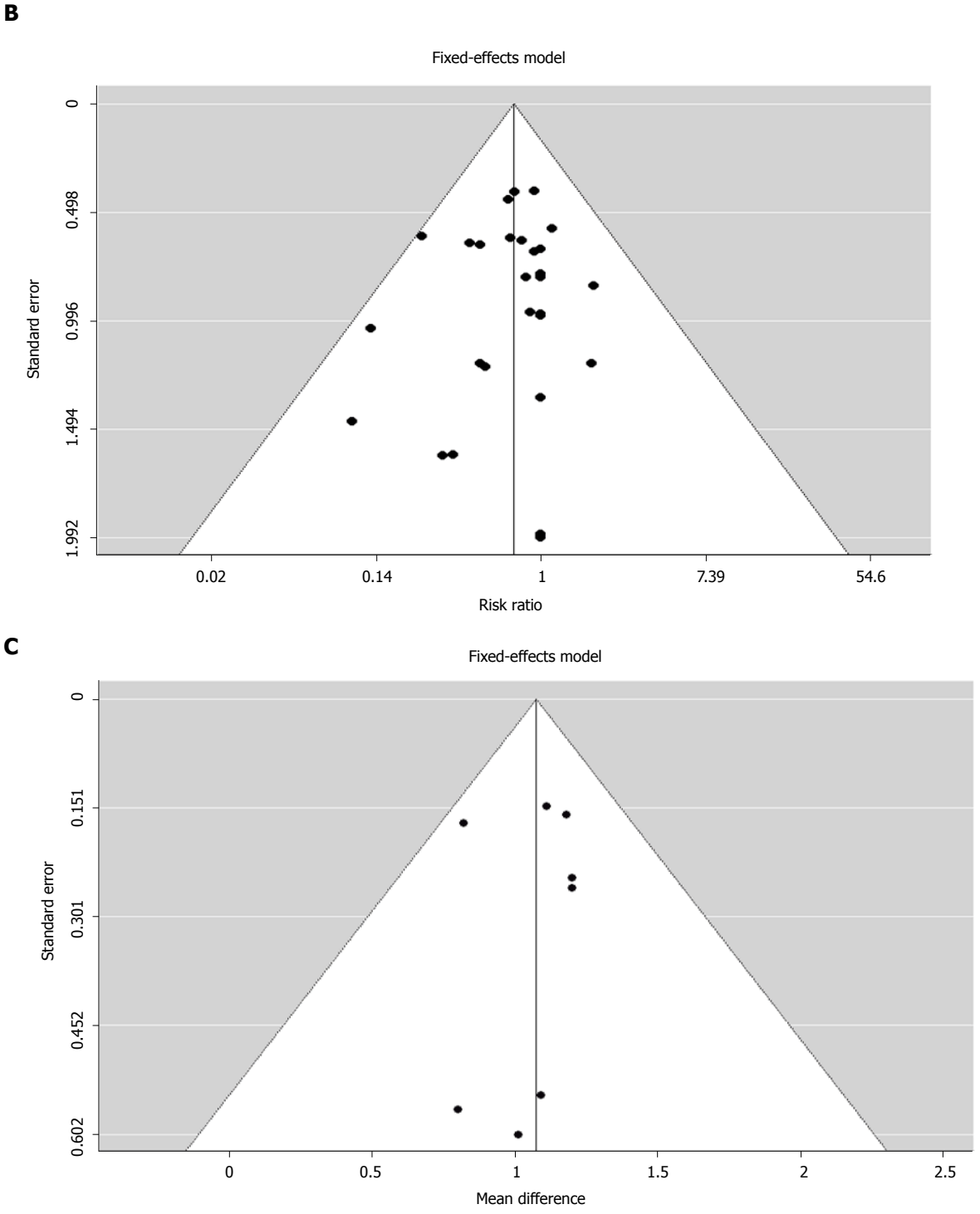


Figure 10 Funnel plots showing the relationship between the relative risk and its standard error for (A) 7 studies used in a random effects meta-analysis evaluating the efficacy of Medilac-S® in combination with conventional drug therapy on change in mean endoscopic score (B) 8 studies used in a fixed effects meta-analysis evaluating the efficacy of Medilac-S® in combination with conventional drug therapy on change in mean endoscopic score and (C) 30 studies used in a fixed effects meta-analysis evaluating the efficacy of Medilac-S® in combination with conventional drug therapy on change in the number of reported adverse events.

analyses.

By conducting a more focused review, we were also able to analyze specific probiotic-drug combinations to elucidate that which is most effective. Medilac-S® was shown to be the most effective in inducing remission when partnered with SASP. We hypothesize this may be due to the stability of SASP in the upper GI tract, which allows for greater quantities of the drug to reach the damaged epithelium[92]. The exact dosage and duration of use of the probiotic remains to be elucidated due to

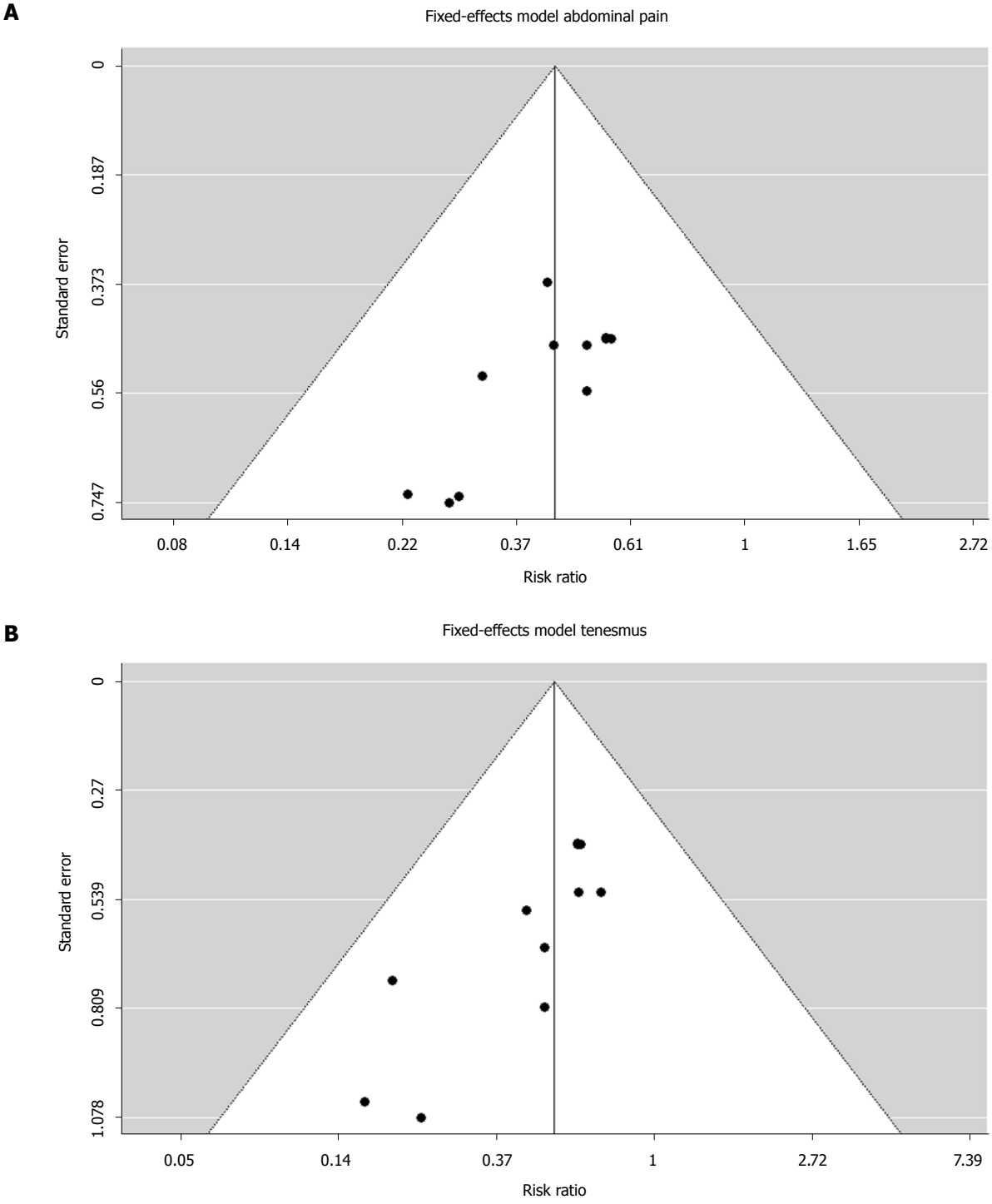


Figure 11 Funnel plot showing the relationship between the relative risk and its standard error for each of 11 studies used in a fixed effects meta-analysis with a moderator for concomitant drug therapy evaluating the effect of Medilac-S® in combination with conventional drug therapy on number of reported clinical symptoms for (A) abdominal pain and (B) tenesmus.

insufficient variation amongst studies to test the effects of these variables, however the majority of studies in our review (94.3%; 50/53) used the recommended dose of 3.0 x 10^9 colony forming units (cfu)/d.

SASP remains the most common anti-inflammatory drug used in China for mild-to-moderate UC[93], however, long term use presents many side-effects[94]. Our results found that the incorporation of probiotic Medilac-S® with SASP and other aminosalicylates (mesalazine, olsalazine, balsalazide) reduced the risk of AEs, suggesting the role of probiotics in the prevention of AEs associated with anti-inflammatory drug use. Prior studies evaluating the effects of probiotics on IBD commonly report no significant differences between

probiotic-treated and conventionally-treated participants[15,95]. Due to limited assessments and systematic reporting of AEs from studies evaluating probiotic-treated IBD, further evidence is required to effectively assess the benefit of probiotic intervention on drug-induced side effects. Further study is also required to assess the effects of probiotic adjunctive therapy on varying disease severity of UC, however, probiotics are most commonly used, and most effective, in individuals with mild-to-moderate UC[14].

Researchers have suggested various mechanisms of action for probiotics in the prevention and treatment of IBD and UC, including maintenance of microbial gut microflora[15], reduced GI inflammation[96], protection against pathogens[97], and improving immune system function[98]. Although few studies have elucidated the potential mechanisms for the beneficial effects of the two Medilac-S® strains specifically (*E. faecium* R0026 and *B. subtilis* R0179), a study by Zhong *et al*[99], found the probiotic decreased and prevented the growth of various enteric bacterial pathogens and Tompkins *et al*[19] found both strains to adhere to human intestinal cells (HT-29) in culture.

Research also suggests the gut microflora and, subsequently, probiotics which influence the gut microflora, may play an important role in drug pharmacokinetics[86,87,100]. Gut microflora are a determinant for azo-containing compounds such as SASP and other aminosalicylate pro-drugs[86]. Orally ingested pro-drugs are broken down in the large intestine through a two-step azo-bond reduction mediated by the azoreductase enzyme found in the natural gut microflora[101]. Many probiotic strains, including those found in Medilac-S®, also contain the azoreductase enzyme, and a recent unpublished evaluation by one of the authors (TT) demonstrated that the bacterial strains in Medilac-S®, particularly the *E. faecium* R0026, *in vitro* facilitate the breakdown of SASP into its active moiety 5-ASA and sulphapyridine.

These findings are consistent with studies, such as Lee *et al*[102], conducted in animal models which found probiotic administration significantly improved the breakdown of SASP to 5-ASA and sulphapyridine. Significant metabolic breakdown of SASP was not observed in a 2010 study by Lee *et al*[103] evaluating the influence of a 9×10^8 CFU multi-strain probiotic (*Lactobacillus acidophilus*, *Bifidobacterium lactis* and *Streptococcus salivarius*) in patients suffering from rheumatoid arthritis. However, the probiotic was given only twice daily for a short one-week treatment period. Therefore, further exploration on the mechanism of action of probiotics and the natural gut microflora in the breakdown of pro-drugs such as SASP is required, with different treatment dosages and durations reviewed.

Limitations

We cannot rule out the potential for some risk of bias amongst included studies and possible publication bias, however, results concerning publication bias should be considered exploratory because neither unpublished literature nor the potentially missing articles were located. Most studies presented an unclear risk of bias in assessed categories, such as techniques for randomization, allocation concealment, and the blinding of participants or study personnel. Some included studies also demonstrated a high risk of bias in reporting because results were either reported without pre-specification or expected outcomes failed to be included. We hypothesize this style of reporting is a result of the guidelines and trends in China[104-107].

Furthermore, the use of Chinese diagnostic guidelines from different years of publication, which are appropriate and independently validated in their own right, results in diagnostic techniques and testing scales which are not completely uniform or analogous to the more commonly seen Western guidelines. Finally, in reporting the efficacy of different drug-probiotic combinations, results indicated SASP outperformed mesalazine, however, due to the limited number of studies using balsalazide and olsalazine, further evidence is required to draw firm conclusions on other Medilac-S® and aminosalicylate combinations.

In conclusion, moderate-quality evidence, as seen by improvements in the Sutherland index, endoscopy and histology scores, a decrease in patient-reported clinical symptoms of UC (abdominal pain, diarrhea, tenesmus and blood/mucous in the stool), and a decrease in AEs suggests Medilac-S®, in conjunction with conventional aminosalicylates, is effective in inducing clinical remission of UC and improving symptoms of the GI tract in Chinese populations. Therefore, for this application, this probiotic should be considered as best practice for standard care in clinical practice. Additional work is required in non-Chinese populations to substantiate its use. Further analytical evidence is also required to determine the benefit of Medilac-S® combination therapy for the maintenance of UC remission.

Due to the unknown risk of bias amongst many study categories, more robust and well conducted RCTs are needed to draw further conclusions about which combination of Medilac-S® and conventional UC treatment is most effective. Future studies should also attempt to evaluate the impact on SASP, SP and 5-ASA levels with varying Medilac-S® dosages. It is suggested that authors of clinical studies in China include more detailed information on the study design and technique implementation for future clinical trials, particularly when tracking the maintenance of symptom remission, to further improve upon study quality.

ARTICLE HIGHLIGHTS

Research background

Ulcerative colitis (UC), an inflammatory bowel disease (IBD) of the colonic gastrointestinal tract, is steadily increasing across the globe, particularly in Asian countries such as China, where rapid industrialization and urbanization are contributing factors to the growing onset. Mild-to-moderate UC is the most

prevalent amongst diagnosed cases, and although targeted pharmacological therapies, such as aminosalicylates, have been at the forefront of UC therapy, growing evidence suggests the integral role of intestinal microflora in UC pathogenesis. Subsequently, researchers are interested in the use and development of alternative therapies, such as probiotics, for the management and treatment of this colonic disease. This systematic review and meta-analysis addresses the use of a probiotic product, Medilac-S®, as adjunctive therapy for the induction of clinical UC remission and improvement of UC symptoms in a defined Chinese population, through the evaluation of 53 randomized, controlled trials (RCTs). Past reviews of probiotics for the induction of UC remission have described the positive effects of probiotic combination therapy in patients, however, many of these reviews demonstrated significant variability in study populations and probiotic treatments, making it difficult to interpret results accurately. This study therefore aims to provide a more focused analysis through the evaluation of one disease state, one probiotic and one population.

Research motivation

The incidence of UC has increased rapidly around the globe and although current pharmacological therapies elicit high response rates, they also present high-risk side effects or adverse events (AEs), growing rates of non-adherence and high costs to patients. Growing evidence also illustrates the important role of gut microflora in UC pathogenesis and the influence of the intestinal microbiome on drug pharmacokinetics. Therefore, it is important to identify treatments, such as probiotics, which can mediate the gut microflora to improve symptoms of UC and also improve responses to currently available therapies, whilst mitigating potential side effects.

Research objectives

Our primary objective was to conduct an up-to-date systematic review and meta-analysis to assess the efficacy of Medilac-S® as an adjunctive to conventional oral drugs for the induction of UC clinical remission within a Chinese population. One prior systematic review and meta-analysis, published by Hu *et al*, had, to date, discussed the efficacy of the probiotic Medilac-S® on the induction and maintenance of remission in UC patients. However, since its publication, a large number of new studies had been published and remained to be evaluated in a meta-analytic setting. In this review, we assessed 53 RCTs which highlighted the efficacy of the probiotic Medilac-S®, in combination with conventional aminosalicylates, to induce UC clinical remission within a Chinese population, improve UC symptoms and decrease AEs. This supports suggestions of the important role of the gut microbiome in the modulation of IBDs and presents a new potential treatment to mitigate the effects of the microflora on worsening UC symptoms.

Research methods

The review protocol was registered in PROSPERO and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the review to ensure up-to-date methodology and study reasoning. Nine databases, both English and Chinese, were searched from 2000 to 2017, unrestricted by language or trial size to identify RCTs evaluating the therapeutic effects of Medilac-S® combination therapy with conventional aminosalicylate drugs in the treatment of UC within a Chinese population. If the study met the inclusion criteria, then outcome data extraction and assessment of both study quality and risk of bias was independently performed by two authors. Any disagreement was resolved by discussion and if consensus could not be reached, a third author was addressed. The included studies were evaluated on clinical remission, changes in patient-reported clinical symptoms, maintenance of remission and relapse rate, Sutherland index, endoscopic score, histological score and AEs. Meta-analysis was conducted on each outcome of interest using a fixed effect or a random effect model, depending on the significance of the heterogeneity. For dichotomous outcomes (*e.g.*, clinical efficacy), risk ratios (RR) were calculated while the mean difference was used for continuous variables (*e.g.,* histology scores). CIs were calculated at 95% and, when possible, the type of the conventional drug was applied as a moderator in the model of analysis. The overall quality of evidence supporting the outcome was assessed through the use of the Cochrane Collaboration tool and a risk of bias analysis was conducted on each study. The risk of bias parameters included the type of randomization method, allocation concealment, blinding of participants, personnel and outcome assessments, incomplete outcome data, selective reporting and other sources of bias. Additionally, selective reporting (reporting bias) and other types of bias were also considered. The potential for publication bias across studies was analyzed using the rank correlation test Kendall's Tau, which tested for asymmetry in a funnel plot showing the relationship of the effect size [log (RR)] and its standard error (SE) among studies.

Research results

Fifty-three studies involving 3984 patients were identified and included in the systematic review. Forty-five studies were analyzed for the primary outcome of clinical remission and results demonstrated that combination Medilac-S® therapy is significantly more effective than conventional drug therapy alone (RR = 1.21, CI: 1.18-1.24, $P < 0.0001$). Moreover, sulfasalazine (SASP) outperformed mesalazine as a concomitant drug. Further meta-analysis also provided evidence that the combination of Medilac-S® significantly improved the Sutherland index score ($P < 0.05$), endoscopic score ($P = 0.0001$), histological score ($P < 0.0001$) and the number of patient reported symptoms ($P < 0.0001$), which include, abdominal pain, tenesmus, blood and mucous in stool, and diarrhea. The proportions of individuals who received combination therapy and complained of the aforementioned symptoms were 44%, 53%, 40% and 47% respectively of the proportion of individuals in the control group reporting the symptoms. The test for difference in the RR with different drugs also revealed that SASP in combination with Medilac-S® is more effective than mesalazine as a concomitant drug. The meta-analysis comparing the number of AE's found that addition of Medilac-S® to conventional drug plays a role in significantly reducing ($P = 0.0175$) AE incidence, with the proportion of individuals in the treatment arm reporting an AE estimated to be 72% of the proportion of individuals reporting an AE in the control arm. Due to the insufficient data to evaluate relapse rate as a function of follow-up time, a descriptive analysis was conducted on the maintenance of remission. It was found that 80% (8/10) of the studies presenting the outcome showed that the recurrence rate of UC was significantly lower in the Medilac-S® combination group. The quality and risk of bias amongst included studies found the majority of the studies presented a low risk of attrition bias, reporting bias and other potential sources of bias. However, failure to report the methods for randomization or implementation of blinding resulted in unclear risk of bias evaluations. Thus, evidence from studies is considered of moderate-quality. Since no restrictions on the severity of UC were made, this confounding factor was not considered in the analysis because of the very limited number of studies with severe UC patients. Additionally, due to the limited number of studies which included the aminosalicylate drugs olsalazine and balsalazide, sub-analysis could not be conducted to compare their efficacy as concomitant medications.

Research conclusions

This systematic review and meta-analysis is the most up-to date, comprehensive review evaluating the effectiveness of probiotic Medilac-S® adjunctive therapy in treatment of UC. It critically examined currently available data and found evidence that Medilac-S® as adjunctive therapy to conventional oral aminosalicylate medications significantly increases UC clinical remission and leads to improvements in the Sutherland index, endoscopy and histology scores, patient-reported clinical symptoms, and AEs. Although review has provided further insight to the global community on the application of this probiotic therapy for inducing symptom remission, further analytical evidence is also required to determine the benefit of Medilac-S® combination therapy for the maintenance of UC remission. The uniformity in study design of the included studies, such as *per os* administration of Medilac-S® and concomitant therapies, minimizes the heterogeneity of medication delivery method across studies and facilitates a more applicable future global clinical application due to ease of practical use. The most effective combination: Medilac-S® with SASP, was also identified through sub-analysis presented in this review. In addition, it was concluded that Medilac-S® has significant effect in reducing the incidence of AEs in UC treatment and thus, indicates another option for patients with low tolerance of conventional drug treatments. This new finding is of importance because the side effects and tolerance of the anti-inflammatory drugs in UC treatment is a big concern of both physicians and patients and the previous studies have shown conflicting results in the function of probiotics in reducing the occurrence of AEs. This meta-analysis has great value for clinicians as evidence from this study implies that Medilac-S® in conjunction with conventional oral therapy, predominantly, SASP, should be considered as standard care for UC in the Chinese population.

Research perspectives

Through the use of a focused meta-analysis and sub-analyses, evaluating Medilac-S® for UC remission within the Chinese population, heterogeneity across studies was limited, which allowed for greater accuracy when defining results. Although evidence from the study suggests the incorporation of Medilac-S® into standard UC therapy for Chinese populations, future studies should aim to conduct additional work with the probiotic in non-Chinese populations to substantiate its use. Additional research can also be conducted to evaluate variables of Medilac-S® treatment such as optimal treatment dosage and treatment duration in participants with varying levels of UC severity. In addition, future Chinese clinical trials evaluating probiotics are recommended to use large sample sizes and incorporate rigorous study design methodology, which includes reporting of blinding, the techniques for randomization and allocation concealment, as it limits risk of bias, and will aid researchers in drawing firmer conclusions on the benefits of probiotics, like Medilac-S® for IBD.

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META-ANALYSIS

Impact of body mass index on short-term outcomes of laparoscopic gastrectomy in Asian patients: A meta-analysis

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Abstract

AIM

To perform a meta-analysis to investigate the correlation between body mass index (BMI) and the short-term outcomes of laparoscopic gastrectomy (LG) for gastric cancer (GC) in Asian patients.

METHODS

The PubMed, Cochrane, EMBASE, and Web of Science databases were searched for studies that focused on the impact of obesity on the short-term outcomes of LG for GC in Asian patients who were classified into a high BMI (BMI $\geqslant$ 25 kg/m^2) or low BMI group (BMI < 25 kg/m^2). The results are expressed using the pooled odds ratio (OR) for binary variables and standard mean difference (SMD) for continuous variables with 95%

confidence interval (CI), and were calculated according to the fixed-effects model while heterogeneity was not apparent or a random-effects model while heterogeneity was apparent.

RESULTS

Nine studies, with a total sample size of 6077, were included in this meta-analysis. Compared with the low BMI group, the high BMI group had longer operative time (SMD = 0.26, 95%CI: 0.21 to 0.32, $P < 0.001$), greater blood loss (SMD = 0.19, 95%CI: 0.12 to 0.25, $P < 0.001$), and fewer retrieved lymph nodes (SMD = -0.13, 95%CI: 0.18 to 0.07, $P < 0.001$). There was no significant difference between the high and low BMI groups in postoperative complications (OR = 1.12, 95%CI: 0.95 to 1.33, $P = 0.169$), the duration of postoperative hospital stay (SMD = 0.681, 95%CI: -0.05 to 0.07, $P = 0.681$), postoperative mortality (OR = 1.95, 95%CI: 0.78 to 4.89, $P = 0.153$), or time to resuming food intake (SMD = 0.00, 95%CI: -0.06 to 0.06, $P = 0.973$).

CONCLUSION

Our meta-analysis provides strong evidence that despite being associated with longer operative time, greater blood loss, and fewer retrieved lymph nodes, BMI has no significant impact on the short-term outcomes of LG for GC in Asian patients, including postoperative complications, the duration of postoperative hospital stay, postoperative mortality, and time to resuming food intake. BMI may be a poor risk factor for short-term outcomes of LG. Other indices should be taken into account.

Key words: Obesity; Body mass index; Laparoscopic gastrectomy; Gastric cancer; Meta-analysis

Core tip: The impact of body mass index (BMI) on the short-term outcomes of laparoscopic gastrectomy (LG) for gastric cancer in Asian patients have been controversial due to inconsistent results of previous studies. Our meta-analysis demonstrates that despite being associated with longer operative time, greater blood loss, and fewer retrieved lymph nodes, a high BMI could not be significantly associated with short-term outcomes of LG in Asian patients. BMI may be a poor risk factor for short-term outcomes of LG. Other indices should be taken into account.

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INTRODUCTION

Gastric cancer (GC), the second most prevalent cause of cancer-related deaths worldwide, has been a source of increasing concern[1]. Since 1994, when laparoscopic technique was first used for GC[2-6], laparoscopic gastrectomy (LG) has become increasingly popular for treating early GC (EGC) due to decreased intraoperative blood loss, less pain, and shorter hospital duration[7-10]. The prevalence of obesity is increasing steadily in Asian countries. Obesity may increase the risk of health disorders, such as hypertension, cardiovascular disease, and type 2 diabetes mellitus[11,12], and is regarded as a risk factor for worse surgical outcomes of complicated surgical procedures[13]. Furthermore, patients with obesity have a higher risk of operative difficulties, as well as wound infection[14-16]. Recently, the impact of obesity on short-term outcomes of LG in patients has been controversial due to inconsistent results of several studies. Obesity leads to a longer duration of postoperative hospital stay and time to resuming food intake in studies performed by Chen *et al*[17] and Yang *et al*[18], while Jung *et al*[19] reported that obesity was not a risk factor for these impacts. The studies performed by Chen *et al*[20], Shimada *et al*[21], and Yamada *et al*[22] suggested that the association between obesity and LG was significant, while Shin *et al*[23] and Oki *et al*[24] reported the opposite conclusion.

To date, although several studies used the body mass index (BMI) to assess the impact of obesity on the short-term outcomes of LG, the results have been controversial and limited. Hence, we conducted this meta-analysis to summarize all of the available evidence.

MATERIALS AND METHODS

Search strategy

The PubMed, Cochrane, EMBASE, and Web of Science databases were searched up to July 30, 2018 using the search terms (obesity) OR (metabolically benign) OR (obesity, morbid) OR (pediatric) OR (overweight) AND (body mass index) OR (index, body mass) OR (Quetelet index) OR (index, Quetelet) OR (Quetelet's index) OR (Quetelets index) AND (stomach neoplasms) OR (neoplasm, stomach) OR (stomach neoplasm) OR (gastric neoplasms) OR (gastric neoplasm) OR (neoplasm, gastric) OR (neoplasms, gastric) OR (cancer of stomach) OR (stomach cancers) OR (gastric cancer) OR (cancer, gastric) OR (cancers, gastric) OR (gastric cancers) OR (stomach cancer) OR (cancer, stomach) OR (cancers, stomach) OR (cancer of the stomach) OR (gastric cancer, familial diffuse) AND (laparoscopy) OR (laparoscopies) OR (celioscopy) OR (celioscopies) OR (peritoneoscopy) OR (peritoneoscopies) OR (surgical procedures, laparoscopic) OR (laparoscopic surgical procedure) OR (procedure, laparoscopic surgical) OR (procedures, laparoscopic surgical) OR (surgery, laparoscopic) OR (laparoscopic

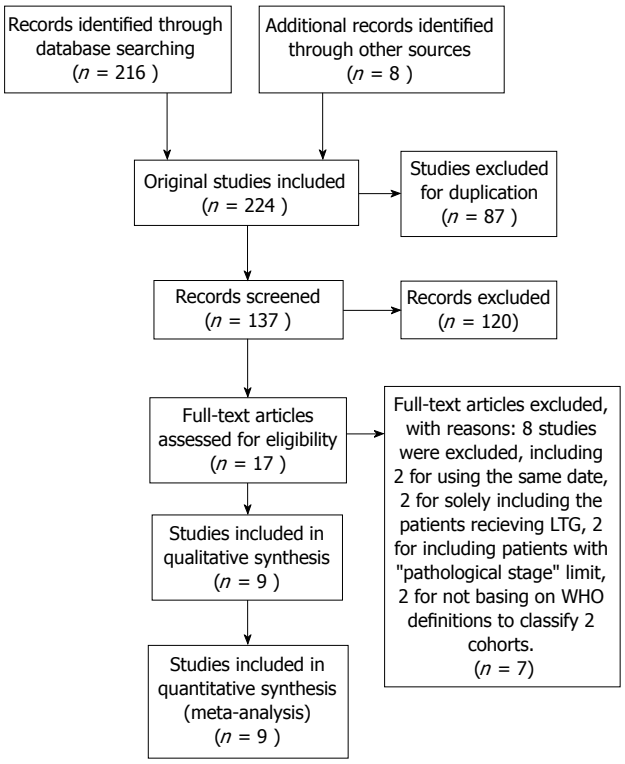


Figure 1 Flowchart of study selection in the meta-analysis. LTG: Laparoscopic total gastrectomy.

surgical procedures) OR (laparoscopic surgery) OR (laparoscopic surgeries) OR (surgeries, laparoscopic) OR (surgical procedure, laparoscopic) AND within the "Title/Abstract" and "Asian" limits. No restrictions were applied for language, country, or publication date. Moreover, lists of all relevant review articles were manually screened to identify further studies.

Selection criteria

Studies were included if they met the following predefined criteria: (1) all patients underwent LG; (2) all patients were diagnosed by esophagogastroduodenoscopy, postoperative pathological diagnosis, endoscopic ultrasound, or computed tomography (CT); (3) all studies were included without "age" or "pathological stage" limit; and (4) the risk estimates were adjusted for other confounding factors. Meeting abstracts, systematic reviews, case reports, studies without usable or extractable data, and those solely focusing on laparoscopic total gastrectomy (LTG) were all excluded. Publications with smaller data sets were excluded while the data were presented in more than one publication.

Outcome measures analyzed

Operative time, blood loss, and the number of retrieved lymph nodes were defined as indices of difficulties in LG. Postoperative complications, the duration of postoperative hospital stay, postoperative mortality, and time to resuming food intake were estimated as indices to assess the impact of BMI on the short-term outcomes of LG. The cutoff points to divide patients into a high BMI and a normal BMI group were based on World Health Organization definitions (overweight, BMI $\geqslant$ 25 kg/m^2; healthy-weight, BMI < 25 kg/m^2)[25,26]. Postoperative complications were defined as those requiring surgical or conservative treatment according to the Clavein-Dindo classification system. All of the postoperative complications observed in the included studies conform to this definition.

Data extraction and quality assessment

Data were extracted from the included studies by two independent investigators, and disagreements were resolved through consensus or consultation with a third investigator. Study characteristics such as the authors' names, year of publication, number of participants, operative time, blood loss, number of retrieved lymph nodes, postoperative complications, duration of postoperative hospital stay, postoperative mortality, and time to resuming food intake were recorded. The Newcastle-Ottawa Scale was used to assess the quality of the included studies.

Statistical analysis

The pooled odds ratio (OR) for binary variables and standard mean difference (SMD) for continuous variables with 95% confidence interval (CI) were calculated using a fixed-effects model while heterogeneity was not apparent or a random-effects model while heterogeneity was apparent. *P* for I^2 statistic was used to evaluate the heterogeneity in this meta-analysis, with $P < 0.05$ suggesting substantial heterogeneity among the included studies. The *Galbraith plot* test was performed to assess the potential source of heterogeneity. A sensitivity analysis was performed (when the number of included studies $\geqslant$ 9) to evaluate the stability of the results by excluding each study from the meta-analysis one by one. Publication bias was evaluated using funnel plots and the Egger's test (when the number of included studies $\geqslant$ 9). Duval's trim and fill method was used to solve publication bias. Statistical analyses were performed using STATA 12.1 (StataCorp, Texas, United States). A *P*-value < 0.05 indicated statistical significance.

RESULTS

Of the 224 studies identified using the predefined search strategy, 207 were excluded after screening titles and abstracts because they did not meet the predefined criteria; they were duplicate; or their full-text could not be accessed and insufficient data to make calculations from the abstracts. After performing full-text evaluations, eight studies were excluded, including two for using the same date, two for solely including the patients receiving LTG, two for including patients with "pathological stage" limit, and two for not being based on WHO definitions to classify the two cohorts. Thus, nine studies[17-24,27] with a sample size of 6077 were included in the meta-analysis

Table 1 Characteristics of nine studies included in the meta-analysis

Study	Country	Study type	Inclusion period	Sample size	Type of gastrectomy	BMI cutoff point	Adjustment	Quality
Chen *et al*[20]	China	RC	2007-2010	531	LG	25	1, 3, 5	9
Chen *et al*[17]	China	RC	2004-2016	1691	LAG TLG	25	1, 2, 4, 5, 6, 7	8
Jung *et al*[19]	South Korea	RC	2006-2012	1512	LDG	25	1, 2, 3, 4, 6, 7	8
Lee *et al*[27]	South Korea	RC	-2005	1485	LAG	25	1, 2, 3, 4, 5, 7	9
Oki *et al*[24]	Japan	RC	2005-2009	138	TLDG	25	1, 2, 4, 5, 6, 7	8
Shimada *et al*[21]	Japan	RC	2007-2014	173	LADG	25	1, 2, 3, 4, 5, 6, 7	8
Shin *et al*[23]	South Korea	RC	2003-2005	192	LG	25	1, 2, 5, 6, 7	8
Yamada *et al*[22]	Japan	RC	1999-2005	141	LADG	25	1, 5, 6, 7	9
Yang *et al*[18]	China	RC	2009-2012	214	LAG	25	1, 2, 3, 5, 6, 7	8

1: Postoperative complications; 2: Postoperative hospital stay; 3: Mortality; 4: Time to resuming food intake; 5: Operative time; 6: Blood loss; 7: Retrieved lymph nodes. BMI: Body mass index; RC: Retrospective cohort; LG: Laparoscopic gastrectomy; TLG: Totally laparoscopic gastrectomy.

Table 2 Summary statistics of pooled odds ratio on various postoperative complications comparing high body mass index and normal body mass index groups receiving laparoscopic gastrectomy

Complication variable	No. of studies	No. of pooled patients	Pooled OR	95%CI	Test of heterogeneity	Test of overall effect
					P value	*P* value
Overall complications	9	6077	1.12	0.95-1.33	0.734	0.169
Anastomotic leakage	6	3939	1.31	0.62-2.79	0.642	0.476
Anastomotic stricture	4	3587	0.85	0.27-2.66	0.489	0.775
Anastomotic bleeding	5	3798	0.63	0.27-1.45	0.942	0.277
Abdominal abscess	5	3801	1.56	0.91-2.67	0.615	0.103
Pancreatic leakage	6	3937	0.52	0.20-1.35	0.581	0.179
Ileus	4	3584	1.96	0.79-4.83	0.382	0.144
Wound	6	3939	1.77	0.92-3.42	0.289	0.087

OR: Odds ratio; CI: Confidence interval.

(Figure 1). The outcomes of the quality assessment are shown in Table 1. All of the included studies obtained at least eight points, meaning that they were defined as high-quality.

Meta-analysis

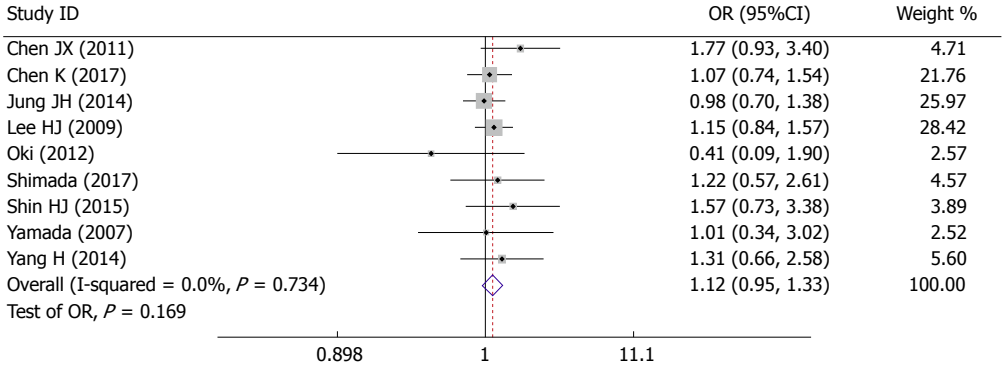
Correlation between BMI and short-term outcomes of LG: There was no significant difference between the two cohorts in overall postoperative complications (OR = 1.12, 95%CI: 0.95 to 1.33, *P* = 0.169; Figure 2A), various postoperative complications (Table 2), the duration of postoperative hospital stay (SMD = 0.681, 95%CI: -0.05 to 0.07, *P* = 0.681; Figure 2B), postoperative mortality (OR = 1.95, 95%CI: 0.78 to 4.89, *P* = 0.153; Figure 2C), or time to resuming food intake (SMD = 0.00, 95%CI: -0.06 to 0.06, *P* = 0.973; Figure 2D). Heterogeneity was not apparent in any of these outcome results according to the fixed-effects model. Sensitivity analysis demonstrated that no study could affect the pooled OR for postoperative complications (Figure 3A). Visual assessments of the funnel plots (Figure 4A) and the Egger's test (Figure 5A) showed no evidence of publication bias for postoperative complications (*P* = 0.849).

Correlation between BMI and difficulties in LG: The high BMI group had longer operative time (SMD = 0.26, 95%CI: 0.21 to 0.32, *P* < 0.001; Figure 2E), greater blood loss (SMD = 0.19, 95%CI: 0.12 to 0.25, *P* < 0.001; Figure 2F), and fewer retrieved lymph nodes (SMD = -0.13, 95%CI: 0.18 to 0.07, *P* < 0.001; Figure 6). Heterogeneity was not apparent in any of these outcome results according to the fixed-effects model. Sensitivity analysis demonstrated that no study could affect the pooled SMD for the operative time (Figure 3B). Visual assessment of the funnel plots (Figure 4B) and the Egger's test (Figure 5B) showed no evidence of publication bias for the operative time (*P* = 0.887).

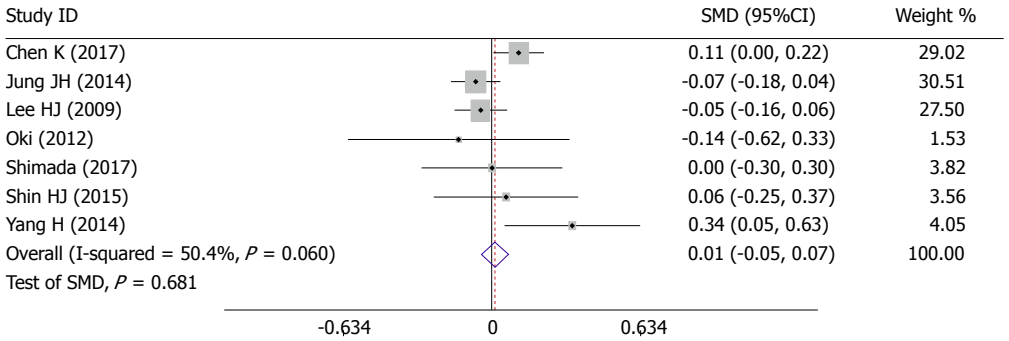
DISCUSSION

Obesity is traditionally considered a challenge for many surgeons who perform abdominal operations[28-30]. Until now, the impact of obesity on the short-term outcomes of LG for GC has been controversial[29,31]. This meta-analysis, including nine retrospective cohorts, aimed to investigate the correlation between obesity and the short-term outcomes of LG. Patients included were divided into a high BMI ($\geqslant$ 25 kg/m^2) and a normal BMI (< 25 kg/m^2) group based on the World Health Organization definition of obesity. Splenic hilar lymph node dissection is necessary for LTG, but it is difficult to expose the deep location of the splenic hilum and complicated vessels. LTG has been regarded as a risk factor for short-term outcomes of LG for GC[17]; therefore, studies solely focusing on LTG were excluded. Additionally, owing to the insufficient representativeness of the sample in the study with "pathological stage" limit, we excluded two studies

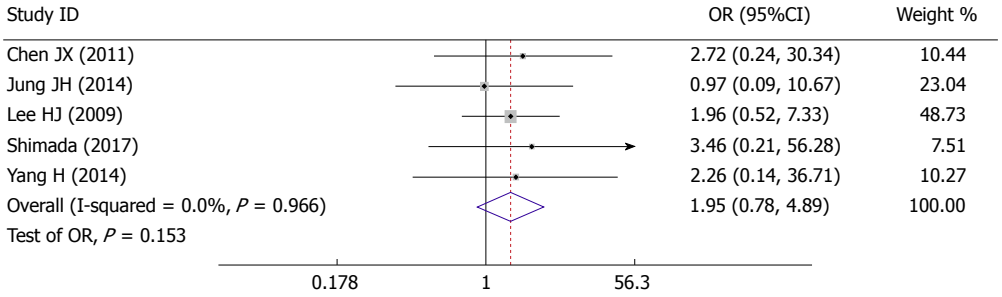
A


Study ID
OR (95%CI)
Weight %
Chen JX (2011) 1.77 (0.93, 3.40) 4.71
Chen K (2017) 1.07 (0.74, 1.54) 21.76
Jung JH (2014) 0.98 (0.70, 1.38) 25.97
Lee HJ (2009) 1.15 (0.84, 1.57) 28.42
Oki (2012) 0.41 (0.09, 1.90) 2.57
Shimada (2017) 1.22 (0.57, 2.61) 4.57
Shin HJ (2015) 1.57 (0.73, 3.38) 3.89
Yamada (2007) 1.01 (0.34, 3.02) 2.52
Yang H (2014) 1.31 (0.66, 2.58) 5.60
Overall (I-squared = 0.0%, P = 0.734) 1.12 (0.95, 1.33) 100.00
Test of OR, P = 0.169
0.898
1
11.1

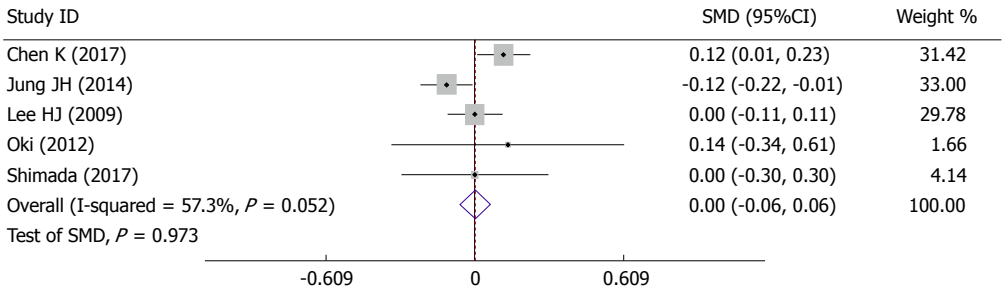
B


Study ID
SMD (95%CI)
Weight %
Chen K (2017) 0.11 (0.00, 0.22) 29.02
Jung JH (2014) -0.07 (-0.18, 0.04) 30.51
Lee HJ (2009) -0.05 (-0.16, 0.06) 27.50
Oki (2012) -0.14 (-0.62, 0.33) 1.53
Shimada (2017) 0.00 (-0.30, 0.30) 3.82
Shin HJ (2015) 0.06 (-0.25, 0.37) 3.56
Yang H (2014) 0.34 (0.05, 0.63) 4.05
Overall (I-squared = 50.4%, P = 0.060) 0.01 (-0.05, 0.07) 100.00
Test of SMD, P = 0.681
-0.634
0
0.634

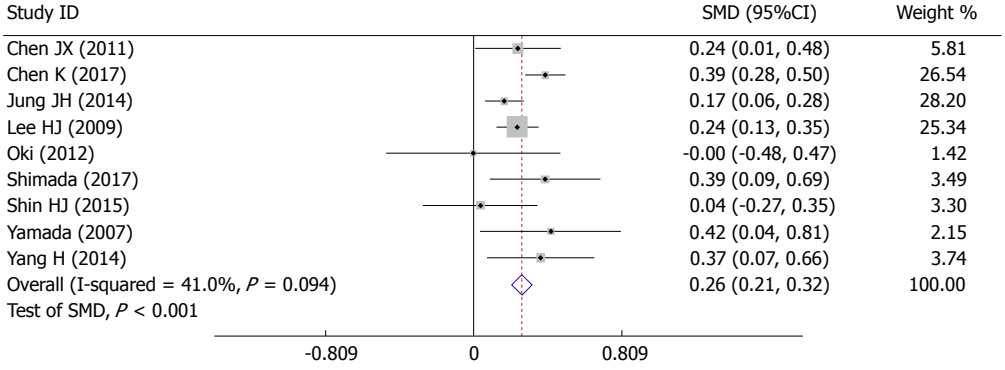
C


Study ID
OR (95%CI)
Weight %
Chen JX (2011) 2.72 (0.24, 30.34) 10.44
Jung JH (2014) 0.97 (0.09, 10.67) 23.04
Lee HJ (2009) 1.96 (0.52, 7.33) 48.73
Shimada (2017) 3.46 (0.21, 56.28) 7.51
Yang H (2014) 2.26 (0.14, 36.71) 10.27
Overall (I-squared = 0.0%, P = 0.966) 1.95 (0.78, 4.89) 100.00
Test of OR, P = 0.153
0.178
1
56.3

D


Study ID
SMD (95%CI)
Weight %
Chen K (2017) 0.12 (0.01, 0.23) 31.42
Jung JH (2014) -0.12 (-0.22, -0.01) 33.00
Lee HJ (2009) 0.00 (-0.11, 0.11) 29.78
Oki (2012) 0.14 (-0.34, 0.61) 1.66
Shimada (2017) 0.00 (-0.30, 0.30) 4.14
Overall (I-squared = 57.3%, P = 0.052) 0.00 (-0.06, 0.06) 100.00
Test of SMD, P = 0.973
-0.609
0
0.609

E


Study ID
SMD (95%CI)
Weight %
Chen JX (2011) 0.24 (0.01, 0.48) 5.81
Chen K (2017) 0.39 (0.28, 0.50) 26.54
Jung JH (2014) 0.17 (0.06, 0.28) 28.20
Lee HJ (2009) 0.24 (0.13, 0.35) 25.34
Oki (2012) -0.00 (-0.48, 0.47) 1.42
Shimada (2017) 0.39 (0.09, 0.69) 3.49
Shin HJ (2015) 0.04 (-0.27, 0.35) 3.30
Yamada (2007) 0.42 (0.04, 0.81) 2.15
Yang H (2014) 0.37 (0.07, 0.66) 3.74
Overall (I-squared = 41.0%, P = 0.094) 0.26 (0.21, 0.32) 100.00
Test of SMD, P < 0.001
-0.809
0
0.809

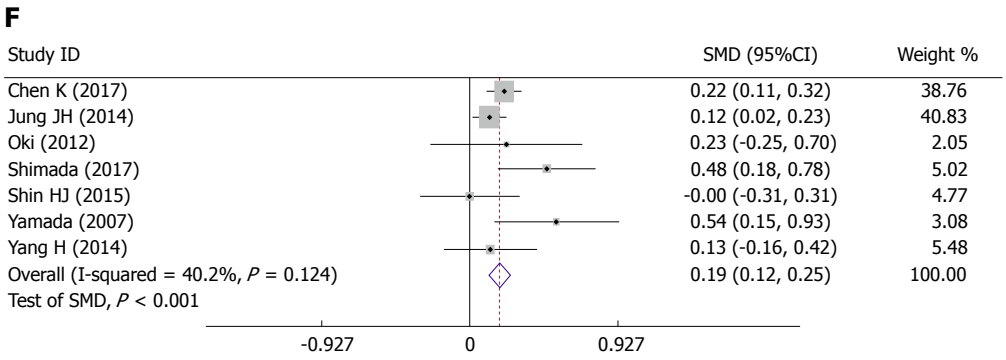


Figure 2 Correlation between body mass index and short-term outcomes/difficulties in laparoscopic gastrectomy. A: Correlation between body mass index (BMI) and postoperative complications in laparoscopic gastrectomy; B: Correlation between BMI and the duration of the postoperative hospital stay; C: Correlation between BMI and postoperative mortality; D: Correlation between BMI and the time to resuming food intake; E: Correlation between BMI and the operative time; F: Correlation between BMI and blood loss. SMD: Standard mean difference.

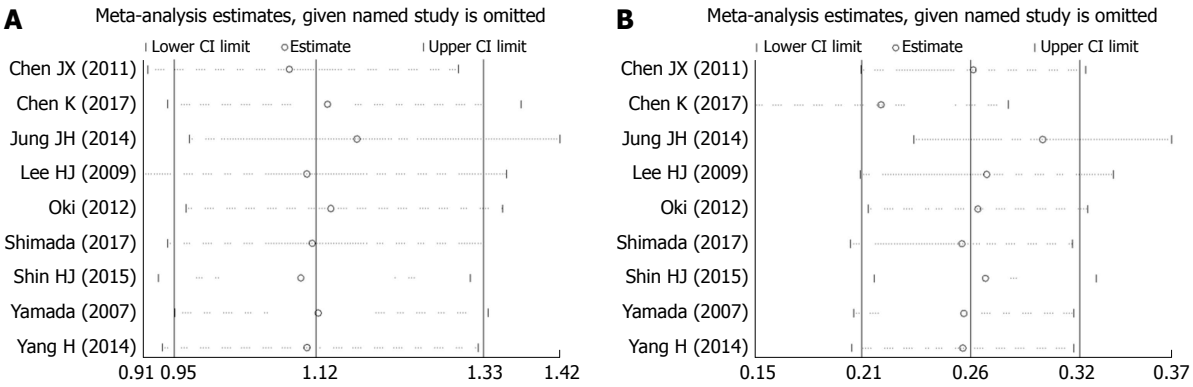


Figure 3 Sensitive analysis of association of postoperative complications and operative time with body mass index. A: Sensitive analysis of correlation between body mass index (BMI) and postoperative complications in laparoscopic gastrectomy; B: Sensitive analysis of correlation between BMI and the operative time.

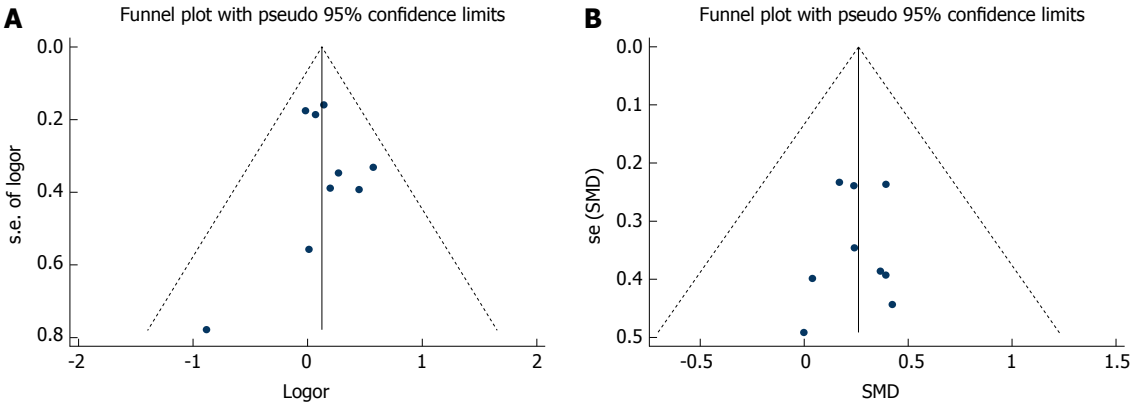


Figure 4 Funnel plot analysis of association of postoperative complications and operative time with body mass index. A: Funnel plot analysis of correlation between body mass index (BMI) and postoperative complications in laparoscopic gastrectomy; B: Funnel plot analysis of correlation between BMI and the operative time. SMD: Standard mean difference.

with this limit (one for solely including patients with early stage GC and the other for solely including patients with advanced GC).

Operative time, blood loss, and the number of retrieved lymph nodes were defined as indices of difficulties in LG. Our study has clearly demonstrated that the correlation between BMI and operative difficulties was significant. Patients undergoing LG with a high BMI have longer operative time (SMD = 0.26, 95%CI: 0.21 to 0.32, $P < 0.001$), greater blood loss (SMD = 0.19, 95%CI: 0.12 to 0.25, $P < 0.001$), and fewer retrieved lymph nodes (SMD = -0.13, 95%CI: 0.18 to 0.07, $P < 0.001$). Likely due to hindered exposure to the stomach and pancreas, LG performed in patients with obesity is more technically

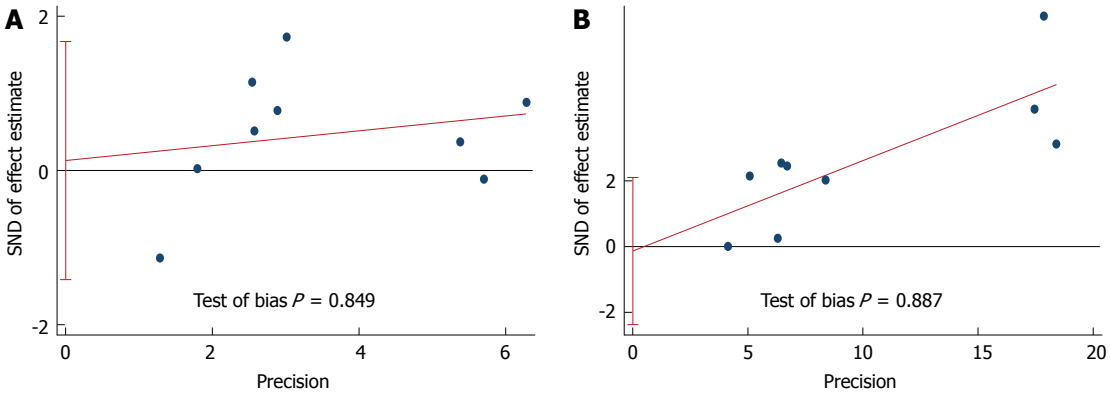


Figure 5 Egger's test of association of postoperative complications and operative time with body mass index. A: Egger's test of correlation between body mass index (BMI) and postoperative complications in laparoscopic gastrectomy; B: Egger's test of correlation between BMI and the operative time.

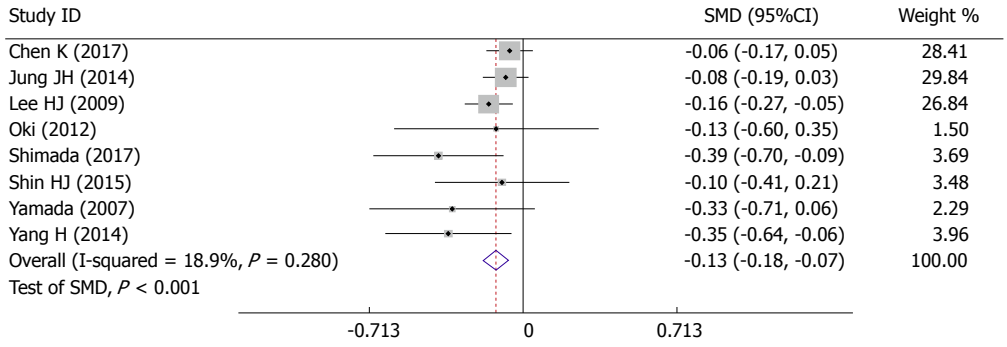


Figure 6 Correlation between body mass index and the number of retrieved lymph node. SMD: Standard mean difference.

demanding. The thickened mesentery, omentum, and ligamentum are very common in obese patients under certain circumstances and may lead to difficulties in the operative procedure, especially in ligation, dissection, or anatomy of the vessels and lymph nodes. Fatty stomach and omentum can also result in severe challenges owing to the stomach pulled by the surgeon. Blood bleed during the operation, caused by excessive incrassate and fat mesenteries, is hard to stop in this narrow area surrounded by adipose tissue. It can be inferred that sensation recovery from anesthesia would be delayed in virtue of distribution of anesthetic agents affected by increased technical difficulties during exposure of an adequate operative field. Each of these potential factors contributes to longer surgical time and increased blood loss[19]. As to the lower number of retrieved lymph nodes, it may be conferred that dissection of lymph nodes for patients with obesity could be limited by excess adipose tissue and structures. Obtaining lymph nodes from a mass of fat tissue could be more difficult than normal tissue and may be regarded as the other contributing factor to fewer retrieved lymph nodes; however, in all studies, the number of retrieved lymph nodes in the obese group was greater than the standard (> 15) recommended by the National Comprehensive Cancer Network (NCCN) guidelines, which suggests that LG can also ensure the curative effect in obese patients with GC.

Postoperative complications, the duration of postoperative hospital stay, postoperative mortality, and time to resuming food intake were estimated as the impact of BMI on the short-term outcomes of LG. Our meta-analysis provided strong evidence that the correlation between BMI and postoperative short-term outcomes was not significant. In addition, anastomotic leakage, anastomotic stricture, anastomotic bleeding, abdominal abscess, pancreatic leakage, ileus, and wound infection would also be included in subgroup analysis. The results showed that BMI is not significantly associated with either overall postoperative complications or a particular one. The most critical factor contributing to this condition would be anastomosis. The excessive torsion of remnant stomach and duodenum could be avoided during the procedure of anastomosis performed by an experienced surgeon, especially in totally laparoscopic gastrectomy (TLG) which is becoming prevalent in Asian areas[25]. In addition, the lower number of retrieved lymph nodes resulting from increased surgical difficulties also indicated that surgeons would be more careful and cautious during the operative procedure, and the injury of tissues and structures would be avoided to some extent. High-quality pre- and postoperative management could also help surgeons improve the patients' overall conditions and identify minor problems through observed indices on time, such as the amount of intro-abdominal bile drainage and the wound healing condition. Milder procedures and smaller wounds as well as careful pre-

and postoperative management result in lower rates of postoperative complications[21]. Furthermore, to an extent, the results suggest that the assessment of obesity based solely on BMI may be insufficient. The distribution and amount of abdominal fat in an individual patient may not be accurately reflected by BMI, since it is a simple calculation based on weight and height[23]. For instance, patients with a large amount of subcutaneous fat may have normal amounts of visceral and intra-abdominal fat that would not alter the difficulties and short-term outcomes of LG. Recent studies confer that visceral fat area is a more accurate predictor of intro- and postoperative outcomes than high BMI in obese patients due to its feasibility to evaluate the distribution of intra-abdominal fat[32-34].

Limitations

Although we have searched recent publications using a rigorous search strategy, there are still some limitations to this meta-analysis. First, although all of the included studies obtained at least eight points, almost all of them were retrospective cohort studies. Although the randomized clinical trials (RCTs) are the gold standard for study design, it is hardly feasible to allocate patients with different BMIs randomly. Second, nine studies were included with a total sample size of 6077, which is relatively small. A larger sample size is needed to support the evidence. Third, as patients in Western countries have a higher BMI compared to Asian patients, our results should be considered carefully when being applied to other races, and more relevant studies should be performed worldwide.

In conclusion, our meta-analysis clearly supports that although high BMI in Asian patients with GC could increase the difficulties in LG with regard to operative time, blood loss, and the number of retrieved lymph nodes, there was no significant association between BMI and postoperative short-term outcomes, including postoperative complications, the duration of the postoperative hospital stay, postoperative mortality, and time to resuming food intake in Asian patients. It strongly demonstrates that a high BMI may not be a risk factor for short-term outcomes of patients undergoing LG if performed by an experienced surgeon with careful pre- and post-operative management, in contrast with the perspectives reported by previous studies. It may not be enough to estimate difficulties and postoperative outcomes in patients with GC undergoing LG using BMI as the only index to assess obesity. Other indices, for instance, VSA, should be taken into account.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the second most prevalent cause of cancer-related deaths worldwide. Since 1994, laparoscopic gastrectomy (LG) has become increasingly popular for treating early GC in patients. The prevalence of obesity is increasing steadily in Asian countries. Obesity is regarded as a risk factor for worse surgical outcomes of complicated surgical procedures. Furthermore, patients with obesity have a higher risk of operative difficulties, as well as wound infection.

Research motivation

Recently, the impact of obesity on the short-term LG in patients has been controversial due to several studies. For instance, some studies reported that the association between obesity and LG was significant, while others reported the opposite conclusion.

Research objectives

To date, although several studies evaluating the body mass index (BMI) as an index to assess obesity and short-term outcomes of LG, the results have been controversial and limited. Hence, we conducted this meta-analysis to summarize all of the available evidence.

Research methods

The PubMed, Cochrane, EMBASE, and Web of Science databases were searched for studies that focused on the impact of obesity on the short-term outcomes of LG for GC in Asian patients who were classified into a high BMI (BMI $\geqslant$ 25 kg/m^2) or low BMI group (BMI < 25 kg/m^2). The results are expressed using the pooled odds ratio (OR) for binary variables and standard mean difference (SMD) for continuous variables with 95% confidence interval (CI), and were calculated according to the fixed-effects model while heterogeneity was not apparent or a random-effects model while heterogeneity was apparent.

Research results

Nine studies, with a total sample size of 6077, were included in this meta-analysis. Compared with the low BMI group, the high BMI group had longer operative time (SMD = 0.26, 95%CI: 0.21 to 0.32, P < 0.001), greater blood loss (SMD = 0.19, 95%CI: 0.12 to 0.25, P < 0.001), and fewer retrieved lymph nodes (SMD = -0.13, 95%CI: 0.18 to 0.07, P < 0.001). There was no significant difference between the high and low BMI groups in postoperative complications (OR = 1.12, 95%CI: 0.95 to 1.33, P = 0.169), the duration of postoperative hospital stay (SMD = 0.681, 95%CI: -0.05 to 0.07, P = 0.681), postoperative mortality (OR = 1.95, 95%CI: 0.78 to 4.89, P = 0.153), or time to resuming food intake (SMD = 0.00, 95%CI: -0.06 to 0.06, P = 0.973).

Research conclusions

Our meta-analysis provides strong evidence that despite the longer operative time, greater blood loss, and fewer retrieved lymph nodes, the association between BMI and the short-term outcomes of laparoscopic gastrectomy for GC, including postoperative complications, the duration of postoperative hospital stay, postoperative mortality, and time to resuming food intake was not significant. BMI could be a poor risk factor for short-term outcomes of LG. Other indices should be taken into account.

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META-ANALYSIS

Scoring systems for prediction of mortality in decompensated liver cirrhosis: A meta-analysis of test accuracy

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Abstract

AIM

To compare the accuracy of the scoring systems Child-Turcotte-Pugh (CTP), Model for End-stage Liver Disease score (MELD), MELD-Na, and MELD to Serum Sodium ratio (MESO) to predict the mortality in decompensated liver cirrhosis.

METHODS

The PubMed, Web of Science, Cochrane Library, EMBASE, and Ovid databases were systematically searched from inception to September 2018 for relevant articles, and we evaluated the quality of the included studies. The accuracy of scoring systems was analyzed with Stata 12 and MetaDiSc 1.4.

RESULTS

Sixteen studies involving 2337 patients were included. The pooled areas under the summary receiver operating characteristic curves (AUROCs) of CTP, MELD, MELD-Na, and MESO to predict mortality were 0.81,

0.78, 0.85, and 0.86, respectively. Within 3 mo, the AUROCs of CTP, MELD, and MELD-Na in predicting mortality were 0.78, 0.76, and 0.89, respectively. The AUROCs of CTP, MELD, and MELD-Na at 3 mo were 0.86, 0.78, and 0.86, respectively. The AUROCs of CTP, MELD, and MELD-Na at 6 mo were 0.91, 0.83, and 0.90, respectively. The AUROCs of CTP, MELD, and MELD-Na at 12 mo were 0.72, 0.75 and 0.84, respectively. In cirrhotic patients with bleeding, the AUROCs of CTP and MELD were 0.76 and 0.88, respectively.

CONCLUSION

MESO has the highest AUROC in all assessed scoring systems. Considering the different time points, MELD-Na has good accuracy in predicting the mortality of decompensated liver cirrhosis. Compared to CTP, MELD is better in predicting variceal bleeding.

Key words: Liver cirrhosis; Decompensated; Mortality; Accuracy; Meta-analysis

Core tip: Liver cirrhosis, especially decompensated liver cirrhosis, is a common chronic disease that is also the leading cause of death among nonmalignant diseases worldwide. The poor survival of decompensated cirrhosis has pushed doctors to find more accurate prognostic scoring systems to recognize and manage patients. No meta-analysis has focused on comparison of the prediction accuracy for those patients in the past. This study aimed to compare the test accuracy of four systems [Child-Turcotte-Pugh, Model for End-Stage Liver Disease score (MELD), MELD-Na, and MELD to Serum Sodium ratio] quantitatively and to pinpoint the more reliable scoring system for forecasting the mortality of decompensated liver cirrhosis patients clinically.

Wu SL, Zheng YX, Tian ZW, Chen MS, Tan HZ. Scoring systems for prediction of mortality in decompensated liver cirrhosis: A meta-analysis of test accuracy. *World J Clin Cases* 2018; 6(15): 995-1006 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/995.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.995

INTRODUCTION

Liver cirrhosis is a common chronic disease that is also the leading cause of deaths among nonmalignant diseases worldwide. Its development includes an asymptomatic phase called "compensated" cirrhosis, followed by a progressive phase characterized by hypertension and/or liver dysfunction, including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatorenal syndrome, and hepatocellular carcinoma, which is called "decompensated" cirrhosis[1]. Decompensated cirrhosis is associated with a risk of death that is 9.7 times higher than the risk in the general population[2]. The poor survival of patients with decompensated cirrhosis has pushed doctors to explore more efficient treatment methods and to find more accurate prognostic scoring systems to recognize and manage the patients[3-5]. On one hand, accurate prognostic scoring systems could help clinicians make better diagnoses and select effective therapies with less time, thus improving the prognosis of patients. In addition, the mathematical model could be used as a tool to better allocate donated organs to recipients in need among the liver transplantation community[6,7].

Until now, various scoring systems have been used to predict the mortality of liver decompensated cirrhosis, including the Child–Turcotte–Pugh (CTP), Model for End-stage Liver Disease score (MELD), MELD-Na, MELD to Serum Sodium ratio (MESO) and so on. The CTP[8] is a "modified Child score" that was first proposed in 1964, and it has been widely used for several decades for the prognostication of patients with cirrhosis[9]. Due to the lack of statistical weighting and factors resulting from complications, such as renal and pulmonary dysfunction, CTP is limited in predicting the mortality of decompensated cirrhosis patients[10]. Thus, in 2001, MELD was established by UNOS for allocation. This scoring system added serum creatinine, total serum bilirubin, international normalized ratio for prothrombin time evaluation, and the etiology of cirrhosis as predicting factors. Compared to CTP, MELD is more objective and clinically useful for defining disease severity[11,12].

In the following years, research emerged claiming that serum Na was a predictor of mortality in patients with cirrhosis and might improve the accuracy of MELD[13-15]. Then, based on MELD, refined models were established for prediction of mortality in liver disease. Biggins *et al*[16] developed an evidence-based model, "MELD-Na," which was calculated with the formula "MELD-NA = MELD + 1.59 (135-Na)". Huo *et al*[17], based on the MELD, devised serum sodium ratio index (MESO) to enhance the precision of MELD's predictions in compensated and decompensated patients. It is expressed as "MESO index = (MELD Score/SNa mEq/L)*10". The performances of all scoring systems are diverse in their application, and it remains unknown which scoring system is better. Previous meta-analyses, which used simple pooling to evaluate prediction accuracy for the assessment of the prognostic value in liver cirrhosis, have only compared CTP and MELD, which made the conclusions less convincing[18].

To our knowledge, no meta-analysis has focused on the comparison of the prediction accuracy of mortality in all four scoring systems in decompensated liver cirrhosis patients. This study aimed to quantitatively compare the test accuracy of all four systems (CTP, MELD, MELD-Na, and MESO) and to pinpoint the more reliable scoring system to forecast the mortality of decompensated liver cirrhosis patients clinically.

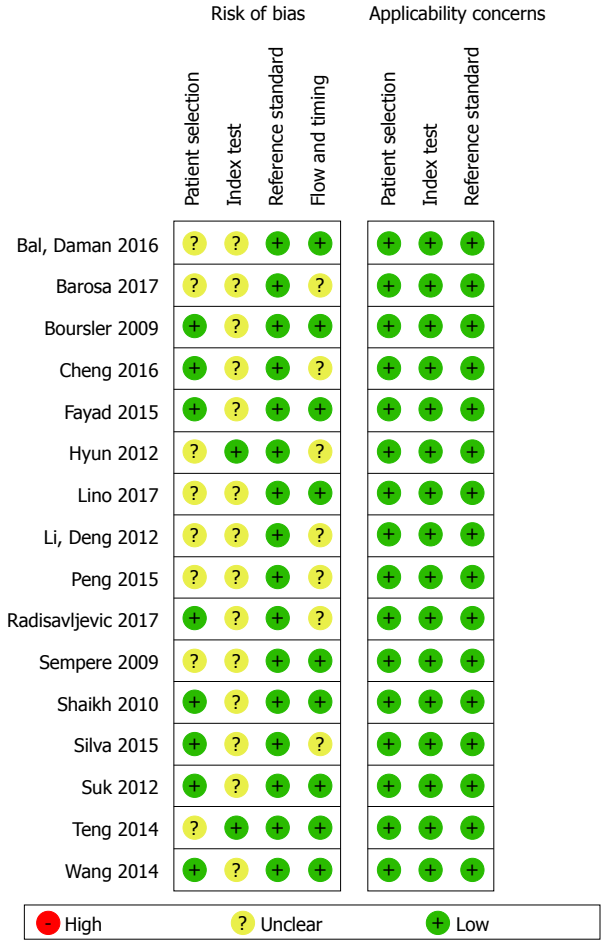

Figure 1 Results of quality assessment of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 scale.

MATERIALS AND METHODS

Literature search and study selection

The PubMed, Web of Science, Cochrane Library, EMBASE, and Ovid databases were systematically searched from inception to September 2018. For the literature search, the following keywords or corresponding terms were used: ("Child-Turcotte-Pugh score" OR "CTP" OR "Child score" OR "Child-Pugh score" OR "Model for End-stage liver disease score" OR "MELD" OR "MELD-Na" OR "MELD to Serum sodium ratio" OR MESO) AND "Decompensated liver cirrhosis" AND ("outcome" OR "prediction" OR "sensitivity" OR "specificity" OR "diagnostic accuracy"). In addition, relevant original articles were retrieved through literature review. Studies that met the following requirements were included in our research: (1) The study population included decompensated liver cirrhosis patients with various causes; (2) Scoring systems were used to predict the mortality of decompensated liver cirrhosis patients; and (3) It provided sufficient data with evaluation outcomes such as true negativity (TN), true positivity (TP), false negativity (FN), and false positivity (FP), or data that could be used to calculate these results. Language, publication year, sample size, and study design were not strictly limited in the inclusion criteria.

When the same patient population was studied in more than one publication, only the one with most relevant data was included in this review. Two investigators, Wu and Tian, independently reviewed the potentially eligible studies and then cross-checked their results. Disagreements between them were resolved by discussion. Unsettled disagreements were referred to a third researcher, Zheng, for a final decision.

Data extraction

Apart from evaluation outcomes such as TN, TP, FN, and FP, we also extracted the following data from the selected studies: first author, country, sample size, etiology, endpoint, cut-off values of the scoring system, and sex and age of the population.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies 2 scale[19] was used to evaluate the quality of the included studies. Four domains were related to bias (patient selection, index text, reference standard, and flow and timing) and three domains were related to applicability (patient selection, index text, and reference standard). For quality assessment, 14 of 16 articles were graded as having low bias in more than four domains, which indicated that the quality was good. The detailed results of the quality assessment of all included studies is shown in Figures 1 and 2.

Statistical analysis

Due to the diversity of the cut-off values in different scoring systems, a bivariate model (a random model) was used to estimate the summary diagnostic odd ratios (DORs), summary sensitivities, and summary specificities. The summary receiver operating characteristic curve (SROC) and the area under the SROC (AUROC) were used to measure the predictive value of each scoring system. When the number of studies was $\leqslant 3$, we considered simple pooling to evaluate the above results.

Statistical heterogeneity among studies included the threshold effect and the non-threshold effect. Spearman correlation analysis of the sensitivity logarithm and (1-specificity) logarithm [logit (true positive rate) *vs* logit (false positive rate)] was used to assess the effect of the threshold. The merge sensitivity, specificity, and DOR would be used to evaluate the diagnostic efficiency when the effect of threshold was removed ($P > 0.1$); otherwise, fitting SROC and computing AUROC were alternatives. Cochrane's Q-test and the I^2 statistic were used to assess the non-threshold effect. $I^2 > 50\%$ indicates substantial heterogeneity between studies; if so, a random effects model was used in simple pooling. Subgroup analyses were conducted according to the end-points to identify the potential source of heterogeneity. Further, we used Deek's funnel plot asymmetry to assess potential publication bias.

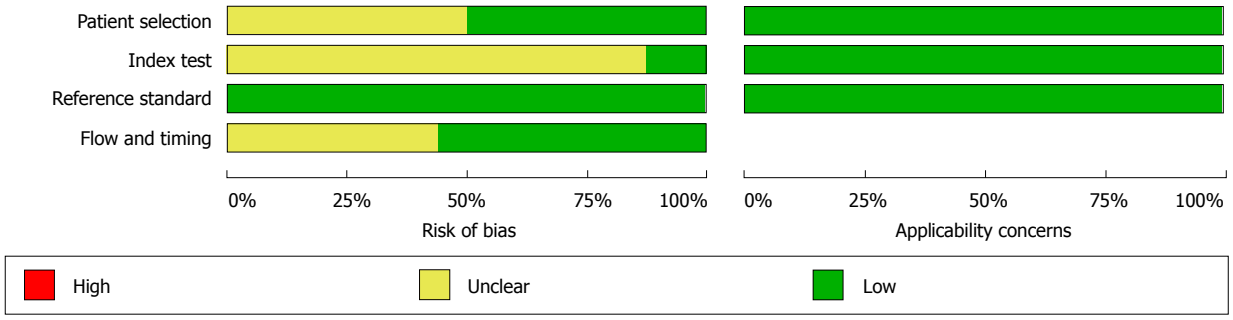

Figure 2 The overall quality of the included studies.

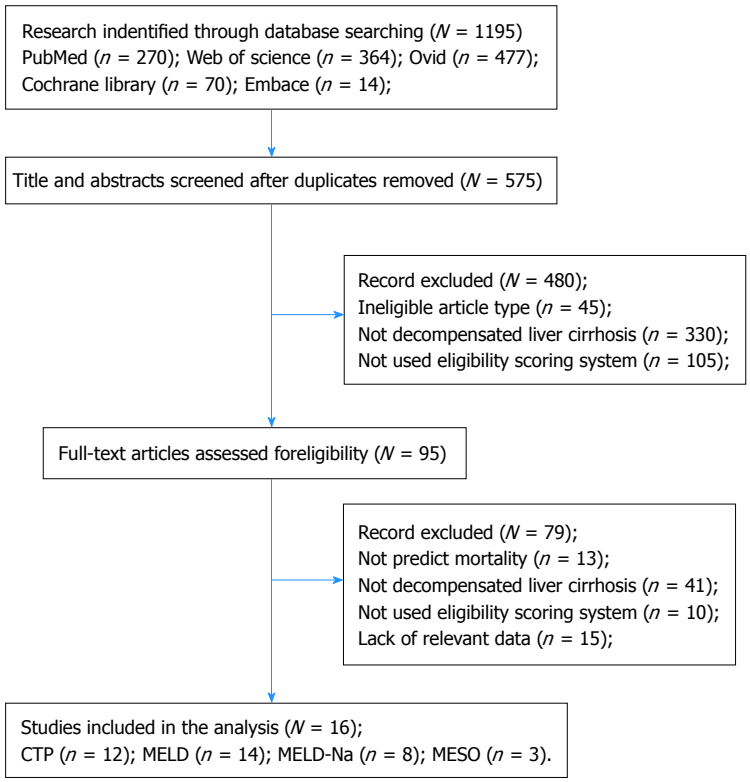

Figure 3 Flow diagram of study selection. CTP: Child–Turcotte–Pugh; MELD: Model for End-stage Liver Disease score; MESO: MELD to Serum Sodium ratio.

Stata 12.0, Meta-DiSc 1.4, and Review Manager 5.3 were used to analyze the data and calculate all the parameters. All comparisons were considered statistically significant if $P \leqslant 0.05$ (two-sided test). To our knowledge, no protocol of the present review has been published or registered.

RESULTS

Basic information

Sixteen eligible[20-35] studies involving 2337 decompensated liver cirrhosis patients were included in this meta-analysis, and the flow diagram for the selection of the articles is shown in Figure 3.

Overall, there were 12 studies involving 1722 decompensated liver cirrhosis patients for the analysis of CTP; 14 studies involving 2034 patients for MELD; 8 studies involving 1340 patients for MELD-Na; and 3 studies involving 422 patients for MESO. The characteristics of the included studies are listed in Table 1.

Overall analysis

Twelve studies assessed the performance of CTP in predicting the mortality of patients. The spearman correlation coefficient for logit (true positive rate) *vs* logit (false positive rate) for CTP was 0.34 (P = 0.28), indicating no effect of threshold. The summary sensitivity was 0.73 (95%CI: 0.64-0.81) and the summary specificity was 0.75 (95%CI: 0.67-0.82). The forest plot is shown in Figure 4A. The AUROC of CTP was 0.81 (95%CI: 0.77-0.84) (Figure 5A). The linear regression of funnel plot asymmetry found no publication bias for the performance of CTP (P = 0.50) (Figure 6A).

Table 1 The characteristics of studies included in the meta-analysis

Study	Country	Study design	Sex (M/F)	Age (yr)	Number of patients	End-point of observation	Scoring system	Etiology
Radisavljevic *et al*[20], 2017	Peru	p	79/8	54	87	29 mo	CTP, MESO, MELD	Alcohol
Iino *et al*[21], 2017	Japan	r	39/8	60	47	1.5 mo	CTP, MELD	HBV, HCV, Alcohol, Others
Barosa *et al*[22], 2017	Portugal	r	Unknown	62	49	1, 3 mo	CTP, MELD, MELD-Na	Alcohol, HCV
Cheng *et al*[23], 2016	China	p	87/12	48	98	1, 3, 6, 12 mo	CTP, MELD, MELD-Na	HBV
Bal *et al*[24], 2016	India	r	177/41	50	218	1.6 mo	MELD-Na	Ethanol, Crypto/NAFLD,HCV
Silva *et al*[25], 2015	Brazil	p	140/52	54	192	1 mo	MELD, CTP	Alcohol, HBV, HCV, Cryptogenic, Others
					189	3 mo	MELD, CTP	
Fayad *et al*[26], 2015	Brazil	p	94/29	54	123	In hospital	MELD, MELD-Na, MESO	HBV, HCV, Alcohol, Cryptogenic, Others
Suk *et al*[27], 2012	Korea	p	46/11	48	57	36 mo	MELD, MELD-Na	Alcohol, Viral, Alcohol + Viral
Li *et al*[28], 2012	China	r	133/79	56	212	3, 6, 12 mo	MELD, MELD-Na, MESO	HBV, HCV, Alcohol, Primary biliary cirrhosis, Other
Shaikh *et al*[29], 2010	India	p	72/38	47	110	In hospital	MELD, CTP	HBV, HCV
Boursier *et al*[30], 2009	France	p	93/61	59	154	6 mo	CTP, MELD, MELD-Na	Alcohol, Viral, Others
Hyun *et al*[31], 2012	Korea	r	63/23	54	83	6 mo	CTP	HBV
Peng *et al*[32], 2015	China	r	94/51	57	145	In hospital	MELD, CTP	HBV, HCV, Alcohol, Unknown, Others
Sempere *et al*[33], 2009	Spain	r	142/59	59	201	1.5, 3, 12, 36 mo	MELD, CTP	Alcohol, Viral, Others
Teng *et al*[34], 2014	China	r	110/22	51	132	1.5 mo	MELD, CTP	Alcohol, HBV, HCV,
Wang *et al*[35], 2014	China	p	340/89	49	429	3, 12 mo	CTP, MELD-, MELA-Na	HCV, HBV, Alcohol, Biliary, Others

p: Prospectively study; r: Retrospectively study; CTP: Child–Turcotte–Pugh; MELD: Model for End-stage Liver Disease score; MESO: MELD to Serum Sodium ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease.

Fourteen studies assessed the performance of the MELD score in predicting the mortality of patients. The spearman correlation coefficient for MELD was -0.10 (P = 0.74), indicating no effect of threshold. The summary sensitivity was 0.65 (95%CI: 0.59-0.71) and the summary specificity was 0.82 (95%CI: 0.76-0.86). The forest plot is shown in Figure 4B. The AUROC of the MELD score was 0.78 (95%CI: 0.74-0.81) (Figure 5B). The linear regression of funnel plot asymmetry found no publication bias for the performance of MELD (P = 0.60) (Figure 6B).

Eight studies assessed the performance of MELD-Na in predicting the mortality of patients. The Spearman correlation coefficient for MELD-Na was 0.67 (P = 0.07), indicating the threshold effect; thus, the sensitivity and specificity were not calculated. The AUROC of the MELD-Na score was 0.85 (95%CI: 0.81-0.88) (Figure 5C). The linear regression of funnel plot asymmetry found no publication bias for the performance of MELD-Na (P = 0.51) (Figure 6C).

There were only three studies available to assess the prediction value of MESO. We used simple pooling to evaluate the ability for prediction. The Spearman correlation coefficient was 0.50 (P = 0.67), indicating no threshold effect. The I^2 was 66.0%, indicating high heterogeneity, so we used a random model. The summary sensitivity was 0.67 (95%CI: 0.58-0.74) and summary specificity was 0.84 (95%CI: 0.79-0.88). The AUROC of MESO was 0.86 (95%CI: 0.79-0.93).

Overall, MESO was the best model in predicting the mortality of the decompensated cirrhosis patients according to the AUROC.

Subgroup analysis

We analyzed the prediction ability at different time points for CTP, MELD, and MELD-Na. The time points were divided as within 3 mo, 3 mo, 6 mo, and 12 mo. The results of analysis at different time points are shown in Table 2. In all models (CTP, MELD, and MELD-Na), AUROC was the highest at 6 mo and the lowest at 12 mo. For the prediction ability at different time points, MELD-Na had the highest AUROC in the within 3 mo group (0.89) and the 12-mo group (0.84). Both MELD-Na and CTP had the highest AUROC in the 3-mo group (0.86) among the four models. The AUROC of CTP was the highest in the 6-mo group (0.91).

Furthermore, the overall mortality rates of variceal hemorrhage patients have been reported to be up to 30%-50% and 1-year mortality as high as 70% historically[36].

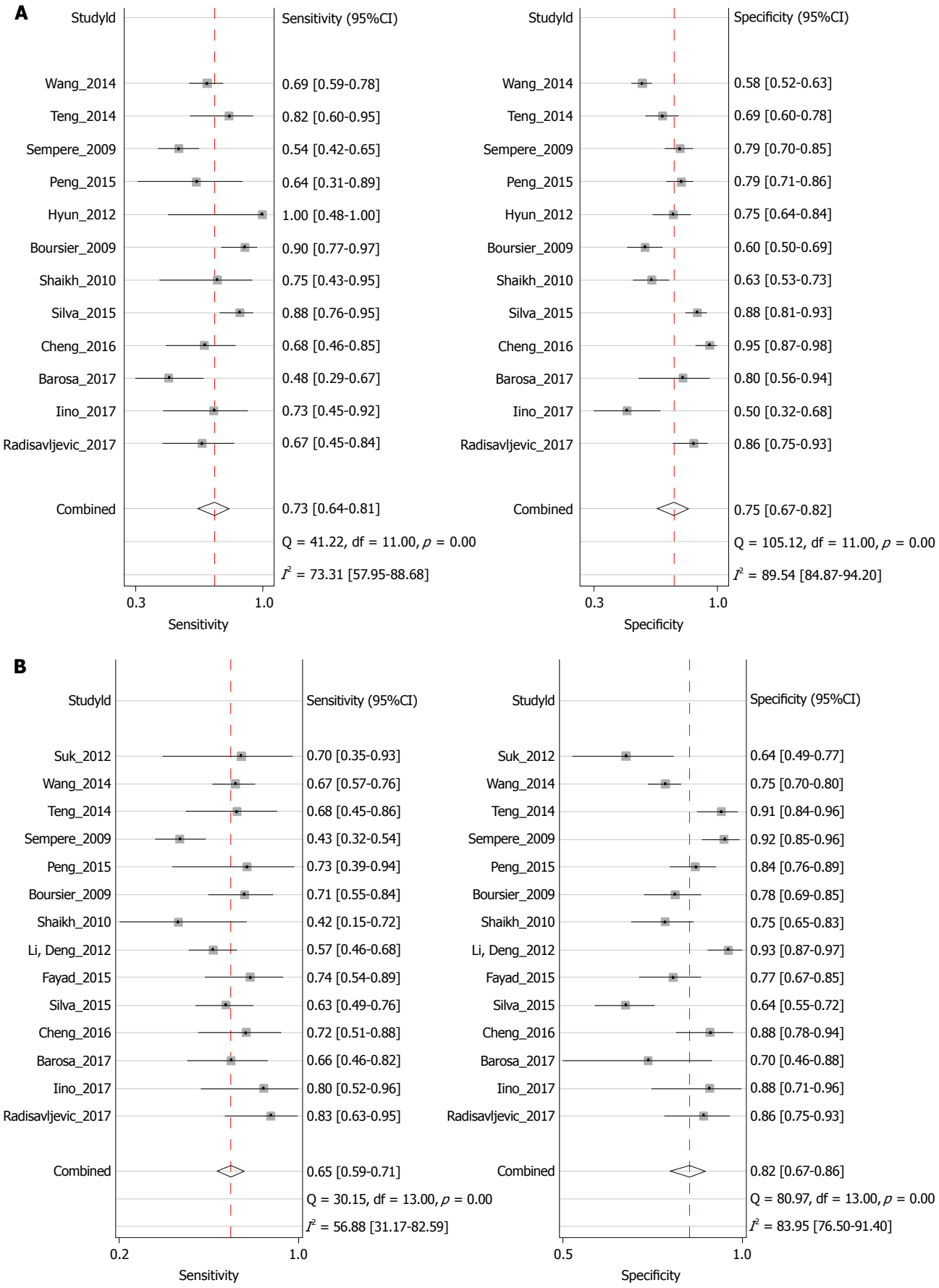

Figure 4 Forest plots of pooled results of different scoring systems. A: Child–Turcotte–Pugh score; B: Model for End-stage Liver Disease score.

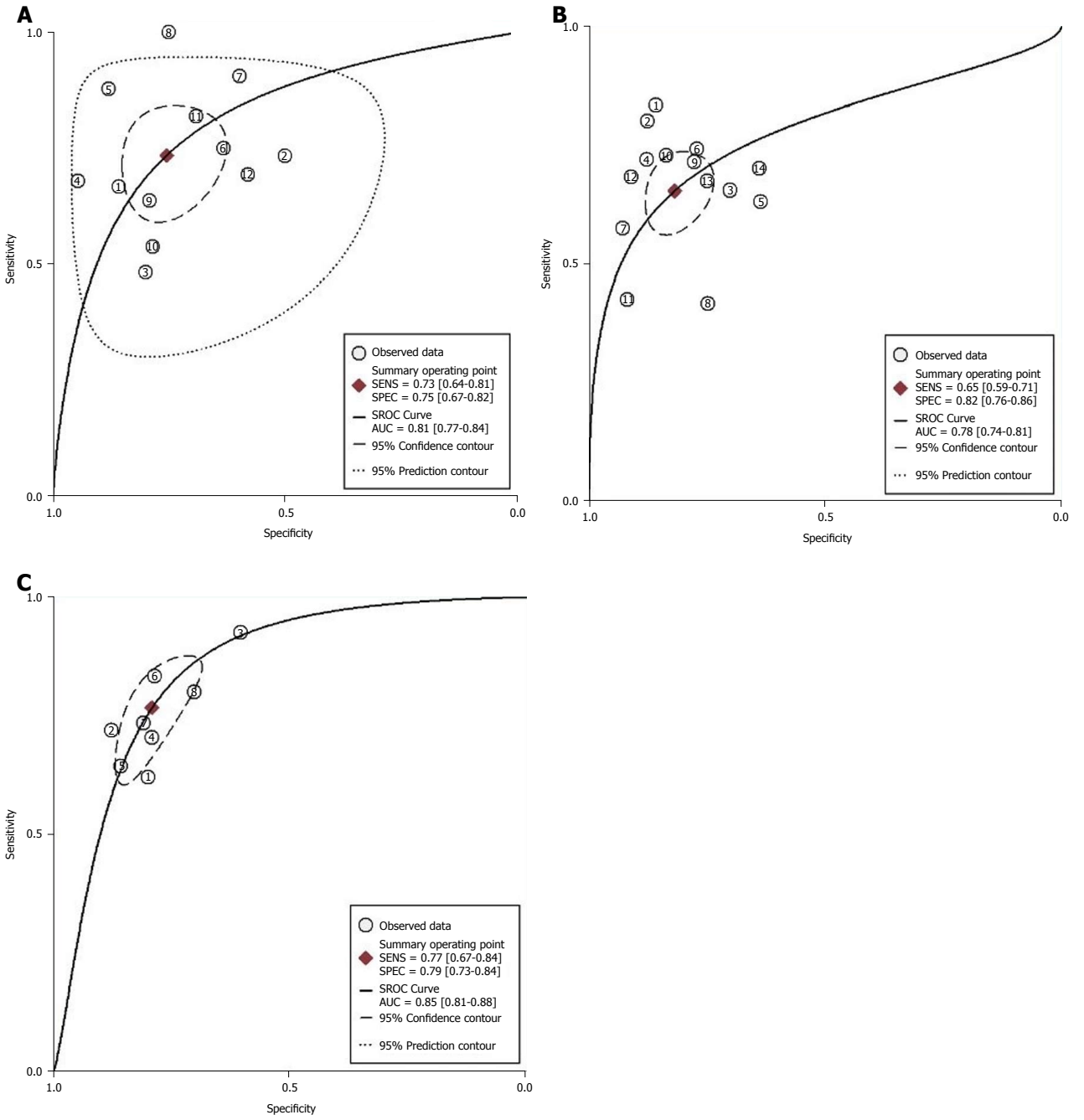

Figure 5 Summary receiver operating characteristic curves of different scoring systems. A: Child–Turcotte–Pugh; B: Model for End-stage Liver Disease (MELD) score; C: MELD-Na.

Thus, we conducted subgroup analysis to assess the performance of CTP and MELD score in predicting short-term mortality between variceal hemorrhage and others. The results showed that the AUROC of MELD was higher than that of CTP score (0.88 *vs* 0.76) in variceal hemorrhage patients. The detailed results are shown in Table 3.

DISCUSSION

This systematic review of the prognostic accuracy of CTP, MELD, MELD-Na, and MESO index included 16 studies involving 2337 patients. All their AUROC values were greater than 0.7, which demonstrated that the CTP, MELD, MELD-Na, and MESO index have certain prognostic value. MESO has the highest AUROC in all the assessed scoring systems.

CTP, as a reference for cirrhosis prognosis, has been used for more than 30 years. The drawback was that its indexes were subjective and unstable. Compared with the CTP score, MELD has some advantages. On one hand, three in four parameters were from a laboratory, which was more objective, stable, and easy, and only the index "etiology of cirrhosis" was affected by subjective factors explained by a clinician[37]. Additionally, the MELD score value was constant, and there

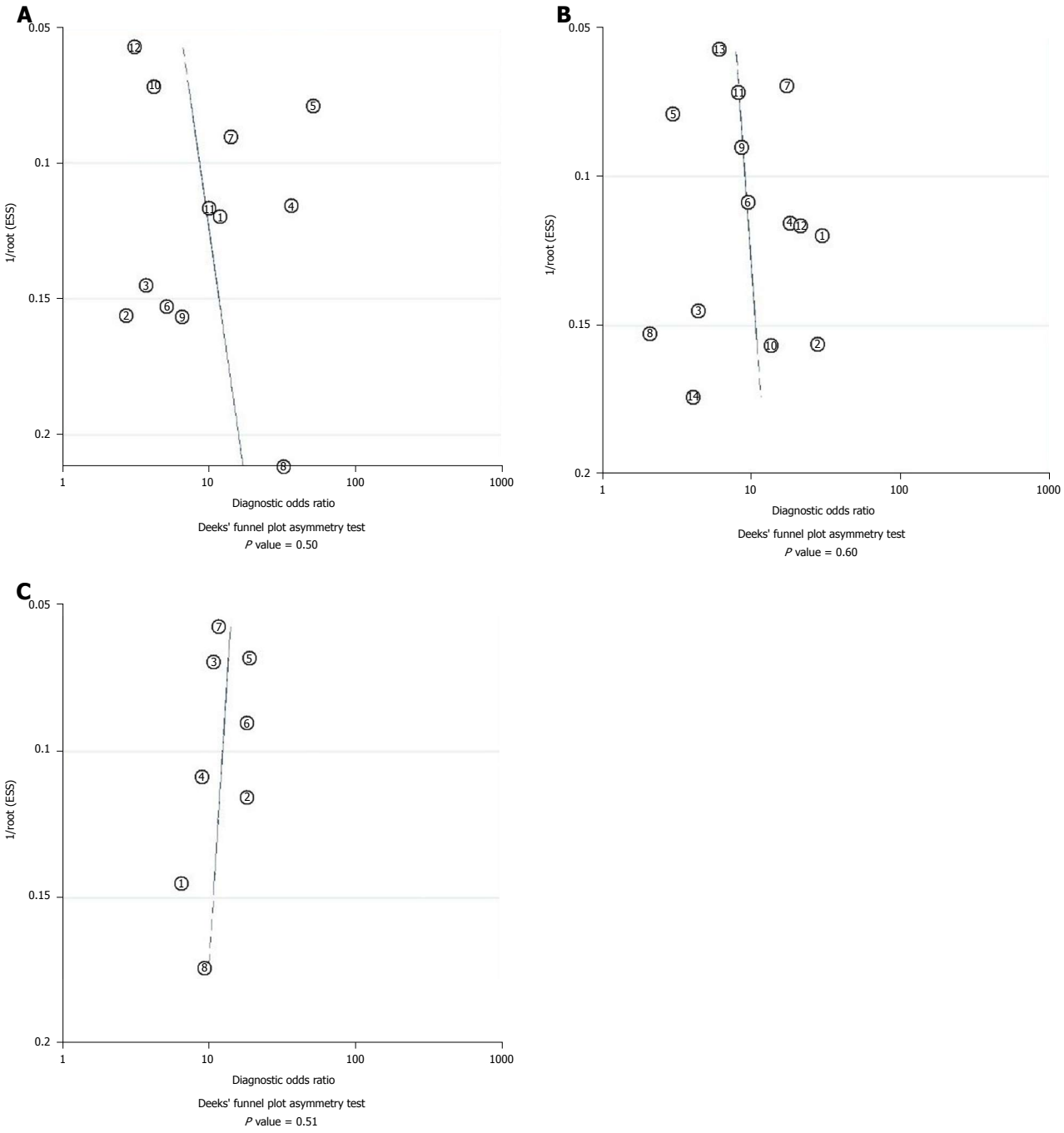

Figure 6 Results of linear regression test of funnel plot asymmetry for publication bias. A: Child–Turcotte–Pugh; B: Model for End-stage Liver Disease (MELD) score; C: MELD-Na.

was no "top value" or "bottom value" to predict the state of an illness. As a tool for allocation[12,38], MELD was based on verifiable measures of disease severity with minimal emphasis on waiting time[39]. Based on this meta-analysis with decompensated liver cirrhosis patients, MELD cannot replace CTP completely, and CTP still has good value for clinical application, particularly in 6-mo and 12-mo mortality prediction. CTP remains a reliable model to predict, and it might be suitable for the individual assessment of decompensated liver disease in daily clinical practice due to its simplicity and practicality[40]. Although CTP seemed subjective to some extent, clinical experience may be used to estimate the real state of illness rapidly and exhaustively, while some objective laboratory measurement parameters cannot. After all, there is significant clinical uncertainty.

Our meta-analysis results demonstrated that the prognostic accuracy of MELD-Na and MESO was higher than that of MELD. At different end-points, all the AUROC of MELD-Na was greater than or equal to 0.84. MELD-Na was superior to CTP and MELD for predicting mortality after 12 mo, indicating that MELD-Na was a good model to predict long-term mortality in decompensated liver cirrhosis patients than CTP and

Table 2 Results of subgroup analysis of Child–Turcotte–Pugh, Model for End-stage Liver Disease score, and Model for End-stage Liver Disease-Na score in predicting mortality at different time points

End-point (mortality)	Number of studies	Sensitivity (95%CI)	Specificity (95%CI)	Positive (95%CI)	Negative (95%CI)	DOR (95%CI)	I^2	AUROC
CTP								
< 3 mo	8	0.72 (0.61, 0.81)	0.73 (0.65, 0.79)	2.6 (1.9, 3.7)	0.39 (0.26, 0.58)	7 (3, 14)	0	0.78
3 mo	5	0.79 (0.60, 0.91)	0.79 (0.59, 0.90)	3.7 (1.8, 7.6)	0.26 (0.13, 0.55)	14 (4, 46)	96	0.86
6 mo	3	0.90 (0.80, 0.96)	0.69 (0.64, 0.75)	3.0 (2.1, 4.5)	0.16 (0.08, 0.33)	18 (8, 40)	0	0.91
12 mo	3	0.68 (0.58, 0.72)	0.68 (0.64, 0.72)	3.3 (1.5, 7.3)	0.49 (0.40, 0.60)	7 (3, 20)	84	0.72
MELD								
< 3 mo	9	0.66 (0.59, 0.73)	0.87 (0.81, 0.91)	5.1 (3.4, 7.7)	0.39 (0.31, 0.48)	13 (7, 24)	6	0.76
3 mo	6	0.70 (0.60, 0.78)	0.78 (0.65, 0.87)	3.1 (2.0, 4.9)	0.39 (0.29, 0.52)	8 (4, 15)	95	0.78
6 mo	3	0.74 (0.65, 0.82)	0.83 (0.79, 0.87)	4.4 (2.4, 8.2)	0.30 (0.23, 0.43)	15 (7, 34)	56	0.83
12 mo	4	0.60 (0.51, 0.68)	0.88 (0.79, 0.93)	4.8 (3.0, 7.7)	0.46 (0.39, 0.55)	10 (6, 17)	92	0.75
MELD-Na								
< 3 mo	4	0.82 (0.69, 0.91)	0.82 (0.64, 0.92)	4.6 (2.2, 9.8)	0.21 (0.12, 0.37)	22 (9, 53)	89	0.89
3 mo	4	0.75 (0.63, 0.84)	0.84 (0.80, 0.87)	4.6 (3.5, 6.0)	0.30 (0.20, 0.46)	15 (8, 30)	0	0.86
6 mo	3	0.82 (0.73, 0.88)	0.85 (0.80, 0.88)	5.3 (3.7, 7.7)	0.22 (0.15, 0.32)	25 (14, 43)	0	0.90
12 mo	3	0.72 (0.63, 0.76)	0.83 (0.80, 0.86)	4.2 (3.4, 5.1)	0.37 (0.30, 0.45)	12 (8, 18)	0	0.84

CTP: Child–Turcotte–Pugh; MELD: Model for End-stage Liver Disease score; DOR: Diagnostic odd ratio; AUROC: Area under the summary receiver operating characteristic curve.

Table 3 Results of Child–Turcotte–Pugh and Model for End-stage Liver Disease score for predicting mortality in variceal hemorrhage patients within 3 mo

Subgroup	Number of study	Sensitivity (95%CI)	Specificity (95%CI)	Positive (95%CI)	Negative (95%CI)	DOR (95%CI)	I^2	AUROC
CTP								
Variceal hemorrhage	4	0.70 (0.58, 0.80)	0.71 (0.62, 0.78)	2.4 (1.8, 3.1)	0.42 (0.30, 0.60)	6 (3, 10)	19	0.76
Others	4	0.78 (0.46, 0.94)	0.74 (0.61, 0.84)	3.1 (1.5, 6.3)	0.30 (0.09, 1.02)	10 (1, 72)	0	0.81
MELD								
Variceal hemorrhage	4	0.66 (0.53, 0.77)	0.87 (0.84, 0.90)	5.2 (3.9, 7.1)	0.39 (0.27, 0.56)	13 (7, 24)	0	0.88
Others	5	0.68 (0.57, 0.77)	0.87 (0.75, 0.93)	5.1 (2.4, 10.7)	0.37 (0.25, 0.54)	14 (5, 40)	0	0.79

CTP: Child–Turcotte–Pugh; MELD: Model for End-stage Liver Disease score; DOR: Diagnostic odd ratio; AUROC: Area under summarized receiver operating characteristic.

MELD. As hyponatremia was associated with increased morbidity and mortality in cirrhosis[41], MELD-Na and MESO were developed by incorporating the important parameter "serum Na" and using the novel algorithm in the MELD score, considering the deficiency of MELD. Some academics also confirmed that MELD-Na was a valid model to predict mortality in short- or long-term liver disease[42-44], and so did MESO[17,45].

When comparing CTP with MELD in variceal hemorrhage patients, the better choice has been inconsistent[46,47]. In our results, we found that the MELD was seemingly superior to CTP. The AUROC of MELD was 0.88 while that of CTP was 0.76 in predicting short-term mortality in variceal hemorrhage patients. The specific application of MELD would help the clinical management of variceal hemorrhage patients and suggest the prognostic evaluation.

The AUROC was the largest for 6-mo mortality among all end-points for all models (including CTP, MELD, and MELD-Na), which indicated that different end-points may affect the prediction accuracy of the scoring systems in decompensated patients. This result implied that the scoring systems would have the best effect for predicting the 6-mo mortality of decompensated cirrhosis patients.

According to our result and clinical practice, the indicators included in CTP is subjective, however, CTP is easy for doctors to get in daily practice and has high prognosis accuracy in medium term (6 mo). As for MELD, the score is presented in a continuous manner and the indicators are objective, but it does not consider the complication which doctors think might put threat on patients directly. There is no denying that MELD has prognosis value in variceal hemorrhage patients in this study. MELD-Na and MESO both consider the effect of serum Na on mortality of patients, and their prognosis accuracy is high. To be noticed, the number of studies about the MESO for prognosis in decompensated cirrhosis patients is not enough, and further study is needed to validate our finding with more original studies taken into consideration.

Limitations

There were some limitations in our meta-analysis. First, the number of the included studies was relatively small, which restricted the detailed analysis for heterogeneity. Second, several closely related studies were not included in the analysis because of the lack of necessary

data.

Conclusion

Overall, MESO shows promising value with the highest AUROC in all assessed scoring systems. MELD-Na has the best performance for predicting mortality at various time points. In particular, MELD has a unique advantage for patients with variceal hemorrhage.

In the future, more sensitive indicators could be added into the model for optimizing the original scoring system, or a more accurate model should be proposed for prognosis. Multicenter and long-term studies with larger samples would be helpful for the scoring systems to predict the mortality more precisely in decompensated liver cirrhosis patients.

ARTICLE HIGHLIGHTS

Research background

Liver cirrhosis is a common chronic disease worldwide and decompensated cirrhosis is associated with a high risk of death. To find accurate prognostic scoring system not only could help clinicians to make better decisions but also has a wide significance in the context of organ allocation for decompensated cirrhosis patients.

Research motivation

There are so many scoring systems to predict the mortality of decompensated cirrhosis patients, while it is uncertain which scoring system is better. We performed a meta-analysis to compare the accuracy of four scoring systems: Child–Turcotte–Pugh (CTP), Model for End-stage Liver Disease score (MELD), MELD-Na, and MELD to Serum Sodium ratio (MESO) for predicting the mortality in decompensated liver cirrhosis. It is beneficial for confirming a high accuracy scoring system to use in clinical practice.

Research objectives

The main objective is to quantitatively compare the test accuracy of scoring systems and to pinpoint the more reliable scoring systems to forecast the mortality of decompensated cirrhosis patients. It will help us to assess the state of an illness and make better decision.

Research methods

We searched PubMed, Web of science, Cochrane Library, EMBASE, and Ovid databases from inception to September 2018 for relevant articles and evaluated the quality of original articles by the Quality Assessment of Diagnostic Accuracy Studies 2 scale. As for statistical heterogeneity, threshold effect and non-threshold effect were assessed by Spearman correlation and Cochrane's Q test, respectively. And optimum model was chosen to estimate the accuracy like diagnostic odd ratios, area under the summary receiver operating characteristic curve (AUROC). We used Deek's funnel plot asymmetry to assess potential publication bias. Stata 12.0, Meta-DiSc 1.4, and Review Manager 5.3 were tools to be used.

Research results

Sixteen eligible studies involving 2337 decompensated liver cirrhosis patients were included in this meta-analysis. The overall analysis showed MESO had promising value with highest AUROC in all assessed scoring systems. MELD-Na had the best performance for predicting mortality at various time points. MELD had a unique advantage for patients with variceal hemorrhage.

Research conclusions

The study confirmed the best model in predicting the mortality of the decompensated cirrhosis patients at different time points, and MELD or CTP is better for predicting short-term mortality in variceal hemorrhage patients. Additionally, the number of the included studies was relatively small, which restricted the detailed analysis for heterogeneity.

Research perspectives

Further research would focus on more sensitive indicators that could be added into the model for optimizing the original scoring system, and a new model should be proposed for prognosis prediction more accurately. In addition, multicenter and long-term studies with larger samples could answer the question more convincingly.

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CASE REPORT

Gangrenous cholecystitis: A silent but potential fatal disease in patients with diabetic neuropathy. A case report

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Author contributions: All authors contributed equally to the manuscript.

Informed consent statement: A signed consent was obtained and saved for this case report by the patient through the standard institutional consent document and saved by the institution. Most importantly, there are no patient identifiers on the case or the images. In American institutions, medical record from a patient is not allowed to print out and give to anyone else. This is according to the law of HIPPA. Again, there is no patient identifier on the entire case so this patient is completely anonymous.

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Abstract

Gangrenous cholecystitis (GC) is a severe and potentially deadly complication of acute cholecystitis. We present a 83-year-old gentleman with a past medical history of type 2 diabetes mellitus with significant associated neuropathy, presenting to a community hospital in a major metropolitan area with 10 days nausea and vomiting and a benign abdominal exam. While the patient was admitted for hyperglycemia, he was subsequently found to have severe GC requiring urgent surgical intervention.

Key words: Gangrenous cholecystitis; Diabetes mellitus; Hyperglycemia; Complications; Case report

Core tip: We present an 83-year-old gentleman with type 2 diabetes mellitus and associated neuropathy who was found to have severe gangrenous cholecystitis (GC) requiring urgent surgical intervention but without any of the cardinal symptoms of GC.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by deficiency in production of insulin by the pancreas, or by of the insulin produced. This subsequently leads to an increased concentrations of glucose in the blood[1]. The prevalence of DM has markedly increased over the past few decades with nearly 300 million people worldwide with the disease today[2]. DM is itself a specific group of metabolic disorders that share common phenotype of hyperglycemia. The two broad categories, or types, of DM are classified by the underlying pathogenic process leading to elevated blood sugar levels. Type 1 DM exhibits almost complete insulin deficiency, while type 2 DM is an intricate constellation of pathology including insulin resistance, increased glucose production and impaired insulin secretion[3]. Important complications from DM include cardiovascular disease, stroke, diabetes retinopathy, renal failure and neuropathy[4].

Gangrenous cholecystitis (GC) is a severe and potentially deadly progression of acute cholecystitis that occurs in up to 30% of cases[5]. It is the end result of persistent and severe inflammation, where there is such significant distension of the gallbladder that the wall becomes ischemic[6]. Risk factors include male gender, age > 45 years, history of diabetes and heart disease[7]. Although clinical signs of peritonitis are sometimes absent, these patients typically present with at least one or more of the following symptoms: right upper quadrant abdominal pain, loss of appetite, jaundice, and/or fever[8]. These patients almost universally undergo emergent cholecystectomy to avoid fatal complications[6].

Diabetic neuropathy is among the most common complications of DM, and is clinically important because it can diminish symptoms of life-threatening such as myocardial ischemia[9]. We present an 83-year-old gentleman who was admitted for hyperglycemia but was later found to have a severe GC without an exam findings concerning for peritonitis. To our knowledge, this is the fourth case ever reported of GC in a patient with DM presenting with non-specific abdominal symptoms and reassuring physical exam[10-12].

CASE PRESENTATION

An 83-year-old male with a 20 year history of type 2 DM, with advanced diabetic neuropathy, hypertension and hyperlipidemia presented to his primary care physician's office with a chief complaint of nausea, vomiting, and diarrhea for 10 d. Point of care glucose monitor showed the patient's blood sugar to be > 600 mg/dL, and the patient was transferred to the emergency department (ED) of the associated community hospital.

The patient attributed the nausea and vomiting to a beef sandwich he ate four days preceding the symptoms. He had not been able tolerate food and reported very limited fluid intake. Additionally, the patient noted three loose brown bowel movements daily without gross blood or melena which resolved three days prior to admission. The patient denied abdominal pain, hematemesis, chest pain, shortness of breath or any other associated symptoms. A complete review of systems was otherwise negative.

The patient had a strong family history of both type 1 and 2 DM including his mother, two brothers, and other distant relatives. The patient's social history was significant for occasional alcohol use of 2-3 beers per month. The patient denied tobacco and illicit drug use. The patient's home medications were Pravastatin 20 mg PO daily, Glyburide 1.25 mg PO daily, Lisinopril 10 mg PO daily, and Omeprazole 20 mg PO daily.

In the ED his vital signs were a temperature of 98.2 F, heart rate of 89/min, respiratory rate of 18/min, blood pressure 147/79 mmHg, and O2 Saturation by pulse oximetry 93% on room air. Laboratory results were significant for a white blood count (WBC) of 16.5 k/uL, Sodium 132 mmol/L, Chloride 93 mmol/L, Glucose 598 mg/dL, AST 49 U/L, Alkaline Phosphatase 196 U/L, Albumin 3.1 g/dL, Albumin/Globulin Ratio 0.6 L. Other labs were within normal limits, and urinalysis was negative for ketones.

Physical examination was documented as normal. The patient was alert and oriented to person, time and place. Respiratory exam was clear to auscultation bilaterally. Cardiovascular exam revealed regular rate and rhythm, with no murmurs, rubs or gallop. Abdomen was soft, non-tender, non-distended, with normal bowel sounds, and no organomegaly. Neurological exam showed intact cranial nerves 2-12, reflexes were 2+ and symmetric at the biceps, triceps, knees, and ankles. Plantar responses for flexor, light touch, pinprick, position sense, and vibration sense was impaired in fingers and toes, Rapid alternating movements and fine finger movements are intact. There was no dysmetria on finger-to-nose and heel-knee-shin. There were no abnormal or extraneous movements. Romberg was absent. The skin was warm, dry, with no identified rashes. Imaging in the ED was limited to a plain film of the chest which demonstrated atelectasis *vs* scarring in the lateral left base, without infiltrates.

The patient was admitted to the general medicine ward for treatment of hyperglycemia. He was initially given 0.2 units/kg of Lantus once, and then put on insulin sliding scale with blood glucose measurements every 6 h. A second abdominal examination was performed several hours after admission because of an elevated alkaline phosphatase, without any concerning findings. Additionally, an abdominal ultrasound was performed which exhibited hepatomegaly with the

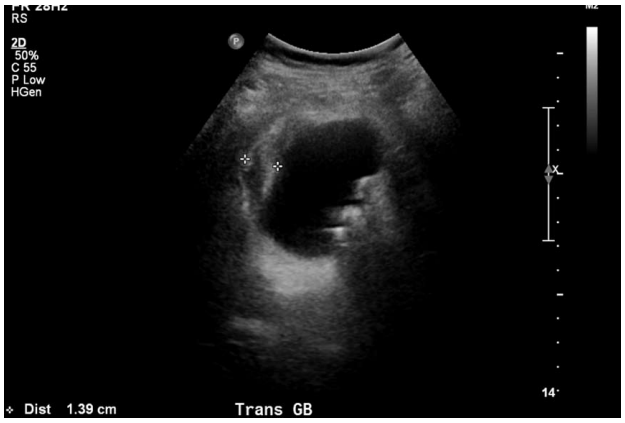

Figure 1 Ultrasound image demonstrating a pronounced gallbladder wall thickening and stones, consistent with acute colecystitis.

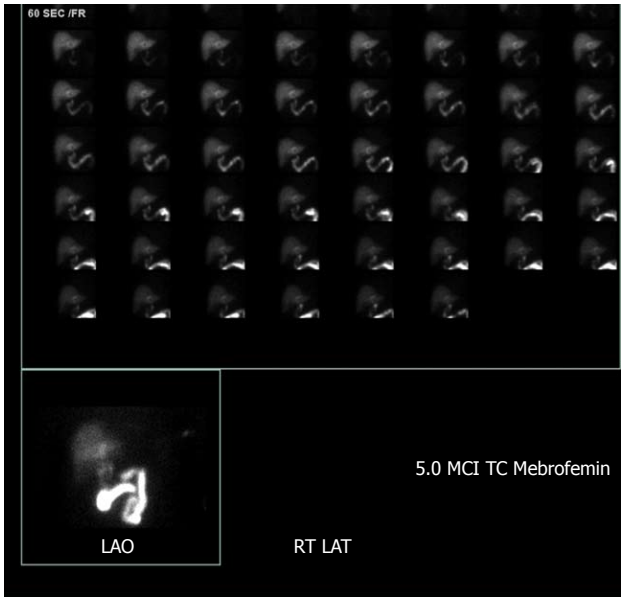

Figure 2 HIDA scan image demonstrates non-visualization of the gallbladder one hour after radiotracer injection, consistent with cystic duct obstruction.

liver measuring to 18 cm in length. While no hepatic biliary tract obstruction was noted on ultrasound, his gallbladder was found to have a thickened wall, with pericholecystic fluid and multiple hyper-echoic calculi (Figure 1). These findings were strongly concerning for acute cholecystitis.

The patient was started on 3.375 g of Piperacillin/Tazobactam, every 6 h. The patient's condition improved overall by hospital day two. He denied nausea, vomiting and abdominal pain. Given his reassuring vials, exam and symptomatology in the face of an abnormal ultrasound, a HIDA scan was performed which also suggested acute cholecystitis (Figure 2).

Soon after, the patient developed a low-grade fever of 100.4 F, with chills and rigors. A set of blood cultures was obtained, and general surgery was consulted. They recommended continuing Ⅳ antibiotics and preparation for surgery. Demerol (Meperidine) and Tylenol (acetaminophen) were added for fever and pain.

The patient thereafter underwent a laparoscopic cholecystectomy. The findings were significant for a severly gangrenous gallbladder, with copious purulent drainage from gallbladder, subhepatic abscess, and cholelithiasis, and this was confirmed in post-operative histopathology. The patient's abdomen was irrigated copiously during the procedure. There were no peri-operative complications.

On the next hospital day, the patient was feeling well without complaints including no abdominal pain, fevers, rigors or chills. Abdominal examination continued to be benign, and the surgical wound was well approximated. WBC trended down to normal limits. Alkaline phosphatase had down trended from 196 U/L on admission to as low as 127 U/L post-operatively. The patient's diet was advanced to regular diabetic diet, which he tolerated well, and he was later discharged home.

The hyperglycemia seen in this patient was likely multifactorial, due to chronically poor compliance with diabetic medications and diet as well as acute infection. The patient's HbA1c was 10.5% during this hospitalization and an endocrinologist was consulted who started the patient on an insulin regimen on discharge with regular follow ups.

FINAL DIAGNOSIS

Gangrenous cholecystitis.

TREATMENT

Cholecystectomy.

OUTCOME AND FOLLOW-UP

Clinic follow up.

DISCUSSION

This case illustrates the sometimes difficult nature of identifying underlying diseases in patients with severe diabetes and associated complications. This patient had an elevated Alkaline Phosphatase and a mild leukocytosis in the setting of nausea and vomiting. This prompted further investigation in the form of medical imaging despite benign abdominal exam ultimately leading to diagnosis of acute cholecystitis with gangrenous gallbladder. This joins the ranks of three similar cases which have been reported in the literature, all with a history of DM[10-12].

Fagan *et al*[13] asserted that several variables, including WBC > 15000, history of diabetes, African American race, abnormal liver function tests (elevated ALT, AST, ALP, lipase levels) and pericholecystic fluid were associated with GC. An additional study found after multivariate analysis that in patients with cholecystitis those with history of diabetes and leukocytosis were

significantly more likely to have a gangrenous gallbladder. Finally, Contini *et al*[7] have implicated that WBC count was the strongest predictor for presence of gangrene. The patient reported appears to support these findings given his history of diabetes as well as leukocytosis and elevated alkaline phosphatase on presentation.

It is important to recognize the natural history and life-threatening complications of GC. A gangrenous gallbladder almost invariably goes on to perforate and once gangrenous, the overall complication rate approaches 25%. Perforation can lead to abscess formation and peritonitis. Ultimately, mortality rates in GC are reported to be as high as 22%[7,14]. Accordingly, early diagnosis and surgical treatment is critical to mitigate serious complications including mortality in these patients[7,14].

The reason for the insidious nature of this patient's presentation was presumably driven by his neuropathy. Neuropathy leads to a host of consequences including intrabdominal manifestations such as impaired gastric motility and inability to appreciate abdominal pain. While not fully understood, diabetics exhibit complex changes of metabolic, vascular and hormonal factors which both increase nerve fiber damage and diminish the body's ability to repair these nerves[15,16]. Nerve damage from ischemia is thought to contribute to the development of diabetic neuropathy. In autopsies of patients with diabetic neuropathy thickened endoneuronal blood vessel walls and vascular occlusions are commonly found[17]. This is also supported by decreased endoneurinal oxygen tension measured in sural nerves of the patients with advanced polyneuropathy[18].

Impaired neuronal repair is also thought to contribute to diabetic neuropathy[19,20]. This may be due in part to a decrease of neurotrophic peptides which mediate nerve maintenance, repair and regeneration. Specifically, nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, insulin-like growth factors, and vascular endothelial growth factor have all found to contribute to nerve health[20]. Moreover, insulin itself plays an important role as a neurotrophic factor to peripheral neurons; and the low insulin state present in type 1 diabetes may be particularly detrimental to overall nerve health[15,21].

In conclusion, this case illustrates the insidious presentation of a life-threatening surgical disease in a patient admitted for medical management of hyperglycemia. Gangrenous gallbladder is a serious complication of acute cholecystitis which was largely masked by a benign abdominal exam in a patient with severe diabetic neuropathy. This is similar to diabetic patients presenting with "silent" acute coronary syndrome. In conclusion, it is important that in patients with a history of poorly controlled diabetes, a higher index of suspicion should be raised for severe intraabdominal pathology even in the setting of a benign abdominal exam.

EXPERIENCES AND LESSONS

GC is a severe and potentially life-threatening complication of acute cholecystitis that occurs in up to 30% of cases. Risk factors of GC include male gender, age > 45 years, history of diabetes and heart disease. GC can be asymptomatic in patients with DM. Patients with leukocytosis and/or abnormal liver function tests with a history of DM should be considered for further work up, regardless of symptoms or physical examination.

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CASE REPORT

Successful endovascular treatment of endoscopically unmanageable hemorrhage from a duodenal ulcer fed by a renal artery: A case report

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Author contributions: Anami S and Minamiguchi H collected the patient data, prepared the figures and tables and wrote the manuscript; Shibata N, Koyama T, Sato H, Ikoma A, Nakai M, Yamagami T and Sonomura T proofread and revised the manuscript; All authors approved the final version of the manuscript.

Informed consent statement: Written and verbal informed consent was obtained from the patient's family for publication of this case report and the accompanying images.

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Abstract

A 52-year-old woman was admitted with hypovolemic shock. Emergency endoscopy revealed three hemorrhagic duodenal ulcers (all stage A1) with exposed vessels. Two ulcers were successfully treated by endoscopic clipping; however, the remaining ulcer on the posterior wall of the horizontal portion of the duodenum could not be clipped. Because her vital signs were rapidly worsening, we performed transcatheter arterial embolization (TAE) as it is less invasive than surgery. Computed tomography aortography showed that the duodenal hemorrhage was sourced from the lower branch of the right renal artery. In general, the

duodenum is fed by branches from the gastroduodenal artery or superior mesenteric artery. However, this patient had three right renal arteries. The lower branch of the right renal artery at the L3 vertebral level was at the same level as the horizontal portion of the duodenum. Complete hemostasis was achieved by TAE using metallic coils and *n*-butyl-2-cyanoacrylate. After TAE, she recovered from the hypovolemic shock and was discharged from hospital. She has had no recurrence of the hemorrhagic duodenal ulcer for over 1 yr, and follow-up endoscopy showed no necrosis or stricture of the duodenum. Although she developed a small infarct of her right kidney, her renal function was satisfactory. In summary, the present case is the first reported case of hemorrhagic duodenal ulcer in which the culprit vessel was a renal artery that was successfully treated by TAE. Computed tomography aortography before TAE provides valuable information regarding the source of a duodenal hemorrhage.

Key words: Transcatheter arterial embolization; Metallic coils; *N*-butyl-2-cyanoacrylate; Renal artery; Emergency radiology; Case report; Duodenal ulcer

Core tip: We report a rare case of a hemorrhagic duodenal ulcer fed by a renal artery that was successfully treated by transcatheter arterial embolization. Generally, the duodenum is fed by branches from the gastroduodenal artery or superior mesenteric artery. However, this patient had three right renal arteries, and the hemorrhage was fed by the lower branch of the right renal artery. This branch was located at the L3 vertebral level, at the same level as the horizontal portion of the duodenum. To our knowledge, this is the first reported case in which a renal artery fed a hemorrhagic duodenal ulcer.

Anami S, Minamiguchi H, Shibata N, Koyama T, Sato H, Ikoma A, Nakai M, Yamagami T, Sonomura T. Successful endovascular treatment of endoscopically unmanageable hemorrhage from a duodenal ulcer fed by a renal artery: A case report. *World J Clin Cases* 2018; 6(15): 1012-1017 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1012.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1012

INTRODUCTION

Annually, upper gastrointestinal (GI) bleeding affects approximately 100 per 100000 people internationally[1,2]. Endoscopic clipping is the first-line technique to achieve hemostasis. If hemostasis is difficult to achieve using this technique, then second-line treatments include transcatheter arterial embolization (TAE) and surgery[3]. A meta-analysis revealed that recurrent bleeding was more frequent after TAE than after surgery, but TAE is necessary for inoperable or elderly patients because it is less invasive and results in a shorter hospital stay[3,4,5]. TAE involves embolization of the artery responsible for bleeding (typically branches of the gastroduodenal artery (GDA) or superior mesenteric artery). In the present case, we identified the right renal artery as the vessel responsible for a hemorrhagic duodenal ulcer that was difficult to treat endoscopically. We report on this extremely rare case.

CASE REPORT

The patient was a 52-year-old woman. She had a history of recurrent duodenal ulcers caused by nonsteroidal anti-inflammatory drugs. In addition, she suffered the sudden death of a close relative in a traffic accident. She was subsequently unable to eat for several days and began experiencing melena and epigastric pain. She was examined for a consciousness disorder by a local physician, who also noted hematemesis in the patient. On arrival, the patient exhibited impaired consciousness. Her systolic blood pressure was 63 mmHg, pulse rate was 130 bpm, and SpO_2 was 100% in room air. The results of blood tests (Table 1) indicated anemia, so a hemorrhagic duodenal ulcer was suspected. She was admitted to the emergency room of our hospital to undergo therapeutic upper GI endoscopy.

While performing a fluid infusion and blood transfusion, we conducted emergency upper GI endoscopy (GIF-Q260J; Olympus, Tokyo, Japan). The results indicated three hemorrhagic ulcers (all stage A1) with exposed vessels, located along the descending to horizontal portions of the duodenum (Figure 1). Two of the ulcers were successfully treated by endoscopic clipping; however, the remaining ulcer on the most anal side, on the posterior wall of the horizontal portion of the duodenum, could not be clipped. Because her vital signs were rapidly declining, we decided to perform TAE, which is less invasive than surgical treatment. Preoperative contrast-enhanced computed tomography (CT) was not done because her vital signs were too poor.

No clear signs of extravasation were seen on initial aortography or on selective angiography of the GDA and superior mesenteric artery. We then used interventional radiology-CT to perform CT during aortography[6] to identify the culprit artery. Extravasation was detected close to the clipping. Therefore, we repeated the selective angiography of the posterior superior pancreaticoduodenal and inferior pancreaticoduodenal arteries, which run adjacent to this site. No clear extravasation was observed. Closer examination of the first set of CT images revealed that of the three right renal artery branches, the lower branch was near the posterior side of the hemorrhage. Thus, we performed selective angiography of this artery, which finally confirmed the source of extravasation (Figures 2, 3A, 3B, and 3C).

Because the right renal artery has three branches,

Table 1 Results of blood tests on arrival

Parameter	Value
WBC count (/μL)	10290
RBC count (10^4/μL)	219
Hemoglobin (g/dL)	6.8
Hematocrit (%)	21.1
Platelet (10^3/μL)	23.4
PT (/s)	15.3
PT (ratio %)	76
PT INR	1.19
Fibrinogen (mg/dL)	204
FDP (μg/mL)	2.4
D-dimer (μg/mL)	< 0.3
Antithrombin (%)	63

WBC: White blood cell; RBC: Red blood cell; PT: Prothrombin time; INR: International normalized ratio; FDP: Fibrin degradation product.

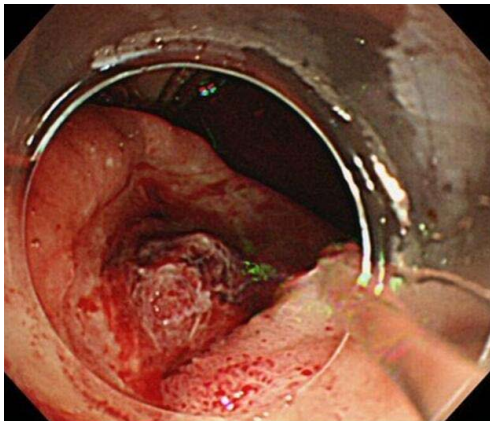

Figure 1 Emergency endoscopy shows an A1-stage hemorrhagic ulcer on the posterior wall of the horizontal portion of the duodenum.

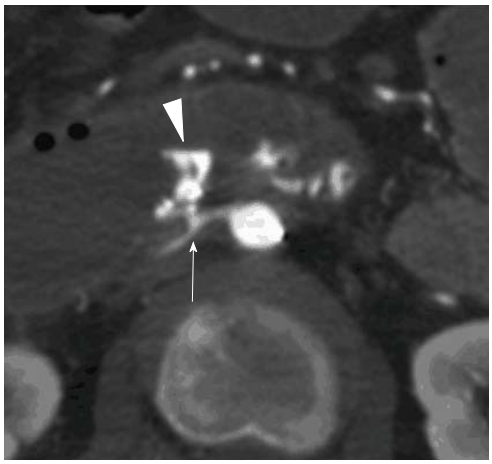

Figure 2 Contrast-enhanced computed tomography shows extravasation into the duodenal lumen (arrowhead) from the right renal artery (arrow).

and the patient's renal function was good, we first embolized the lower branch of the right renal artery using coils (two 2-mm-diameter, 4-cm-long Tornado coils and eight 2-mm-diameter, 3-cm-long Tornado coils; Cook Medical, Bloomington, IN, United States), from the distal to proximal sides of the hemorrhage site. As the distance from the origin of the renal artery to the hemorrhage site was only 7 mm, and the hemorrhagic site appeared to be widening gradually, we added no more coils due to the high risk of coil migration into the aorta and duodenum (Figure 3D). Thereafter, we used *n*-butyl-2-cyanoacrylate (NBCA) glue (B. Braun, Melsungen, Germany) as the embolic material. We injected a total of 2 mL of 33% NBCA mixed with Lipiodol *via* three separate injections (0.5 mL, 0.5 mL, and 1.0 mL). Finally, we achieved complete hemostasis (Figure 3E).

The patient subsequently recovered from her state of shock and was transferred to the intensive care unit. The patient had no recurrence of the hemorrhagic duodenal ulcer at the 1-year follow-up. Endoscopic examination indicated no duodenal stricture or mucosal necrosis and confirmed that the condition had improved to stage S1. Follow-up CT showed unavoidable partial infarction of the right kidney as a result of iatrogenic embolization of the culprit renal artery, but no evidence of renal dysfunction or other abnormality.

DISCUSSION

The first-line treatment for upper GI bleeding is endoscopic therapy, but when such therapy is difficult to perform, endovascular treatment is an eligible alternative[7-14]. In the present case, endovascular treatment was selected because of the potential difficulty of endoscopic therapy and the patient's state of shock.

In general, the arteries feeding the duodenum are the supraduodenal artery and the superior pancreaticoduodenal artery, which branch from the GDA and the inferior pancreaticoduodenal artery, which branches from the superior mesenteric artery[15]. Thus, the culprit artery in cases of hemorrhagic duodenal ulcer is usually one of these three arteries depending on the site of bleeding[9]. Toyoda *et al*[7] reported five patients with duodenal ulcer hemorrhage who underwent prophylactic embolization of the GDA, posterior superior pancreaticoduodenal artery, and anterior superior pancreaticoduodenal artery using TAE because angiography failed to identify any extravasation. Of these, four patients had no recurrence of bleeding during the observation period; however, the remaining patient died, indicating that in this case, an atypical culprit artery could not be ruled out, as in the present case.

Anatomically, the descending and ascending portions of the duodenum are positioned at the level of the second lumbar vertebra (L2), and the horizontal portion is at the L3 level, whereas the bilateral renal arteries are located at the level of L1–L2, according to previous angiographic studies[15,16]. Thus, in the vast majority of cases, when a hemorrhagic duodenal ulcer occurs in the horizontal portion of the duodenum, the relative positions of the structures preclude a renal artery from being the culprit artery. In the present case, the position

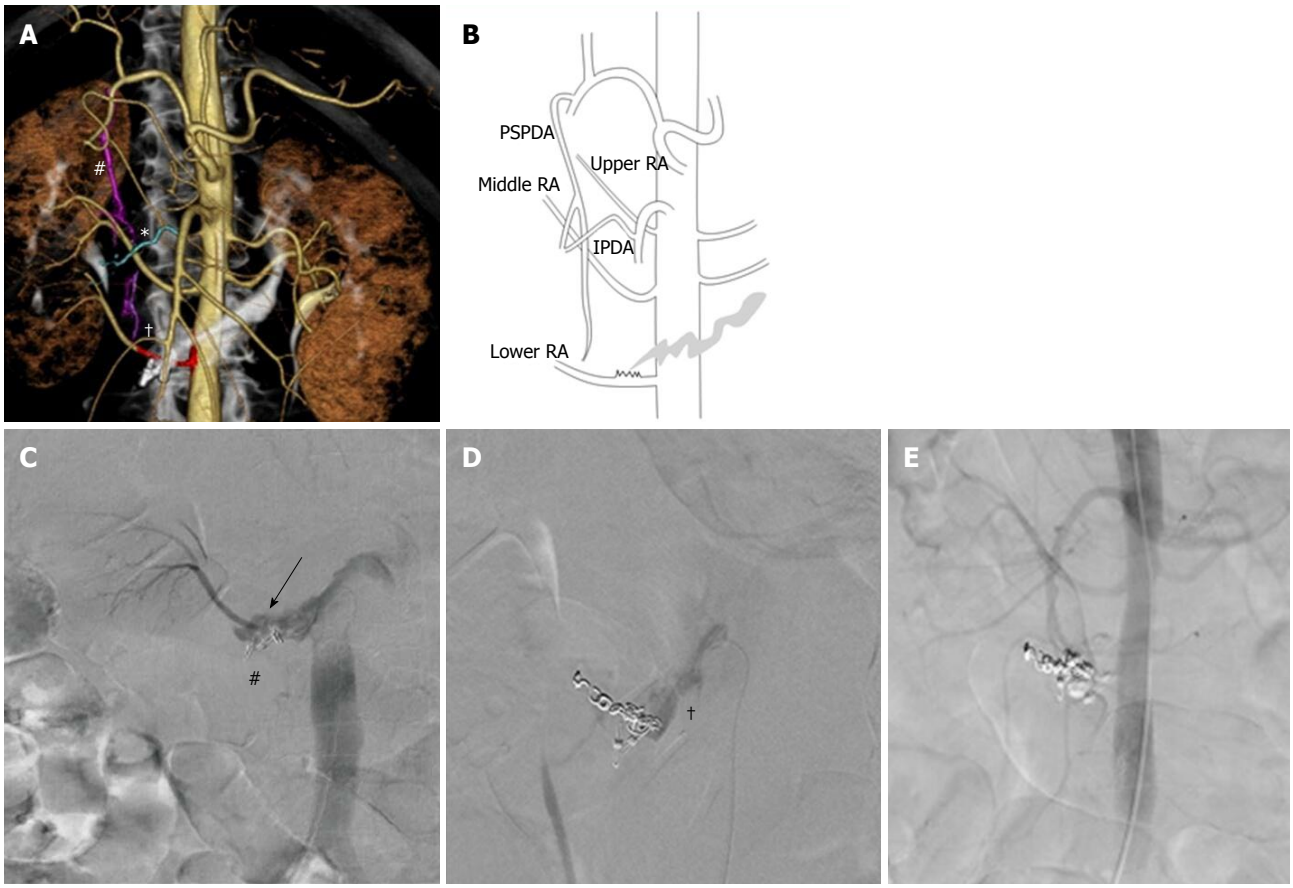

Figure 3 Embolization of the lower branch of the right renal artery. A: 3D volume-rendered computed tomography image obtained during aortography. #Posterior superior pancreaticoduodenal artery (PSPDA; pink); *Inferior pancreaticoduodenal artery (IPDA; blue); †Lower branch of the right renal artery (lower RA; red); B: Schematic of the computed tomography image; C: Extravasation of contrast material is evident before embolization (arrow). #Endoscopic clips; D: Right renal arteriography after coil embolization shows residual extravasation (†); E: Aortography after embolization using coils and n-butyl-2-cyanoacrylate glue shows no extravasation.

of the duodenum was normal, but the branches of the renal artery were anomalous, with three located on the right. As the lower branch of the right renal artery branched at the L3 level, we suspected it to be the culprit artery. This branching pattern is extremely rare, occurring in less than 1% of all cases[16].

In the present patient, we observed no ischemic changes or necrosis in the duodenal mucosa and no stricture during the postoperative observation period; however, there was partial infarction of the right kidney. The most concerning complications observed after TAE performed for GI bleeding generally include ischemia of the GI tract, stricture, and necrosis. The therapeutic outcomes and complication rates differ depending on the embolic materials used. Lang *et al*[11] reported that when performing distal embolization, NBCA was associated with better long-term hemostasis than was gelatin sponge or polyvinyl alcohol. Yonemitsu *et al*[17] reported that while gelatin sponge potentially increases the risk of recurrent bleeding, especially in patients with coagulopathic conditions, the use of NBCA led to satisfactory hemostasis. In addition, TAE using NBCA for upper and lower GI tract bleeding resulted in hemostasis in almost all cases, and no patients suffered GI tract necrosis[18,19]. In another study, hemostasis was achieved in all TAE procedures with NBCA for diverticular hemorrhage of the ascending portion of the duodenum, and although the adverse effects included ulceration occupying half of the duodenal circumference, no strictures or necrosis developed[20]. Nevertheless, an extremely high risk of GI tract necrosis has been reported when using NBCA for embolization of five or more vasa recta with TAE in the lower GI tract[21]. Thus, when utilizing NBCA, careful consideration of the extent of embolization is required. In the present case, no GI mucosal damage was observed during the postoperative observation period, and the only complication observed was partial renal infarction. Thus, the culprit artery (the lower branch of the right renal artery) was not a duodenal feeder, but rather ran along the horizontal portion of the duodenum due to the anomaly. As a result, the artery adhered to the serosa due to the inflammation caused by recurrent ulceration in the horizontal portion of the duodenum. We believe that the area of adhesion eventually penetrated the duodenum.

In summary, we have reported a case of hemorrhagic duodenal ulcer in which the culprit vessel was the right renal artery. To our knowledge, there have

been no other cases reported in the literature. Based on our experience of this case, we believe that performing CT aortography before TAE will provide valuable information to identify the artery responsible for the hemorrhage.

ARTICLE HIGHLIGHTS

Case characteristics

A case of hypovolemic shock with a history of recurrent duodenal ulcers.

Clinical diagnosis

Hemorrhagic duodenal ulcer.

Differential diagnosis

Other hemorrhagic lesions.

Laboratory diagnosis

Vital signs and blood tests on arrival showed hypovolemic shock.

Imaging diagnosis

Emergency endoscopy and computed tomography revealed hemorrhagic duodenal ulcers.

Pathological diagnosis

Not obtained.

Treatment

Interventional radiology.

Related reports

Based on our search of the literature, there are no other reported cases of hemorrhagic duodenal ulcer in which the culprit vessel was the right renal artery.

Term explanation

None.

Experiences and lessons

In patients with a hemorrhagic duodenal ulcer and an anomaly of the right renal artery, the right renal artery could be the culprit vessel.

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CASE REPORT

Didactic surgical experience of thyroid metastasis from renal cell carcinoma: A case report

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Abstract

BACKGROUND

The optimal therapeutic strategy in treating thyroid metastasis from renal cell carcinoma (RCC) has not been clearly established. Here we describe a case of didactic surgical experience of the disease which caused massive intraoperative bleeding.

CASE SUMMARY

A 59-year-old male patient presented with a thyroid left lobe soft mass detected by chest computed tomography scans prior to the surgical treatment of RCC of the left kidney. The thyroid mass was initially considered to be benign, then he underwent left radical nephrectomy. One year after the nephrectomy, stereotactic radio-

surgery was performed for brain metastasis. During follow-up, the thyroid nodule gradually grew, and the patient manifested swallowing discomfort. Under a clinical diagnosis of thyroid follicular neoplasm, left hemithyroidectomy was performed. Although hemithyroidectomy is usually a safe and straightforward procedure, massive bleeding from markedly developed tumor vessels made the operation very difficult. The thyroid tumor was finally diagnosed as metastasis from clear cell RCC.

CONCLUSION

For proper timing of the surgery, a clinician should take into consideration the possibility of thyroid metastasis of RCC when a thyroid lesion is found in patients with RCC or in patients with a previous history of RCC. We recommend that thyroid metastasis of RCC should be resected as early as possible even if a patient has other metastatic sites.

Key words: Renal cell carcinoma; Thyroid metastasis; Hemorrhage; Thyroidectomy; Case report

Core tip: A didactic surgical experience of thyroid metastasis from renal cell carcinoma (RCC) which caused massive intraoperative bleeding is presented. Based on this experience, we recommend that thyroid metastasis of RCC should be resected as early as possible even if a patient has other metastatic sites, unless the patient has appropriate reasons to avoid surgery.

Yamauchi M, Kai K, Shibamiya N, Shimazu R, Monji M, Suzuki K, Kakinoki H, Tobu S, Kuratomi Y. Didactic surgical experience of thyroid metastasis from renal cell carcinoma: A case report. *World J Clin Cases* 2018; 6(15): 1018-1023 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1018.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1018

INTRODUCTION

Thyroid metastasis is a clinically rare entity, accounting for only 1.4% to 3.0% of all thyroid malignancy[1]. The kidneys (renal cell carcinoma, RCC) are the most common primary site (33%) followed by the lungs (16%), breast (16%), esophagus (9%), and uterus (7%)[2]. Although there are several case reports and review articles about thyroid metastasis from RCC[3,4] these have mainly focused on the diagnostic challenges, and thus an optimal therapeutic strategy has not been clearly established. Here we present a case of thyroid metastatic tumor from RCC that was accompanied by massive intraoperative bleeding. Based on this experience, we recommend that thyroid metastasis of RCC be resected as early as possible.

CASE PRESENTATION

Chief complaints

Hematuria.

History of present illness

A 59-year-old Japanese man visited a nearby hospital for the examination of hematuria. Ultrasonographic (US) examination revealed a mass lesion at the left kidney and he was referred to our hospital for further examination and surgical treatment.

History of past illness

Unremarkable.

Physical examination

A solid and painless 3 cm × 2 cm mass was palpable on the left thyroid lobe without lymphadenopathy.

Laboratory testing

The patient showed no alterations in thyroid function tests and other serum laboratory tests.

Imaging examination

The preoperative computed tomography (CT) scans revealed an exophytic mass lesion measuring 8.1 cm × 6.2 cm at the lower pole of the left kidney (Figure 1A) and a mass lesion with heterogeneous contrast-enhancement measuring 4.1 cm × 2.4 cm at the left lobe of the thyroid (Figure 1B). Radiologically, the renal mass lesion was considered to be RCC (cT3N0M0, Stage III). The findings of US for the thyroid mass were consistent with a follicular lesion at that time (Figure 1C).

FINAL DIAGNOSIS

The patient underwent left radical nephrectomy.

TREATMENT

The postoperative clinical course was uneventful. The pathological diagnosis of the renal nodule was clear cell RCC of Fuhrman grade 2. The tumor invaded into the perirenal and renal sinus fat tissue (pT3a). All surgical margins were free from tumor invasion.

OUTCOME AND FOLLOW-UP

One year after the surgery, the patient became aware of memory disturbance. Head CT scans revealed a brain mass lesion. From the findings of head magnetic resonance imaging (MRI), this mass lesion was considered a metastasis of RCC. The patient was treated with stereotactic radiosurgery for brain metastasis and a complete response was realized. During the treatment for brain metastasis, the thyroid mass was gradually enlarged in plain CT scans and the patient manifested swallowing discomfort.

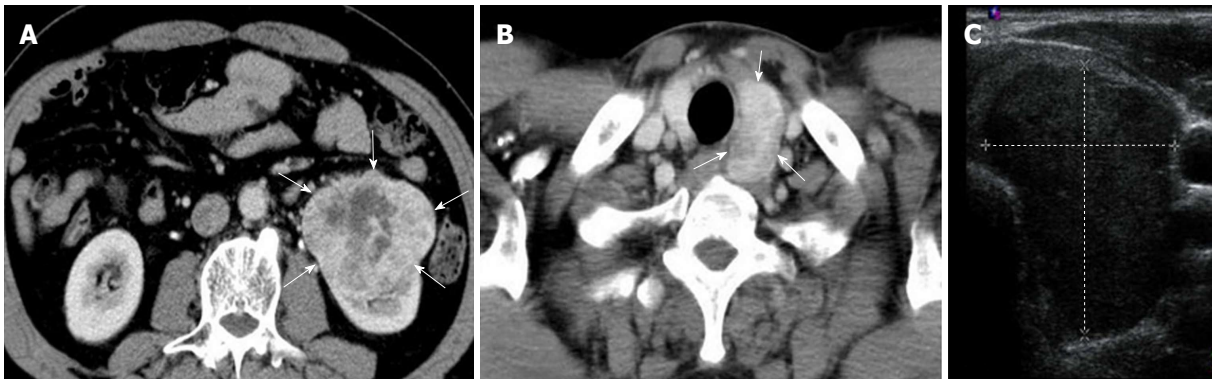

Figure 1 Initial radiological appearance of the kidney tumor and the thyroid left lobe mass. A: Preoperative contrast-enhanced computed tomography (CT) scan image of the left kidney tumor. The image shows a 6.0 cm × 5.0 cm exophytic mass in the lower pole of the left kidney (arrowheads). No lymphadenopathy was identified; B: Contrast-enhanced CT scan revealed a 4.0 cm × 2.5 cm solid mass with a smooth surface in the left lobe of the thyroid gland (arrowheads); C: The ultrasound imaging shows a 3.2 cm × 2.8 cm × 3.3 cm hypoechoic mass lesion without calcification in the left lobe of the thyroid.

Imaging examination for the thyroid lesion

The patient was examined with contrast-enhanced CT scan. The CT scan images four years after initial surgery showed a mass lesion measuring 6.6 cm × 5.8 cm × 9.2 cm in the left lobe of the thyroid gland with heterogeneous strong contrast enhancement and enriched vasculature around the left thyroid lobe (Figure 2). These findings were not apparent in the previous contrast-enhanced CT scans that were carried out for preoperative examination of RCC. It was difficult to diagnose whether the thyroid mass lesion was benign or malignant from the radiological findings.

Clinical diagnosis and treatment for the thyroid lesion

Although fine-needle aspiration cytology was performed, the materials were insufficient and only a small amount of blood cells were found in the cytological specimens. The patient underwent left hemithyroidectomy under a clinical diagnosis of thyroid follicular neoplasm. Intraoperatively, the thyroid gland was extremely highly hemorrhagic, although the tumor was not exposed to the exterior of the thyroid gland. The left lobe was fixed on the deep cervical fascia by a tumor vessel derived from the inferior thyroid artery and measuring approximately 5 mm in diameter. The perioperative bleeding was almost 3000 mL and the operative time exceeded 7 h. The patient manifested hoarseness due to left recurrent nerve paralysis after the surgery.

Pathological examination for the resected thyroid

In pathological examination of the resected specimens, the left lobe of the thyroid was markedly enlarged, measuring 6.5 cm × 5.0 cm (Figure 3A). The cut surface of the resected specimen showed a whitish and partially hemorrhagic solid tumor (Figure 3B). Histologically, many markedly developed blood vessels were found at the surface of the resected thyroid (Figure 4A). Some of these abnormal vessels showed signs of bleeding (Figure 4B). The tumor was composed of atypical cells with clear or eosinophilic cytoplasm, suggesting metastasis of the clear cell RCC (Figure 4C). In immunohistochemical analysis, the tumor cells were diffusely positive for CD10 and vimentin (Figure 4D and E). From these findings, a pathological diagnosis of thyroid metastasis from clear cell RCC was finally made.

Outcome and follow-up of the second surgery

One month after the hemithyroidectomy, CT scans revealed a small nodule in the left lung which had increased in size compared to the previous examination. The nodule was clinically diagnosed as lung metastasis from RCC, and targeted molecular therapy (TMT) with sunitinib was initiated. After 5 mo of the sunitinib therapy, the lung nodule had regressed in the CT scan examination. The patient is currently free of disease at 28 mo after the surgery for thyroid metastasis.

DISCUSSION

RCC is a common malignancy that comprises 3% of adult cancers. It has been reported that nearly 20% to 30% of RCC patients have a metastatic lesion at the time of initial diagnosis and 20% to 30% of patients undergoing nephrectomy for localized RCC develop metastatic disease[5]. Common metastatic sites of RCC are the lungs (45.2%), bone (29.5%), lymph nodes (21.8%), liver (20.3%), adrenal gland (8.9%) and brain (8.1%)[6]. Metastasis of RCC to the thyroid gland is quite rare. The mean time from diagnosis of primary tumor to metastasis to thyroid is considerably long, ranging from 106 to 113 mo[2,7].

Although thyroid metastasis from RCC has some characteristic US findings, such as oval-shaped hypoechoic solid nodules with well-defined smooth margins, no calcifications, prominent chaotic intra-tumoral vascularity and tumor thrombus, these findings are not specific to this disease[8,9]. Thus, it is necessary to perform fine-needle aspiration cytology (FNAC) and to obtain information on the previous history of RCC. When a previous history of RCC is recognized, cytological findings and immunocytochemistry on FNAC-obtained material would be helpful for preoperative diagnosis[10].

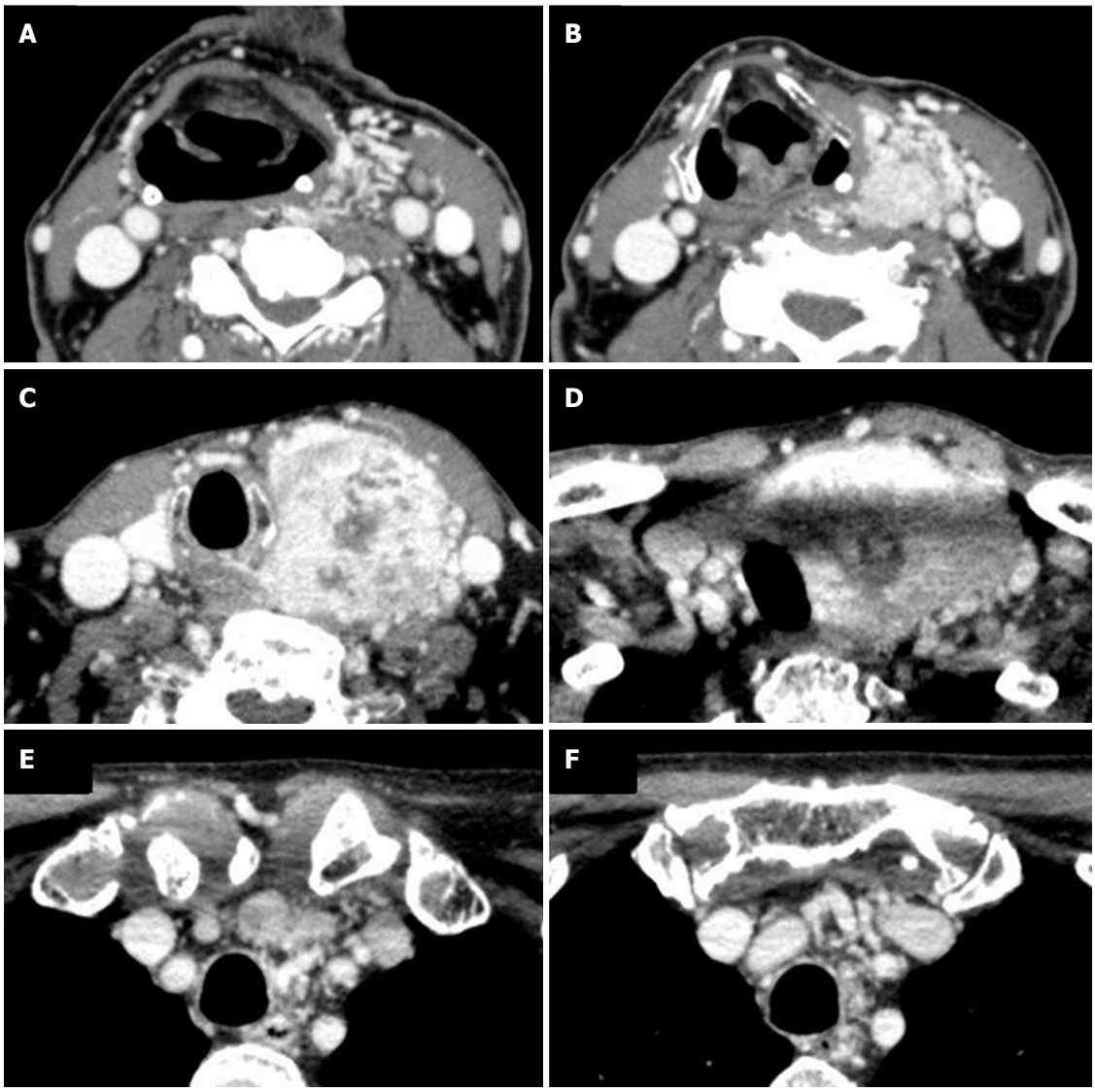

Figure 2 Serial (A-F) contrast-enhanced computed tomography scan images of the thyroid mass 43 mo after the first examination. The computed tomography scan reveals a heterogeneously contrast-enhanced large tumor surrounded by various vascular-like structures. The trachea was compressed but invasion was not apparent.

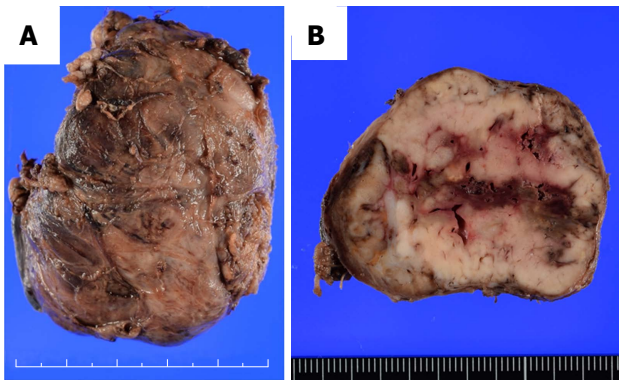

Figure 3 Gross appearance of the resected specimen. A: The left lobe of the thyroid was markedly enlarged (6.5 cm × 5.0 cm); B: The cut surface of the resected specimen showed a whitish and partially hemorrhagic solid tumor. The tumor did not invade beyond the capsule of the thyroid.

However, it is reported that an RCC metastasis was correctly suspected in only 21 of 37 cases (57%) by preoperative FNAC[11]. Thus, a clinician should keep in mind the possibility of metastatic disease to the thyroid gland even when FNAC is negative or inconclusive.

The prognosis for patients with metastatic RCC is generally poor, with a 2-year survival of 10% to 20%[12,13]. Gravis *et al*[5] reported that the presence of at least one glandular metastatic site (pancreas, breast, parotid, thyroid, or contralateral adrenal gland) in the development of metastatic RCC has been associated with a significantly longer overall survival among patients with metastatic RCC, and thus patients with metastatic RCC with glandular metastases should receive more aggressive treatment with a potential for long-term survival.

Although recent advances of TMTs have improved the progression-free survival of RCC[14], cytoreductive surgery still plays an important role in the management of patients with advanced disease[15]. Cytoreductive nephrectomy (CN) refers to radical nephrectomy as a treatment option in metastatic RCC prior to

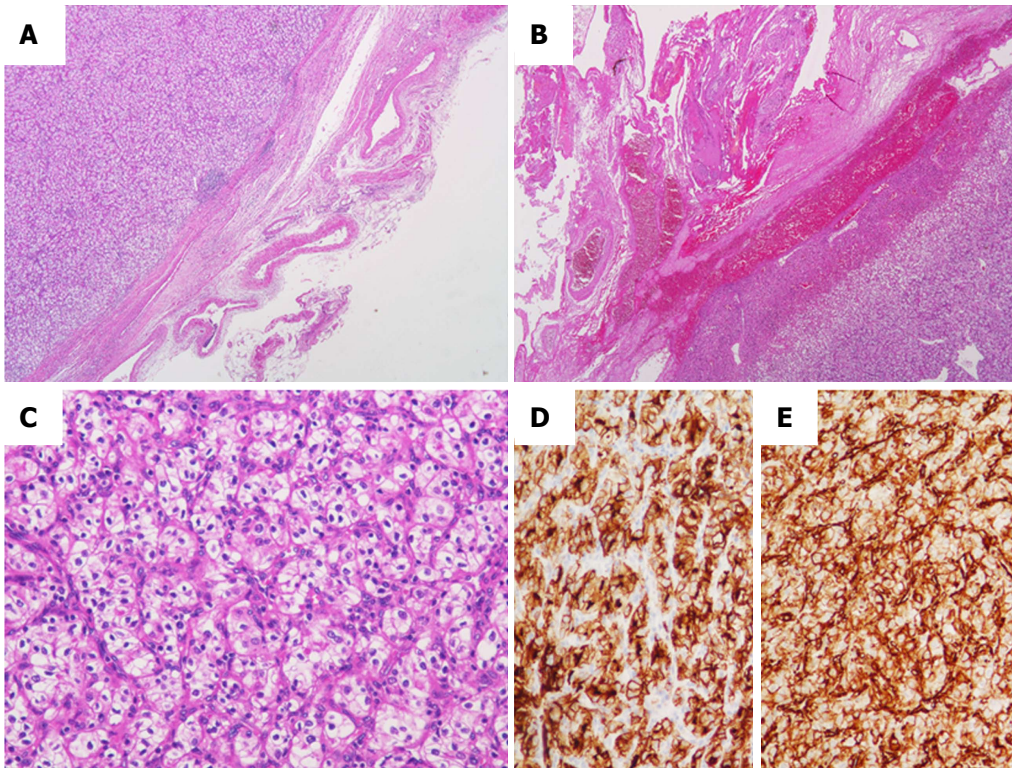

Figure 4 Histological findings of the resected thyroid specimens. A: Many markedly developed blood vessels were found at the surface of the resected thyroid [hematoxylin-eosin (HE) staining, × 20]; B: Some of these abnormal vessels showed the signs of bleeding (HE, × 20); C: The tumor was composed of atypical cells with clear or eosinophilic cytoplasm, suggesting metastasis of clear cell renal cell carcinoma (HE, × 200); D, E: Immunostaining of the thyroid tumor for CD10 (D) and vimentin (E). The tumor cells were diffusely positive for both CD10 and vimentin (× 200).

immunotherapy (IT) or TMT. Evidence of the efficacy of CN has been provided by two large randomized controlled trials, which showed a survival benefit and delayed time-to-progression in patients who underwent CN followed by IT compared to patients with IT alone[16]. Not only the surgical resection of the primary tumor, but that of the metastatic foci prior to the IT or TMT is associated with prolongation of survival when technically feasible[17]. Therefore, metastatic RCC of the thyroid should be resected unless the patients have disseminated metastases or cannot tolerate surgery under general anesthesia.

Thyroid surgery is usually safe, with almost 0% mortality and a low complication rate[18]. Although total thyroidectomy involves a potential risk of serious complications, such as cervical hematoma followed by airway compromise requiring urgent surgical treatment, bilateral recurrent laryngeal nerve injury, and hypoparathyroidism, hemithyroidectomy can be performed safely for most patients. In the present case, massive bleeding from the tumor due to markedly developed tumor vessels made the operation very difficult, even though hemithyroidectomy is usually a safe and straightforward procedure. Based on our experience, we consider that resection of thyroid metastasis from RCC should be performed as early as possible. If the metastatic tumor involves adjacent cervical structures (*e.g.*, internal jugular vein invasion, recurrent laryngeal nerve invasion and involvement of cervical lymph nodes) which is a strong adverse prognostic factor, extensive surgery should be embedded in a systemic treatment concept[11,19].

The reasons for the delay of the surgery in the present case were as follows: first, we prioritized the therapy for brain metastasis over the long-term prognosis of the patient; second, we could not properly diagnose the thyroid mass lesion before operation. As a result, the tumor grew and developed a strong feeding vasculature.

In conclusion, we have presented our didactic surgical experience of a case of thyroid metastasis from RCC which caused massive intraoperative bleeding. Based on our experience, we recommend that resection be performed early whenever possible, even if a patient with thyroid metastasis is asymptomatic and has other metastatic sites at the time of diagnosis, unless the patient has appropriate reasons to avoid surgery. Finally, in order to determine the appropriate timing for surgery, a clinician should take into consideration the possibility of thyroid metastasis when a thyroid mass lesion is found in patients with RCC or in patients having a previous history of RCC.

EXPERIENCES AND LESSONS

We experienced a case of thyroid metastasis from RCC which caused massive intraoperative bleeding: (1) The possibility of thyroid metastasis should be taken into

consideration when a thyroid mass lesion is found in patients with a history of RCC; and (2) The resection of thyroid metastasis of RCC should be performed as early as possible, even if the patient is asymptomatic and has other metastatic sites, unless there are appropriate reasons to avoid surgery.

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CASE REPORT

Gastric cancer with severe immune thrombocytopenia: A case report

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Author contributions: Zhao ZW and Yu JC drafted this manuscript; Kang WM and Yu JC performed the operation for this patient; Ma ZQ and Ye X analyzed the patient data and prepared the figures; all authors read and approved the final manuscript.

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Abstract

BACKGROUND

Primary immune thrombocytopenia (ITP) is a rare autoimmune disease associated with a high bleeding risk. For those patients with gastric cancer, surgical treatment may be the only option for therapy. Here, we present the first case of gastric cancer with severe and medically refractory ITP treated by radical resection of the gastric cancer and splenectomy.

CASE SUMMARY

A 54-year-old female patient was admitted to our surgical department with a 2 mo history of decreased appetite, nausea, vomiting, and weight loss, which progressed to difficulty in feeding 3 d prior to her visit. According to her medical history, she was diagnosed with refractory ITP [platelets (PLT), 3000-8000/μL] 10 years ago. After admission, the patient underwent a splenectomy and a distal subtotal gastrectomy (D2 radical resection) with Roux-en-Y reconstruction simultaneously. She had an uneventful postoperative course with a slight increase in her PLT count. This case is unique in terms of the patient's complication of severe and medically refractory ITP.

CONCLUSION

Simultaneous splenectomy, preoperative PLT transfusion, and early enteral nutrition were important treatment methods for helping this patient recover.

Key words: Gastric cancer; Immune thrombocytopenia; Surgical treatment; Case report

Core tip: Immune thrombocytopenia (ITP) is a rare autoimmune disease with a reduced platelet count. Severe and medically refractory thrombocytopenia is an absolute contraindication to chemotherapy or radiotherapy. For those patients with a malignant tumor, surgical treatment may be the only option despite a high risk of bleeding. This case might contribute to improving our understanding of the behavior and perioperative management of severe and medically refractory ITP patients with gastric cancer.

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INTRODUCTION

Primary immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenia purpura, is an autoimmune disease associated with a reduced platelet (PLT) count without any obvious initiating and/or underlying cause. Severe and medically refractory thrombocytopenia is an absolute contraindication to chemotherapy or radiotherapy. For those patients with gastric cancer, surgical treatment may be the only option for therapy despite a high risk of bleeding. This uncommon condition can be worrisome for surgeons. Here, aiming to lay a foundation for future clinical work, we report the first case of gastric cancer complicated by severe and medically refractory ITP treated by subtotal gastrectomy and splenectomy and a review of the related literature.

CASE REPORT

A 54-year-old woman was admitted to our hospital with a 2-mo history of decreased appetite, nausea, vomiting, and weight loss, which progressed to difficulty in feeding 3 d prior to her visit. A rapid urease test and serum antibody testing demonstrated that she was negative for *Helicobacter pylori* (*H. pylori*). An upper gastrointestinal endoscopy showed irregular erosion on the pylorus with pyloric stenosis. Multiple mucosal biopsies were obtained, and a histological analysis revealed gastric adenocarcinoma. Serum levels of tumor markers were significantly elevated (CA19-9 273.1 U/mL and CA242 > 150.0 U/mL). Abdominal contrast-enhanced computed tomography revealed a thickening wall of the gastric antrum with significantly enhanced, multiple small lymph nodes around the stomach but no obvious retroperitoneal lymph nodes, and a normal spleen. She worked in a plastics factory and was exposed to chemicals and radioactive materials for several years. She was diagnosed with ITP (PLT 3000-8000/μL) 10 years ago. Prednisolone therapy (80 mg/d for 2 wk) was started; and her PLT increased to 50000-60000/μL. However, PLT decreased to 3000-7000/μL immediately after reduction of corticosteroids. Then, dexamethasone therapy (40 mg/d for 4 d) was started. PLT increased to 170000/μL temporarily but decreased to 3000-7000/μL 3 d after therapy. Other medications including immunoglobulins (10 g/d for 4 d), androgen derivatives (danazol 400 mg/d for 3 mo), cyclosporine A (200 mg/d for 2 wk), and thrombopoietin (50 μg/d for 7 d) were administered respectively. However, she no longer responded to any of these medical therapies. Other previous medical history included congenital ventricular septal defect and subclinical hypothyroidism. Her family history was unremarkable. On admission, her physical examination and blood biochemistry laboratory results were within normal limits. Hematological tests revealed a decreased PLT count of 5000/μL and a normal hemoglobin (HGB) level of 111 g/L. Subsequently, she presented with melena and bloody drainage which was observed in the nasogastric tube; the HGB and PLT decreased to 85 g/L and 1000/μL, respectively. Her general condition was examined before surgery. Because of decreased appetite and difficulty in feeding, her weight dropped to 66 kg from her normal weight of 80 kg (body mass index dropped from 30.1 kg/m^2 to 24.8 kg/m^2). Although both cardiac function and pulmonary function were at normal levels, her high nutritional risk may affect the postoperative recovery.

The patient underwent a splenectomy and a distal subtotal gastrectomy (D2 radical resection) with a Roux-en-Y reconstruction simultaneously. A needle catheter jejunostomy was performed to ensure postoperative enteral nutrition (EN). In total, four pheresis units (one pheresis unit contains approximately 2.5-4.0 × 10^{11} PLTs, equal to 10-12 whole blood donor units) of PLT were transfused. The patient's PLT counts fluctuated between 30000-60000/μL during the surgery and PLT were administered accordingly (one pheresis unit was administered 1 h before induction of anesthesia; two pheresis units administered during surgery; and one pheresis unit 2 h after surgery).

The patient resumed EN (oligopeptide, low-fat, isocaloric, non-residue diet; Peptisorb, Nutricia, Schiphol, The Netherlands) on the morning of the 2nd postoperative day. She had an uneventful postoperative course with a slight increase in the PLT count (Figure 1) and was discharged on the 15th postoperative day. The histopathological examination after the subtotal gastrectomy revealed a poorly differentiated gastric adenocarcinoma which had reached the serosal layer. The cancer had also metastasized to 3/30 lymph nodes. The pathological stage was pT4aN2M0, ⅢA. There was no evidence of recurrence, and she showed a consistent and stable increase in the PLT count around 20000/μL for

Table 1 Cases of immune thrombocytopenia patients suffering with gastric malignant tumors

Ref.	PLT level (/μL)	Gastric tumor	*H. pylori*	Treatment for gastric tumor	Prognosis of gastric tumor
Bachmeyer *et al*[6], 2000	40000	Gastric MALT lymphoma	Positive	Chemotherapy	-
Noda *et al*[7], 2004	27000	Gastric MALT lymphoma	Positive	Endoscopic mucosal resection	Without recurrence in 2 yr
Wakata *et al*[8], 2006	73000-10800	Gastric cancer	-	Subtotal gastrectomy and splenectomy	Without recurrence in 2 yr
Villias *et al*[9], 2008	76000	Gastric cancer and GIST	-	Subtotal gastrectomy and splenectomy	-
Hamabe *et al*[10], 2011	52000	Gastric cancer and gastric MALT lymphoma	Positive	Total gastrectomy and splenectomy	Without recurrence in 2 yr

MALT: Mucosal associated lymphoid tissue; *H. pylori*: *Helicobacter pylori*; GIST: Gastrointestinal stromal tumor; PLT: Platelet.

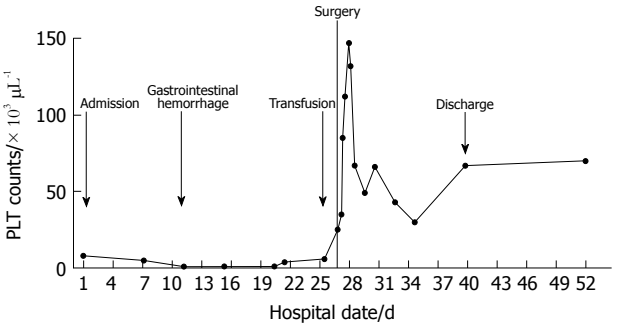

Figure 1 Platelet count fluctuation of the patient during hospitalization. PLT: Platelet.

about 2 years after the operation.

DISCUSSION

ITP is an immune-mediated disease associated with a reduced PLT count lower than 100000/μL[1]. The mechanism of ITP includes that PLT membrane proteins become antigenic and stimulate the immune system resulting in thrombocytopenia due to immune-mediated PLT destruction and/or suppression of PLT production[2]. Some studies defined very severe thrombocytopenia as PLT count < 10000/μL[3]; however, some researchers suggest that the severity of the disease is based clinically on bleeding scores rather than a PLT count[4,5]. In this case, the patient presented with gastrointestinal hemorrhage accompanied with acute anemia. According to Khellaf's bleeding score[4], this patient had a high bleeding score (> 8), which indicated a severe ITP with a high risk of life-threatening hemorrhage. Patients are considered to have medically refractory ITP when they require treatment following failure to respond to medical treatment. Response was defined as PLT count > 30000/μL and at least a 2-fold increase in the baseline count and absence of bleeding[1]. In this case, the patient was considered nonresponse to medication.

To the best of our knowledge, only five cases of ITP patients suffering with gastric malignant tumors have been reported in English in MEDLINE (Table 1)[6-10]. Patients in these cases suffered mild ITP with a PLT level larger than 20000/μL. The commonest pathology is gastric cancer and gastric mucosa associated lymphoid tissue (MALT) lymphoma. *H. pylori* may play a key role in the pathogenesis of both gastric malignant tumors and ITP. Noda *et al*[7] reported a case of regression of ITP after resection of gastric MALT lymphoma and eradicating treatment of *H. pylori*. In terms of treatment, endoscopic resection could be performed only when the tumor is restricted to the mucosa during eradication therapy. Subtotal/total gastrectomy combined with splenectomy is the most appropriate treatment when tumors invade the submucosa. And this is the first case of gastric cancer with severe and medically refractory ITP. The extremely low PLT level led to a high risk of bleeding, especially during the perioperative period.

Corticosteroids with or without intravenous immunoglobulin (IVIg) are the standard first-line treatment for ITP patients with a PLT count < 30000/μL[11]. For patients who have failed corticosteroid therapy, a splenectomy is recommended as a second-line treatment. According to recent research, a short-term response to a splenectomy was achieved in approximately 87% of ITP patients[12-14]. Whereas in patients with a PLT count on admission of < 40000/μL, only 40% may achieve a long-term stable response[14]. In our patient, the thrombocytopenia continued with PLT counts fluctuating between 3000-8000/μL and she showed a poor response to preoperative medical boosting. Considering its satisfactory and high response rates in short-term postoperative time, it is reasonable for patients to undergo a splenectomy in terms of low complication rates and low bleeding risk.

According to some studies, PLT transfusions were recommended only in a few life-threatening cases that require a rapid rise in PLT count to achieve hemostasis, such as intracranial hemorrhage or major surgery[1,15]. Despite the short-term efficacy, PLT transfusion every 30 min to 8 h and a PLT transfusion in conjunction with IVIg or steroids have been effective for increasing PLT levels in emergency situations[16-18]. Traditionally, for safety, most guidelines recommend a PLT count of at least 30000-50000/μL for prophylaxis during surgery[19,20]. Recently, some researchers reported that a perioperative PLT transfusion might be unnecessary for a laparoscopic splenectomy in ITP patients[21,22]. However, there is still a lack of evidence to guide preoperative PLT transfusions used as prophylaxis for surgery, especially for those

with a high bleeding risk. In this case, a PLT transfusion resulted in a rapid rise of PLT count ranging from 30000 to 60000/μL during the operation and ensured a successful surgery.

Postoperative patients with advanced gastric cancer generally suffer from various complications, such as infection and malnutrition[23]. Early EN is important to implement as a way to accelerate rehabilitation of intestinal function and immune response in patients undergoing a gastrectomy, especially in patients with severe complications[24]. Needle catheter jejunostomy was reported to be safe and progressive EN support could be implemented successfully[25,26]. In this patient, the step-by-step EN feeding program was initiated on the 2nd postoperative day using the needle catheter jejunostomy.

In conclusion, we report a case of advanced gastric cancer complicated with severe and medically refractory ITP that was successfully cured by radical resection of the gastric cancer. Simultaneous splenectomy, preoperative PLT transfusion, and early EN were important assistances to the treatment of this patient.

ARTICLE HIGHLIGHTS

Case characteristics

The patient suffered from decreased appetite, nausea, vomiting, and weight loss for 2 mo with a past medical history of thrombocytopenia, which progressed to difficulty in feeding and gastrointestinal hemorrhage.

Clinical diagnosis

The patient was diagnosed with gastric cancer accompanied with severe and medically refractory immune thrombocytopenia.

Differential diagnosis

Mucosal biopsy from endoscopy was useful for differential diagnosis and histological analysis revealed a gastric adenocarcinoma.

Laboratory diagnosis

Laboratory findings revealed elevated tumor markers (CA19-9 and CA242), low platelet count, and decreased hemoglobin.

Imaging diagnosis

Abdominal contrast-enhanced computed tomography revealed a thickening wall of the gastric antrum with significantly enhanced, multiple small lymph nodes around the stomach but no obvious retroperitoneal lymph nodes and a normal spleen.

Pathological diagnosis

The histopathological examination after the subtotal gastrectomy revealed a poorly differentiated gastric adenocarcinoma which had reached the serosal layer and the cancer had also metastasized to 3/30 lymph nodes.

Treatment

The patient underwent a splenectomy and a distal subtotal gastrectomy (D2 radical resection) with a Roux-en-Y reconstruction simultaneously.

Related reports

Five cases of immune thrombocytopenia (ITP) patients suffering with gastric malignant tumors have been reported in English in MEDLINE. Patients in these cases suffered mild ITP with a platelet (PLT) level larger than 25000/μL. The commonest pathologies are gastric cancer and gastric mucosa associated lymphoid tissue (MALT) lymphoma. *Helicobacter pylori* (*H. pylori*) may play a key role in the pathogenesis of both gastric malignant tumors and ITP. Noda *et al*[7] reported a case of regression of ITP after resection of gastric MALT lymphoma and eradicating treatment of *H. pylori*. In terms of treatment, endoscopic resection could be performed only when the tumor is restricted to the mucosa during eradication therapy. Subtotal/total gastrectomy combined with splenectomy is the most appropriate treatment when tumors invade the submucosa.

Experiences and lessons

For patients with cancer and medical refractory ITP, surgical treatment may be the only option for therapy despite a high risk of bleeding. Simultaneous splenectomy, preoperative PLT transfusion, and early enteral nutrition are important treatment methods for postoperative recovery.

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CASE REPORT

Injury to the axillary artery and brachial plexus caused by a closed floating shoulder injury: A case report

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Abstract

BACKGROUND

A floating shoulder may be associated with catastrophic neurovascular injury and requires a multidisciplinary approach for its management. To maximize the likelihood of good patient outcomes, this unique injury pattern should be recognized in patients as early as possible. This can be difficult to achieve, however, as there are currently few reports of floating shoulder in the literature, meaning that associated neurovascular injuries may be overlooked.

CASE SUMMARY

We present here a rare case of floating shoulder with axillary artery injury in a 34-year-old woman. The patient complained of pain and numbness of her left upper limb after losing control of her motorcycle on a highway and falling from the vehicle 2 h ago. No blood pressure reading could be obtained from her left upper limb and no blood oxygen readings could be obtained from any of her left fingers. Computed tomography angiography and duplex ultrasonography revealed interruption of blood flow through the axillary artery, with distal flow being maintained through collateral arteries. The clinical diagnosis including fracture of the left proximal humerus, the left clavicle, and the left scapula, left axillary artery rupture, and left brachial

plexus injury. We successfully performed open reduction and internal fixation of the fracture and vascular repair. The patient showed satisfactory recovery that was observed during 4-mo follow-up.

CONCLUSION

Emergency surgery can be an effective therapeutic option for the closed floating shoulder with catastrophic axillary artery injury.

Key words: Floating shoulder injury; Axillary artery injury; Brachial plexus injury; Complications of floating shoulder; Management of floating shoulder; Clavicle fracture; Case report

Core tip: A floating shoulder with catastrophic neurovascular injury may be overlooked, as there are currently few reports in the literature. This case report describes that brachial plexus and axillary artery injury by the distal fragment of the clavicle in a closed floating shoulder, and we successfully performed open reduction and internal fixation of the fracture and vascular repair.

Chen YC, Lian Z, Lin YN, Wang XJ, Yao GF. Injury to the axillary artery and brachial plexus caused by a closed floating shoulder injury: A case report. *World J Clin Cases* 2018; 6(15): 1029-1035 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1029.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1029

INTRODUCTION

A floating shoulder is a fracture of the scapular neck with ligament disruption, and may or may not involve a clavicular fracture[1,2]. It is often associated with catastrophic neurovascular injury[1-5] and requires a multidisciplinary approach for its management. To maximize the likelihood of good patient outcomes, this unique injury pattern should be recognized in patients as early as possible. This can be difficult to achieve, however, as there are currently few reports of floating shoulder in the literature, meaning that associated neurovascular injuries may be overlooked[5]. We herein report a case involving injury to the axillary artery and brachial plexus caused by a closed floating shoulder injury. Based on a review of the current literature, we suggest how early diagnosis and effective treatment of this uncommon injury can be achieved.

CASE PRESENTATION

A 34-year-old, 80-kg, and alcohol-intoxicated East Asian woman presented to our emergency department after losing control of her motorcycle on a highway and falling from the vehicle (Figure 1). While the patient did occasionally drink, her drinking history was otherwise unremarkable. She also did not smoke and had no history of drug addiction or chronic disease, and was overall a healthy woman. At presentation, pain and swelling of her left shoulder were evident. She also complained of numbness of her left upper limb. Her vital signs upon arrival were as follows: Blood pressure, 135/95 mmHg; heart rate, 82 beats per minute; and respiratory rate, 19 breaths per minute. No blood pressure reading could be obtained from her left upper limb and no blood oxygen readings could be obtained from any of her left fingers. Her Glasgow Coma Scale score was 15.

Closer examination of the patient revealed that capillary refill of all left-hand fingers was disturbed, although the patient's left arm and hand were warm and radial and ulnar pulses at the wrist were absent. Movement of her left shoulder, elbow, and wrist was also restricted along with a local shoulder injury. However, no bruit could be detected. Laboratory results, including complete blood count, electrolytes, and coagulation panels, were also normal, with hemoglobin and hematocrit results of 13.0 g/dL and 38.4%, respectively.

Plain anterior-posterior radiographs and computed tomography (CT) images were subsequently taken (Figure 2), which revealed multiple fractures of the scapular area, implying that it is a floating shoulder injury. Injuries included a fracture of the left clavicle at the middle third and downward displacement of the distal fragment, a displaced comminuted fracture of the left scapula, and a displaced comminuted fracture of the left proximal humerus. In addition, CT angiography (Figure 2) and duplex ultrasonography (Figure 3) revealed interruption of blood flow through the axillary artery, with distal flow being maintained through collateral arteries. During observation, the patient reported increasing numbness and coldness of her left arm. To avoid limb-threatening irreversible ischaemia and amputation, it was decided that emergency vascular repair surgery should be performed immediately.

Case characteristics

A 34-year-old woman presented to the hospital with 2 h of persistent pain and swelling of her left shoulder and numbness of her left upper limb after losing control of her motorcycle on a highway and falling from the vehicle.

Clinical diagnosis

Fracture of the left proximal humerus, left clavicle, and left scapula, left axillary artery rupture, and left brachial plexus injury.

Differential diagnosis

The differential diagnoses included arterial thrombosis and compression. Complete blood count, electrolytes, and coagulation panels, were also normal, with hemoglobin and hematocrit results of 13.0 g/dL and 38.4%,

Figure 1 Closed left "floating shoulder". Marked soft tissue swelling, subcutaneous congestion, and deformity of the left shoulder were observed.

respectively. X-ray and CT images displayed multiple fractures of the shoulder that were indicative of a floating shoulder injury. In addition, CT angiography and duplex ultrasonography revealed interruption of blood flow through the axillary artery, with distal flow being maintained through collateral arteries.

Emergency surgical exploration revealed that the axillary artery was completely amputated by the distal fragment of the left clavicle, and that the brachial plexus had suffered contusions (Figure 4). The proximal axillary artery was also completely occluded by a thrombus that had formed over a tear in the tunica intima. End-to-end anastomoses were thus performed, resulting in shortening of the artery by about 2 cm after excision of traumatized vessel segments (Figure 4). One-stage reconstruction with placement of a locking plate was then performed to treat the patient's clavicle fracture. The displaced comminuted fracture of the left proximal humerus was treated during the second-stage operation 3 wk after the initial injury (after angiogenesis). The fracture of the scapula was not surgically treated.

Revascularization of the patient's upper extremity was achieved by emergency surgery about 10 h after the initial injury. Specifically, the patient's radial and ulnar pulses were restored, and CT angiography confirmed that blood flow was uninterrupted (Figure 5). Furthermore, the blood oxygen concentration of her left upper extremity was 100% and systolic blood pressure measurements were equal in both arms. Postoperative X-ray showed that reduction and internal fixation results were satisfactory (Figure 6). Regarding the injury to the brachial plexus, emergency surgical exploration revealed that the brachial plexus had suffered contusions, and preoperative and postoperative neurological examinations revealed paresthesia resulting from brachial plexus contusion. Before the operation, the patient did not undergo electromyography and magnetic resonance examination due to emergency surgery. The patient was not willing to undergo electromyography and magnetic resonance examination after initial vascular reconstruction. And the patient left our city after discharge before the wound healed. We can only follow her by telephone. During the follow-up period, the patient refused to undergo electromyography and magnetic resonance examination in her city. Three months after injury, the fingers of the left hand can move freely; the movement of the left shoulder, elbow, and wrist became more and more flexible and free; the numbness of the left upper limb was reduced; the strength of the left upper limb was significantly better than before; and she was able to take care of her daily life. At the 4th month of follow-up, the patient felt that the movement, numbness, and strength of the left upper limb were better than before. After the fourth month of follow-up, the patient could not be contacted by telephone and the follow-up was completed, although we have been trying to contact this patient. Overall, the patient showed satisfactory recovery that was observed during 4-mo follow-up.

FINAL DIAGNOSIS

Fracture of the left proximal humerus, left clavicle, and left scapula, left axillary artery rupture, and left brachial plexus injury.

TREATMENT

Emergency surgical exploration revealed that the axillary artery was completely amputated by the distal fragment of the left clavicle, and that the brachial plexus had suffered contusions. End-to-end anastomoses were thus performed. One-stage reconstruction with placement of a locking plate was then performed to treat the patient's clavicle fracture. The displaced comminuted fracture of the left proximal humerus was treated during the second-stage operation 3 wk after the initial injury (after angiogenesis). The fracture of the scapula was not surgically treated.

OUTCOME AND FOLLOW-UP

At the 4th month of follow-up, the patient felt that the movement, numbness and strength of the left upper limb were better than before. Overall, the patient showed satisfactory recovery that was observed during 4-mo follow-up.

DISCUSSION

Since Ganz and Noesberger's first statement of the pathologic anatomy of the floating shoulder, its defining characteristics have been revised by other authors[2,6,7]. Herscovici *et al*[7] defined the floating shoulder as an ipsilateral clavicle fracture with a scapular neck fracture. Goss *et al*[6] stated the definition of the superior shoulder suspensory complex (SSSC), and extended the description of a floating shoulder comprising the SSSC. Egol *et al*[8] suggested that a floating shoulder

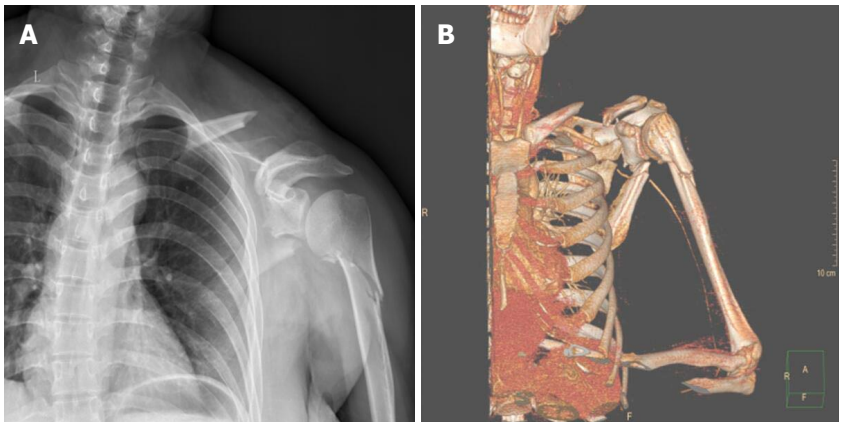

Figure 2 Plain anterior-posterior radiograph and computed tomography image of the left shoulder. A: X-ray demonstrating fractures of the left scapula, left proximal humerus, left clavicle and left shoulder soft tissue swelling; B: 3D computed tomography angiography reconstruction of the left shoulder also demonstrating multiple fractures of the scapular region and interruption of blood flow through the axillary artery.

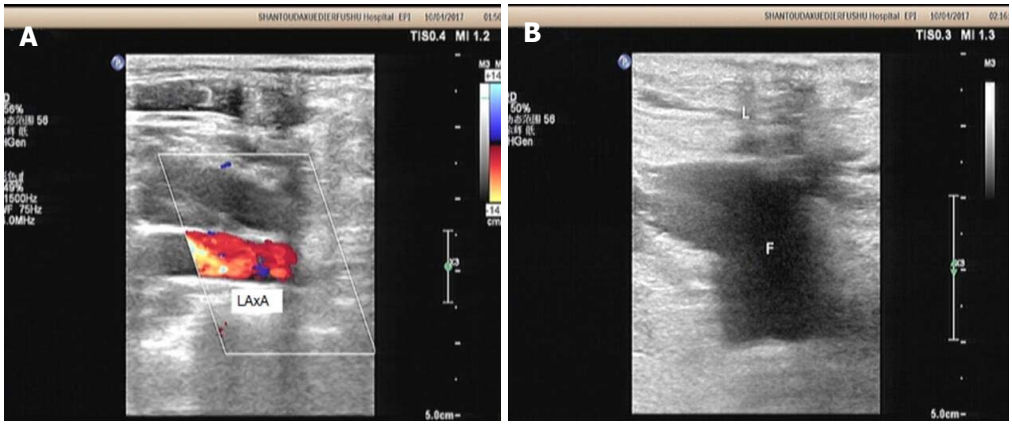

Figure 3 Doppler ultrasound revealed interruption of blood flow through the axillary artery. A: The distal axillay artery was not unclear; B: The perivascular blood accumulation was obvious.

injury involves ipsilateral acromioclavicular joint dislocation with a scapular neck fracture. The most comprehensive definition of a floating shoulder was put forward by Vogels, who asserted that the following fractures of the scapular region are suggestive of this injury: A fracture of the left clavicle at the middle third and downward displacement of the distal fragment, a displaced comminuted fracture of the left scapula, and a displaced comminuted fracture of the left proximal humerus[9]. Despite this progress in understanding, the unified definition of a floating shoulder is still considerably ambiguous, probably because it is a rare injury complex[2].

Indeed, floating shoulder has an incidence rate of approximately 0.10% among trauma patients[10]. It is typically caused by the infliction of high-energy blunt force on the shoulder during road traffic accidents. Consequently, it is associated with a broad range of injuries, with affected patients presenting with a mean of 3.9 co-injuries[11]. The most common co-injuries are those associated with the ipsilateral upper limb, shoulder girdle, brachial plexus, and chest (*e.g.*, rib fractures, blood pneumothorax, and pulmonary contusion), and have an overall incidence of 44%-100% among floating shoulder patients[12]. Of these injuries, chest trauma is the most common (rib fractures, 38%-45%; pulmonary contusion, pneumo- or haematothorax, 15%-50%)[11]. Other common injuries associated with floating shoulder include head injuries (20%), ipsilateral clavicle fractures (15%-40%), and ipsilateral humeral head fractures (12%)[11]. In addition, injuries to the brachial plexus, axillary artery, and subclavian vein can occur[11]. Patient morbidity is highly dependent on the severity of these associated injuries, especially in the presence of neurovascular injuries, which occur in about 10%–12% of floating shoulder patients[11]. A number of these co-injuries occurred in our patient, including a head injury, ipsilateral clavicle fractures, ipsilateral proximal humerus fractures, and injury to the axillary artery and the brachial plexus.

Despite the anatomic proximity of the axillary artery to the clavicle, scapula, and proximal humerus, its injury is rare. There are few reported cases of axillary artery injury following closed trauma in the literature[13]; indeed, we were only able to find a few reports of axillary artery and brachial plexus injury in the English-

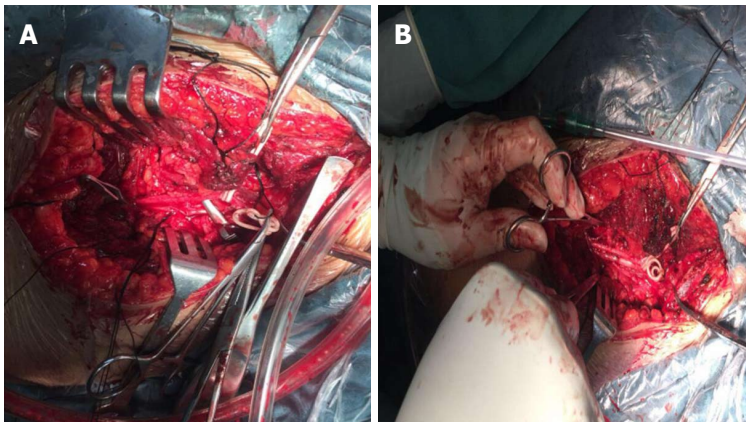

Figure 4 The axillary artery injury and repair. A: Emergency surgery revealed that the axillary artery was completely amputated; B: End-to-end anastomoses were thus performed after excision of traumatized vessel segments.

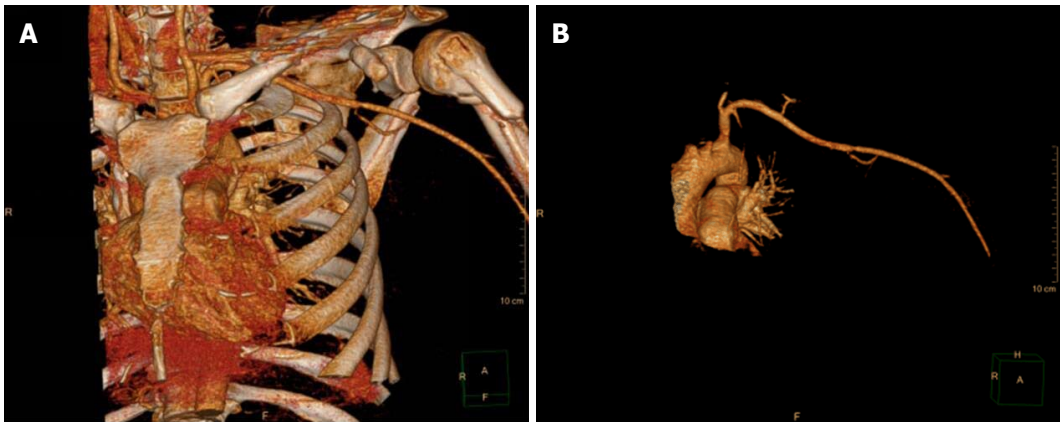

Figure 5 Evidence that axillary artery injury was successfully repaired. A: Computed tomography (CT) angiography confirmed that blood flow of the left axillary artery was restored after vascular repair; B: CT angiography without bone confirmed that blood flow of the left axillary artery was restored after vascular repair.

language literature. In these reports, these injuries mainly resulted from proximal humeral, humeral neck, and rib fractures, shoulder and glenohumeral dislocation, open shoulder injury, and iatrogenic injury. Thus, to the best of our knowledge, this is the first report of axillary artery and brachial plexus injury after an injury pattern such as that described in our patient.

The axillary artery is a continuation of the subclavian artery and is divided into three sections based on its location relative to the pectoralis minor muscle. The first section is defined as the part of the artery superior to the pectoralis minor muscle, the second section lies posterior to the pectoralis minor muscle, and the third section comprises the part of the artery inferior to the pectoralis minor. Although injury can occur anywhere along the course of the artery, previous reports have documented a high rate of injury to its third section. It has been speculated that this is because the axillary artery is fixed and bent by other branch arteries and the humeral head[14]. Injury to the artery may therefore be caused by penetrating sharp bone fragments, overstretching of the vessel, entrapment of the artery within the fracture site, contusion by the humeral head that leads to abrasion of the intima, or even delayed axillary artery thrombosis after a proximal humeral fracture[9]. However, in our patient, the injury occurred in the first section of the axillary artery, and we are inclined to suggest that injury to this section and the brachial plexus resulted from penetration by a distal clavicle fragment.

When arterial injury occurs with a floating shoulder injury, the vascular anatomy of the shoulder has an important role in patient outcome, since any disruption of vascular supply can jeopardize the viability of the entire limb. The main symptoms of ischemia (*i.e.*, paralysis, paresthesia, pain, pallor, and pulselessness) do not always appear in all patients with an injury to the axillary artery because of well-developed collateral vessels around the shoulder joint[14]. Extensive connections among the suprascapular artery, the subscapular artery, and other arteries supply adequate amounts of blood to the distal limb. Therefore, axillary artery injury sites that are near to the origin of the subscapular artery may not impair blood supply to the upper limb. In contrast, injury sites distal to the subscapular artery will most likely result in ischemia of the limb[14].

Axillary artery injuries are also commonly associated with injury to the brachial plexus, with the latter

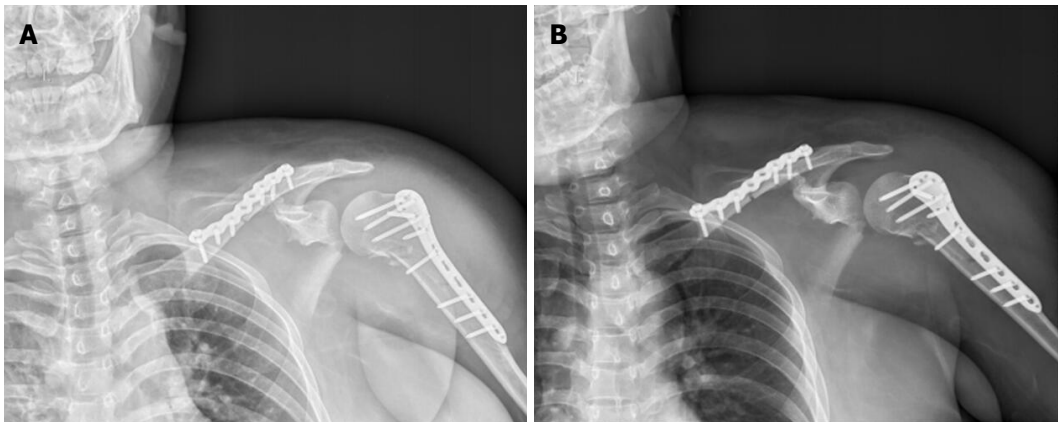

Figure 6 Postoperative radiographs showing reduction and locking plate. A: Positive slice; B: Oblique slice.

occurring in up to 43% of patients with axillary artery injury[13]. Due to the proximity of the axillary artery and the brachial plexus, the area is predisposed to hemorrhagic lesions, brachial plexus compression, and subsequent ischemia[13]. Vascular occlusion alone can also produce permanent neurological damage; thus, minimizing diagnostic time is vital[13]. However, neurological injuries are most frequently caused by the direct infliction of injury on nerve structures by sharp bone fragments[13], with neurological lesions such as these principally affecting patient functional outcomes[13,15].

This case report informs clinical practice guidelines of floating shoulder with arterial injury. Emergency surgery is recommended in cases of vascular compromise[16]. The gold standard for treatment includes open reduction and internal fixation of fractures and vascular reconstruction when the lesion is clinically significant or visible by angiography[13]. Ischemia time and the general condition of the patient determine the order and type of definitive treatment that is to be run[13]. In the case of short ischemic time or only mild ischemia of the limb, a quick reduction and definitive fixation of the fracture may be beneficial. If the ischemia is severe or prolonged, vascular repair is preferred over orthopedic surgery and must be performed immediately. It is recommended that a stable surgical field through prior internal fixation of the fracture be obtained to avoid new injuries and facilitate vascular reconstruction. However, in patients with hemodynamic instability or in patients with ischemia for more than 8 h, quick reduction and temporary fixation, and prior revascularization and subsequent osteosynthesis definitive fixation for fractures are instead recommended[13,17]. The type of vascular repair depends on the type of arterial injury, with possible procedures including thrombectomy, endarterectomy, primary repair, saphenous vein interposition grafting, term-terminal anastomosis, vascular prosthesis[13], and more recently, endovascular techniques. Forearm compartment syndrome may also occur if ischemia time is greater than 6-8 h. In these cases, prophylactic fasciotomies and strict monitoring of compartment pressures should be carried out[13].

To prevent prolonged ischemia, and in turn devastating results such as upper limb amputation and patient death, early diagnosis and treatment of vascular lesions are necessary. We therefore suggest a testable hypothesis that when weak pulsation of the radial and ulnar arteries is observed in a patient with multiple shoulder fractures or shoulder dislocation, the axillary artery injury should be suspected. However, axillary artery injury is difficult to diagnose in some cases. Repeated neurovascular evaluations, along with complementary studies such as Doppler ultrasound and CT angiography or other angiography tests, are essential for diagnosing ischemia. In particular, Doppler ultrasonography can be useful for quantifying the weakness of pulsation. Catheter-based CT angiography can be used to detect damaged areas, and it can facilitate arterial repair by placing stent grafts at the same time. If this fails, open surgical treatment involving direct anastomosis, vein grafting, or artificial vessel grafting should be considered.

The complications of axillary artery and brachial plexus injuries following shoulder trauma are rare but can have serious consequences. This case report stresses the importance of suspecting catastrophic neurovascular injuries in any kind of shoulder trauma, and more importantly, axillary artery injury that can lead to a seriously ischemic limb. The state of the blood vessels should be assessed periodically after the fracture, as the pulse may disappear and ischemic symptoms may appear after a few days. If vascular injury is suspected, early diagnosis and accurate treatment are essential.

There were several strengths in our approach to this case: (1) rapid diagnosis of a floating shoulder with axillary artery injury by detailed physical examination, X-ray, duplex ultrasonography, and CT angiography; (2) perfect collaboration among multiple departments, such as emergency departments, orthopedics, radiology, ultrasound, laboratory, electrocardiogram, vascular surgery, and operating room, in order to race against time; and (3) successful revascularization by emergency surgery. The limitations in our approach to this case

included: (1) there was too little evidence about brachial plexus injury; (2) EMG and MRI were not performed before or after surgery; (3) the follow-up period was too short, and the data of follow-up was too small, such as postoperative imaging examination, postoperative vascular examination, and evaluation of brachial plexus recovery.

CONCLUSION

We emphasize that catastrophic neurovascular injuries can occur with floating shoulder injuries. Therefore, they need to be identified and coordinated by a multidisciplinary team of orthopaedics, trauma and vascular surgeons. We also advise against any attempt at closed reduction of floating shoulder injuries with a pulseless limb as this can have potentially grave consequences; open surgery should instead be indicated without delay with consultation of a vascular surgeon. With swift and proper treatment, the prognosis for patients is good. However, final outcomes are compromised and determined by neurologic morbidity from concomitant brachial plexus injuries. The complications of axillary artery and brachial plexus injuries after shoulder trauma are rare, but can have serious consequences. This case report highlights the importance of suspecting catastrophic neurovascular injury in any type of shoulder trauma, and more importantly, axillary artery injury can result in severe ischemic limbs. The vascular status should be assessed periodically after the fracture, as the pulse may disappear and symptoms may appear after a few days. Early diagnosis and accurate treatment are necessary if vascular injury is suspected.

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CASE REPORT

Pancreatic panniculitis and solid pseudopapillary tumor of the pancreas: A case report

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Author contributions: Tian BL designed the report; Zhang MY collected the patient's clinical data and drafted and reviewed the manuscript; both authors have read and approved the final manuscript to be submitted.

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Abstract

Solid pseudopapillary tumor of the pancreas (SPTP), also known as solid and papillary epithelial neoplasm of the pancreas, is a rare pancreatic exocrine tumor that is difficult to diagnose before surgery. Pancreatic panniculitis is a rare type that occurs in less than 3% of all patients with pancreatic diseases. We here report a 19-year-old woman who presented with persistent left upper quadrant pain without obvious cause for 1 d. The patient also developed subcutaneous nodules involving lower abdomen bilaterally and lower limbs, and subcutaneous nodules were pathologically diagnosed as pancreatic panniculitis. Plain abdominal computed tomography revealed a soft-tissue mass in the body and tail of the pancreas, which was closely associated with the gastric wall. Contrast-enhanced ultrasound showed inhomogeneous echogenicity in the anterior pancreatic body, which had blurred parenchymal demarcation of the body and tail of the pancreas. Contrast-enhanced abdominal computed tomography revealed a mixed density mass with solid and cystic components in the body and tail of the pancreas, and the solid component was markedly enhanced. The lesion was pathologically diagnosed as SPTP after laparoscopic resection. Clinicians should be aware of the clinical manifestation, diagnosis, and treatment of pancreatic panniculitis and SPTP.

Key words: Case report; Pancreatic panniculitis; Solid pseudopapillary tumor of the pancreas; Subcutaneous nodules; Laparoscopy

Core tip: Pancreatic panniculitis is a rare complication of pancreas diseases, and solid pseudopapillary tumor of the pancreas is a rare pancreatic exocrine tumor that is difficult to diagnose before surgery. We describe the diagnosis and treatment of solid pseudopapillary tumor of the pancreas accompanied with pancreatic panniculitis in a young woman. Plain abdominal computed tomography, contrast-enhanced ultrasound, contrast-enhanced abdominal computed tomography and pathological examinations were performed.

Zhang MY, Tian BL. Pancreatic panniculitis and solid pseudopapillary tumor of the pancreas: A case report. *World J Clin Cases* 2018; 6(15): 1036-1041 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1036.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1036

INTRODUCTION

Pancreatic panniculitis is a rare complication of pancreas disorders occurring in 1%-3% of patients, most often accompanied by the pancreatic carcinoma. It often presents multiple and red-brown subcutaneous nodules. The pathogenesis is not fully understood, but it is thought to result from lipolysis and fat necrosis with secondary tissue inflammation induced by pancreatic enzymes[1]. Solid pseudopapillary tumor of the pancreas (SPTP) often occurs in young women, with an average age of 25 years. While the histogenetic origin of SPTP is still unclear, it may arise from the cells related with the gonadal ridge/ovarian primordium during embryogenesis or the embryonic neural crest cells. SPTP exhibits two histological features: Solid and pseudopapillary. In fact, the papillary structure is composed of pseudopapillae that are formed due to degeneration of tumor cells, decreased adhesion of cells, and cystic cavity formation. Clinically, it is usually manifested as an epigastric mass or epigastric pain, and some patients present with both epigastric mass and pain. Some patients may only have epigastric discomfort or fatigue, while others do not have any symptoms. In those asymptomatic patients, pancreatic masses are accidentally found only during routine examinations, and the results of routine biochemical tests are normal[2]. SPTP is unresponsive to radiotherapy or chemotherapy, and surgical resection is the primary treatment of choice. In this report, we describe the diagnosis and treatment of SPTP accompanied with pancreatic panniculitis in a young woman.

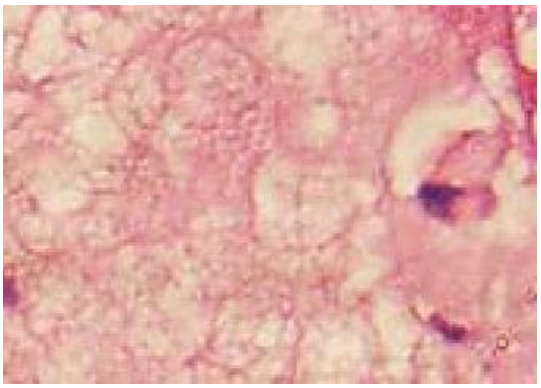

Figure 1 Results of pathological examination. Subcutaneous nodules, fat necrosis (× 200)

CASE REPORT

A 19-year-old woman was presented with persistent left upper abdominal pain without obvious cause for 1 d. She also developed subcutaneous nodules involving lower abdomen bilaterally and lower limbs. She had no abdominal distention, vomiting, or radiative and referred pain. Physical examination revealed a palpable mass with slight tenderness in the left upper quadrant of the abdomen. Subcutaneous nodules were pathologically diagnosed as pancreatic panniculitis (Figure 1). The results of routine blood test at admission were as follows: white blood cell 7.84 × 10^9/L (normal range: 4-10 × 10^9/L), neutrophil-to-lymphocyte ratio 85.5% (normal range: 40%-75%), and hemoglobin 88 g/L (normal range: 115-150 g/L). Liver function test showed albumin 30 g/L (normal range: 40-55 g/L) and alanine aminotransferase 62 U/L (normal range: 8-40 U/L). The result of serum amylase was 869 U/L (normal range: 40-100 U/L), serum lipase was 759 U/L (normal range: 0-110 U/L). Plain abdominal computed tomography (CT) revealed a mass in the body and tail of the pancreas, which required further examinations (Figure 2). After admission, antimicrobial treatment, somatostatin, and hepatoprotective therapies were administered. Contrast-enhanced abdominal CT was highly suggestive of a neoplastic lesion in the body and tail of the pancreas. A SPTP was suspected. The lesion was fed by the common hepatic artery and branches of splenic artery, along with regional portal hypertension (Figure 3). Abdominal contrast-enhanced ultrasound showed a solid mass in the body and tail of the pancreas, and a diagnosis of SPTP was considered (Figure 4).

After antimicrobial drug, somatostatin, and liver-protective drug treatments, routine blood test showed white blood cell 5.62 × 10^9/L, neutrophil-to-lymphocyte ratio 72.8%, and hemoglobin 108 g/L, and liver function test showed albumin 39 g/L and alanine aminotransferase 30 U/L. Serum amylase and lipase, however, declined slowly, showing 479 U/L and 325 U/L. Therefore, traditional Chinese medicine was added to

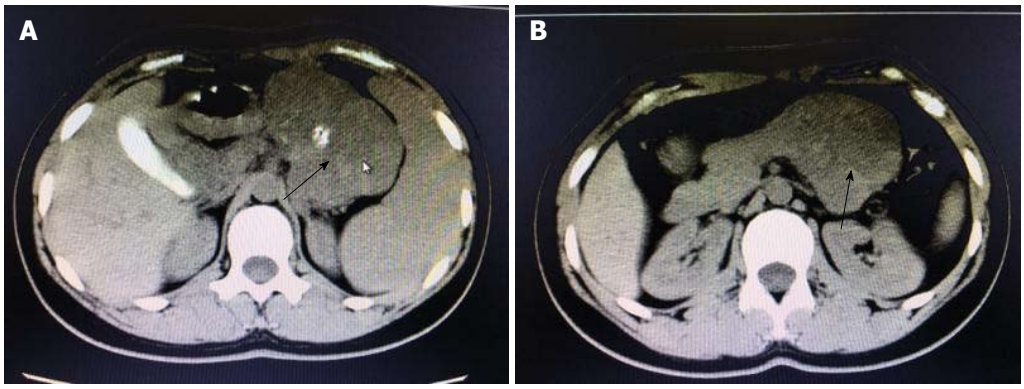

Figure 2 Findings of plain abdominal computed tomography scan. A: Plain abdominal computed tomography reveals a soft-tissue mass in the body and tail of pancreas; B: It has a well-defined border and sized 8.5 cm × 6.1 cm × 6.5 cm, with heterogeneous signal intensity patches and nodular calcifications. It is closely associated with gastric wall. Arrow indicates the mass.

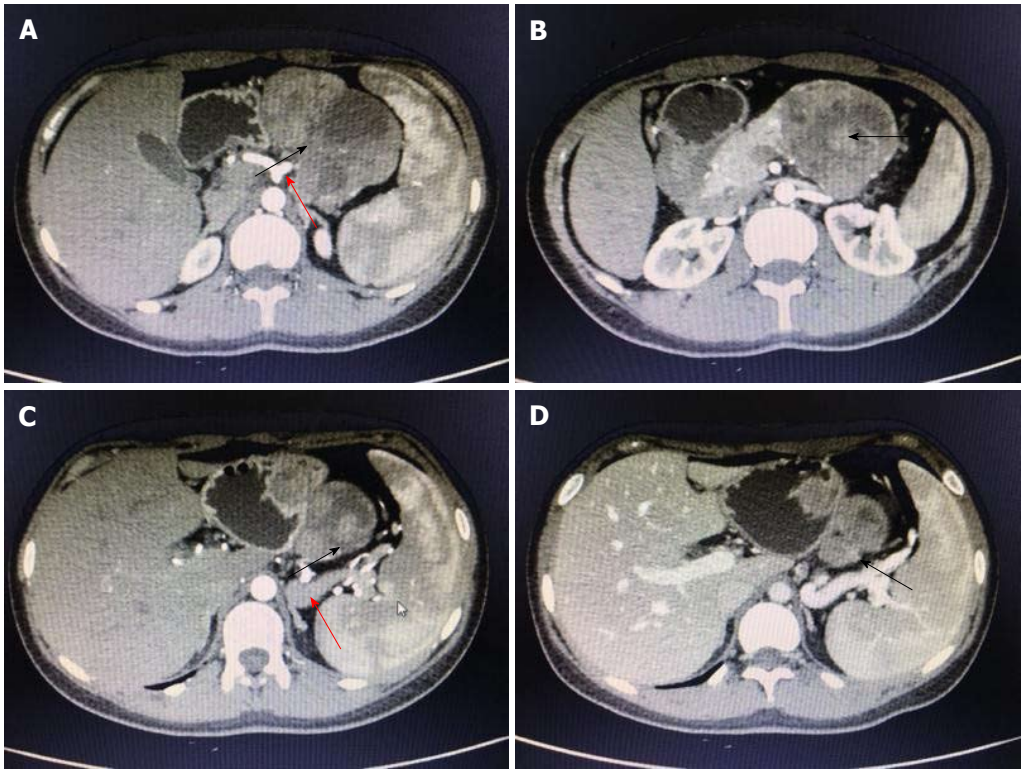

Figure 3 Findings of contrast-enhanced abdominal computed tomography scan. A and B: Contrast-enhanced abdominal computed tomography reveals a mixed density mass with solid and cystic components, sized 6.8 cm × 7.8 cm × 8.8 cm, in the body and tail of the pancreas, with a well-defined border. Nodular calcifications are found inside the lesion; C: The solid component is obviously enhanced, although the degree of enhancement is lower than the normal pancreatic parenchyma; D: The spleen is slightly larger, and the splenic vein is compressed. Multiple collateral circulations are seen in the left upper abdomen. The lesion is fed by the common hepatic artery and a branch of splenic artery (red arrows in A and C, black arrows indicate the mass).

the treatment. Three days later, serum amylase and lipase declined obviously, showing 92 U/L and 98 U/L. After adequate preoperative preparation, the patient underwent laparoscopic resection of the lesion in the pancreatic body and tail with preservation of the spleen. During the operation, a mass sized about 8.5 cm × 8 cm × 7.0 cm was found at the tail of the pancreas. It had an irregular shape and a poorly-defined border with pancreatic body and tail (Figure 5). It was tightly adhered to the splenic vein, and several of its nourished vessels joined the splenic vein. Postoperative pathology suggested that the mass was an SPTP (Figure 5).

DISCUSSION

Pancreatic panniculitis is a rare cause of subcutaneous fat necrosis secondary to elevated serum levels of pancreatic enzymes. It is most often associated with pancreatic cell carcinoma, but has also been seen in patients with pancreatitis. Systematic evidence on pancreatic panniculitis is limited[3]. SPTP is a rare tumor, accounting for about 3% of all pancreatic tumors. It is

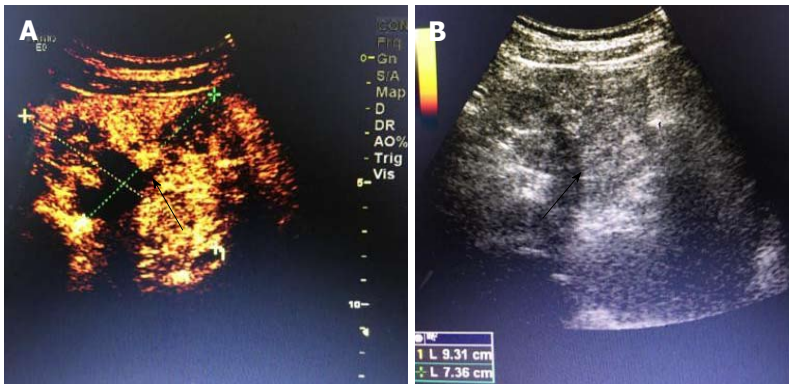

Figure 4 Findings of abdominal contrast-enhanced ultrasonography. A: Abdominal contrast-enhanced ultrasonography shows an abnormal morphology of the pancreas. A mass with inhomogeneous echo, sized about 9.3 cm × 7.2 cm, is found in the anterior pancreatic body; it has a well-defined border and regular shape, but the border with the parenchyma of pancreatic body and tail is poorly defined, with flocculent echo and strong spotty or patchy echo in the central part; B: Color Doppler flow imaging showed a few low-speed arteriovenous blood flow signals, whereas the echoes are homogeneous in the remaining parenchyma. The main pancreatic duct is not dilated. Black arrows indicate the mass.

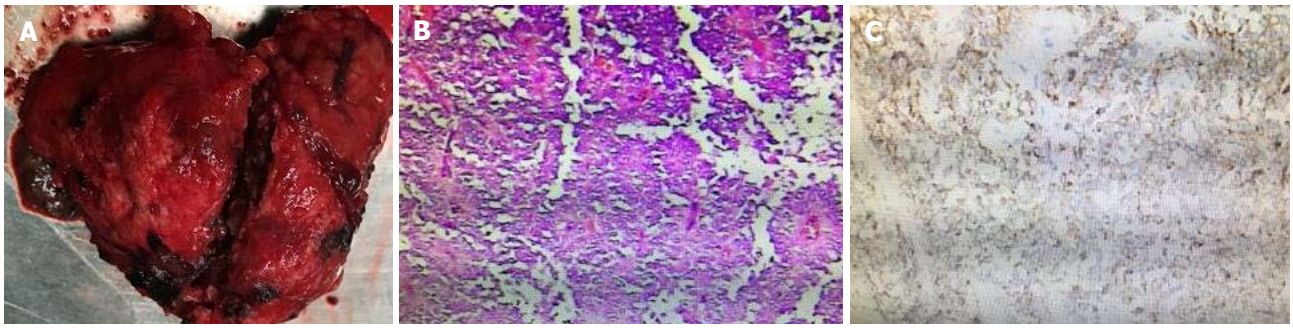

Figure 5 Specimen of the resected pancreas and results of pathological examination. A: Specimen of the resected pancreas; B and C: A solid pseudopapillary tumor of the pancreas, sized about 8.2 cm × 8 cm × 5 cm, showed infiltrative growth and necrosis. No vascular or neural invasion was visible. Immunophenotyping showed synaptophysin(+), CD56(+), CD10(+), β-catenin(+), vimentin(+), AE1/AE3(+), PR(+), plasma chromogranin A(-), E-cadherin(-), and Ki-67(+/3%). B: Hematoxylin and eosin staining (× 100); C: Immunohistochemistry (× 100).

a low-grade malignancy, and usually occurs in young women.

The clinical manifestations of SPTP are atypical. In most cases, a mass is often found within the abdomen accidentally or during physical examination, with or without gastrointestinal symptoms, such as the upper abdominal discomfort and dyspepsia[4-6]. These non-specific gastrointestinal symptoms are mostly associated with compression of nearby organs by tumors. In some special cases, SPTP can cause acute pancreatitis or spontaneous rupture of the pancreatic pseudocyst, which is clinically manifested as acute abdominal pain. Routine blood test, liver function test, renal function test, and tests for the endocrine/exocrine functions of pancreas often show normal results, and the levels of various tumor markers are usually within the normal ranges.

Imaging examination is crucial for the preoperative diagnosis of SPTP. It can determine the size and location of the tumor and its relationship with surrounding tissues, thus providing detailed information to make a surgical protocol[2,7,8]. The typical ultrasonographic finding of SPTP is a cystic/solid mass with mixed density in the pancreas. When the tumor is small, homogeneous hypoechoic echoes can be detected. Color doppler flow imaging often reveals a few blood flow signals on the capsule or parenchyma of the tumor. CT is the most commonly used imaging method for SPTP. On CT scans, SPTP is often round and oval, with lobulation. It has a well-defined border with the pancreas, and its margin is smooth. The solid part is often located in the periphery of the tumor, and the cystic part inside the tumor. The tumor can be located at any part of the pancreas. After enhancement, the parenchyma part is slightly enhanced during arterial phase and markedly enhanced during portal venous phase. The cystic part is hypodense before and after enhancement[9-11].

In our case, routine blood test, serum amylase and lipase test, and liver function test showed slight or obvious abnormalities before the operation, which were significantly improved after treatment. Subcutaneous nodules involving lower abdomen bilaterally and lower limbs reduced after treatment. The diagnosis of SPTP and the differential diagnosis of this lesion from other pancreatic diseases were mainly based on abdominal contrast-enhanced CT and abdominal contrast-enhanced ultrasound. A cystic/solid mass with mixed density was found in the body and tail of the pancreas,

with a well-defined border. Nodular calcifications were seen inside the lesion, and the lesion was fed by the common hepatic artery and a branch of splenic artery. The spleen was slightly enlarged, along with regional portal hypertension. Surgery was performed after adequate preparation, during which a mass with areas of necrosis was found in the body and tail of the pancreas. The tumor had a poorly-defined border with pancreatic body and tail. It was tightly adhered to the splenic vein, and several of its nourished vessels joined the splenic vein.

Postoperative pathology confirmed the result of preoperative imaging diagnosis. Immunophenotyping showed synaptophysin (+), CD56(+), CD10(+), β-catenin(+), vimentin (+), and AE1/AE3(+), which met the diagnostic criteria for SPTP, and was consistent with the histopathological diversity of SPTP[12-14]. Vimentin, β-catenin, synaptophysin, neuron-specific enolase, α1-antitrypsin (α1-AT), S-100, neural cell adhesion molecule CD56, and cluster of differentiation 10 (CD10) can all be expressed in SPTP[15-17]. At present, surgical resection is the only radical treatment for SPTP. However, laparoscopic surgery is a challenging technique, and the selection of specific surgical approaches depends on the location and size of tumor and the findings of intraoperative pathological examination[18]. The most common postoperative complication is pancreatic fistula, followed by pancreatitis, gastrointestinal bleeding, and pseudocyst. The prognosis of SPTP is good, and the postoperative survival rate is high. If the tumor is located in the body and tail of the pancreas, resection of the body and tail of the pancreas is feasible. If the tumor invades or is closely related to the splenic vessels, pancreatectomy combined with resection of the body and tail of the pancreas can be performed[19-22]. No evidence is yet available that local resection has a higher risk of recurrence or metastasis than radical resection. Therefore, clinicians should be aware of the clinical manifestation and treatment of pancreatic panniculitis[23,24]. Although SPTP has good prognosis and the postoperative 5-year survival rate is high, efforts should be made to increase further diagnostic accuracy and optimize therapeutic methods, so as to improve the quality of life of SPTP patients.

ARTICLE HIGHLIGHTS

Case characteristics

A 19-year-old woman presented with persistent left upper abdominal pain without obvious cause for 1 d. The patient also developed subcutaneous nodules involving lower abdomen bilaterally and lower limbs. An irregular mass was found in the pancreatic body and tail on plain abdominal computed tomography (CT), contrast-enhanced abdominal CT, and contrast-enhanced ultrasound.

Clinical diagnosis

Solid pseudopapillary tumor of the pancreas (SPTP), pancreatic panniculitis.

Differential diagnosis

Pancreatic cancer.

Laboratory diagnosis

Abnormal laboratory findings included the results of routine blood: Neutrophil-to-lymphocyte ratio 85.5% (normal range: 40%-75%), hemoglobin 88 g/L (normal range: 115-150 g/L). Liver function test showed albumin 30 g/L (normal range: 40-55 g/L) and alanine aminotransferase 62 U/L (normal range: 8-40 U/L). The result of serum amylase was 869 U/L (normal range: 40-100 U/L), and serum lipase was 759 U/L (normal range: 0-110 U/L).

Imaging diagnosis

Contrast-enhanced abdominal CT revealed a cystic/solid mass with mixed density in the body and tail of the pancreas.

Pathological diagnosis

SPTP, pancreatic panniculitis.

Treatment

Laparoscopic resection of the mass in the pancreatic body and tail with preservation of the spleen.

Related reports

Some articles have described the imaging diagnosis and treatment of SPTP and pancreatic panniculitis, as shown in the References.

Experiences and lessons

Clinicians should be aware of the clinical manifestation and treatment of pancreatic panniculitis. Although SPTP has good prognosis and the postoperative 5-year survival rate is high, efforts should be made to increase further diagnostic accuracy and optimize therapeutic methods, so as to improve the quality of life of SPTP patients.

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CASE REPORT

Intermittent abdominal pain accompanied by defecation difficulties caused by Chilaiditi syndrome: A case report

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Author contributions: Luo XG wrote the paper; Wang J, Wang WL collected the data and relevant images; Yu CZ revised the paper.

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Informed consent statement: The patient was not required to give informed consent as the analysis included completely anonymous data; informed consent was obtained before any medical investigation or initiation of treatment as required.

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Abstract

We report a case of intermittent lower abdominal pain and distension accompanied by defecation difficulties for 3 years due to Chilaiditi syndrome in a 59-year-old male. Before admission to our hospital, the patient had undergone gastroscopy, which showed gastritis and duodenitis, and colonoscopy, which showed cecum deformation and cicatricial changes of the mucous membrane in the colon hepatic flexure. A computed tomography (CT) scan of the abdomen at our hospital confirmed right hepatic atrophy and interposition of the colon. Moreover, CT simulation endoscopy identified cystic dilatation in the colon hepatic flexure with the widest diameter of 8.2 cm. The patient was diagnosed with Chilaiditi syndrome. As the patient was unable to endure his defecation difficulties, he underwent a laparoscope-assisted right hemicolectomy. The patient had a good recovery. During the follow-up period of 9 mo, the patient remained symptom-free.

Key words: Abdominal pain; Diagnosis; Management; Laparoscope-assisted right hemicolectomy; Chilaiditi sign; Chilaiditi syndrome; Case report

Core tip: We report a rare case of intermittent lower abdominal pain and distension accompanied by defecation difficulties due to Chilaiditi syndrome. The incidence of Chilaiditi syndrome is very low and is easily misdiagnosed. Imaging examination is an important diagnostic technique for Chilaiditi syndrome.

Luo XG, Wang J, Wang WL, Yu CZ. Intermittent abdominal pain accompanied by defecation difficulties caused by Chilaiditi syndrome: A case report. *World J Clin Cases* 2018; 6(15): 1042-1046 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1042.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1042

INTRODUCTION

The Chilaiditi sign refers to the abnormal interposition of the colon or small bowel between the liver and right diaphragm, which was first observed in a clinical examination by Cantini in 1865. Subsequently, Demetrius Chilaiditi, a Greek radiologist, reported three cases of hepatodiaphragmatic interposition in 1910. Soon afterwards, this abnormal condition was named Chilaiditi sign. Chilaiditi sign always exists in individuals without clinical symptoms and is often an incidental finding through chest or abdominal radiography. If the Chilaiditi sign is associated with other respiratory and digestive symptoms such as abdominal pain, constipation, vomiting, respiratory distress, anorexia, volvulus, intestinal obstruction and perforation in a patient, the name is designated as Chilaiditi syndrome. The incidental finding at clinical imaging examination is rare, with an incidence of 0.025%-0.28%[1], it is more prevalent in males than in females, with a ratio of 4:1, and the incidence rate increases with age[2], especially in the elderly and the mentally ill[3]. Chilaiditi sign and Chilaiditi syndrome are chronic but benign conditions. Due to the low incidence and lack of specificity in clinical manifestations, clinicians should pay careful attention while making diagnoses to avoid misdiagnosis and mistreatment.

Here, we report a rare case of a 59-year-old male who was initially diagnosed with colitis and constipation. The patient was finally diagnosed with Chilaiditi syndrome by computed tomography (CT) scan and underwent laparoscope-assisted right hemicolectomy.

CASE REPORT

A 59-year-old male patient was admitted to the Department of General Surgery in the Second Affiliated Hospital of Nanjing Medical University (Nanjing, China) due to intermittent lower abdominal pain and distension accompanied by defecation difficulties for 3 years. These symptoms were initially relieved by laxatives but recently started to exacerbate. The patient denied nausea, vomiting, fever, melena and hematochezia. He had undergone several medical examinations including gastroscopy in another hospital, which showed gastritis and duodenitis. His colonoscopy showed cecum deformation and cicatricial changes of the mucous membrane in the colon hepatic flexure. The patient had never underwent surgery. There was nothing remarkable in his past medical and family histories. His vital signs were unremarkable. Upon physical examination, no obvious cardiovascular or respiratory system abnormalities were found. His abdomen was flat and soft. There were no signs of obvious pressure pain, rebound tenderness or abdominal mass. Murphy's sign was negative. Auscultation revealed normal bowel sounds. Blood, urine, stool, as well as liver and kidney function tests, coagulation studies, and electrocardiograms were all unremarkable. Chest X-rays revealed an abnormal gas shadow in the right subphrenic space and a segment of gaseous distended colon, which was interposed between the liver and the right diaphragm. A CT scan of the abdomen confirmed right hepatic atrophy and interposition of the colon (Figure 1). Further imaging by CT simulation endoscopy identified a cystic dilatation in the colon hepatic flexure, where the maximum diameter was 8.2 cm. There was no evidence of bowel wall thickening or bowel obstruction (Figure 2). These findings, together with the symptoms this patient was experiencing, indicated that the patient has Chilaiditi syndrome. There was no urgent indication for surgery. However, the patient was unable to endure his defecation difficulties and finally underwent laparoscope-assisted right hemicolectomy. Postoperative recovery was uneventful. He was discharged after 14 d of hospitalization with close follow-up. During a 4-wk follow-up period, he reported

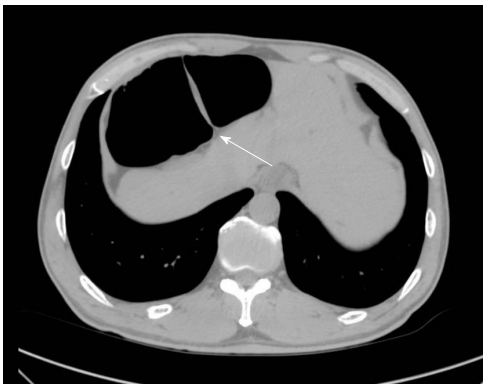

Figure 1 Computed tomography findings. Computed tomography shows an interposition of the colon hepatic flexure between the liver and the right diaphragm.

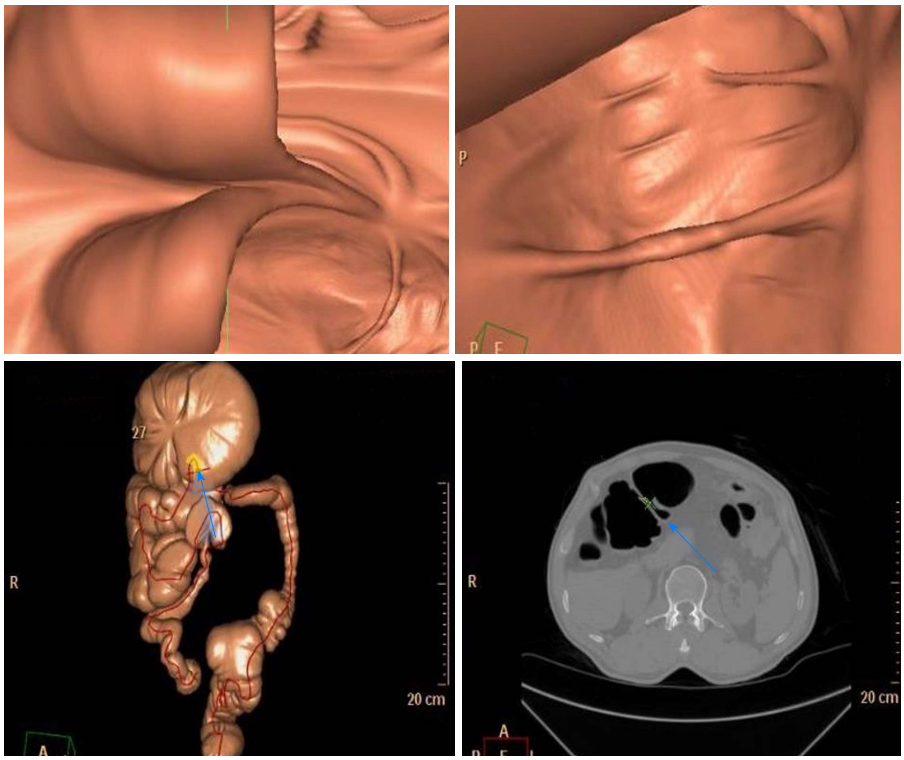

Figure 2 Computed tomography simulation endoscopy findings. Computed tomography simulation endoscopy identified a cystic dilatation in the colon hepatic flexure, which was intertwined between the liver and right diaphragm.

complete resolution of abdominal pain and distension. Moreover, defecation improved due to ameliorated regularity of bowel movements. During the subsequent 9-mo follow-up period, the patient remained symptom-free.

DISCUSSION

Normally, upper abdominal anatomy, including the suspensory ligament of the liver, mesocolon, liver, and the falciform ligament, can maintain a suitable space around the liver. Under normal physiological conditions, it is impossible for interposition of the colon or other organs to occur. The change of the relationship between the colon, the small intestine and the diaphragm is generally due to changes in anatomy. As a result, this change contributes to the occurrence of Chilaiditi syndrome. Under the Chilaiditi sign or Chilaiditi syndrome condition, the colon hepatic flexure, ascending colon, transverse colon, and small bowel, either alone or in combination with the colon, are the most common interposed organs.

The etiology of Chilaiditi syndrome remains controversial[4] and multiple factors have been documented to contribute[5]. Congenital disorders that can lead to Chilaiditi syndrome include small or ptotic liver, deficient falciform ligament, deficient suspensory ligament and congenital malposition or malrotation of the colon, and redundant colon. Furthermore, acquired disorders that can lead to Chilaiditi syndrome include cirrhosis, degeneration of the diaphragm, paralysis of the phrenic nerve, increased intrathoracic pressure caused by emphysema or tuberculosis, and abnormal dilatation of the colon[6]. Some special groups including overweight individuals[7] and persons with high abdominal fat content[8] tend to have higher incidence in migration of the colon or small intestine. In addition, some operations concerning the liver can also cause Chilaiditi syndrome[9]. In our case, the cause of Chilaiditi syndrome is unclear, but the redundant colon and dilatation of colon at the hepatic flexure are presumed to relate to Chilaiditi syndrome. Although the Chilaiditi sign is asymptomatic, we must carefully consider the presence of gases under the diaphragm in chest radiographs. Careful monitoring of these patients is required, as they have the potential risk of perforation complications during various diagnostic and therapeutic processes, such as percutaneous liver biopsy, thoracentesis and colonoscopy[10]. When patients need liver puncture, B ultrasound or CT guidance is necessary to avoid potential intestinal perforation[11].

The diagnosis of Chilaiditi sign seems to be relatively easy because the interposition of the colon is occasionally found on chest films, abdominal plain films or B-ultrasounds, and this sign can be present temporarily or permanently[12]. When the condition is suspected, supplementary lateral chest radiographs, especially in the left decubitus position, are necessary. To differentiate from pneumoperitoneum, in which case patients require emergency surgery, gases can still be seen below the diaphragm in the left decubitus position when the body position is changed[13]. In spite of this, chest and abdominal radiography is still not as sensitive

as CT scans for diagnosis[14].

Differential diagnosis including renal or biliary colic, sub-phrenic abscess, pneumoperitoneum or congenital diaphragmatic hernia must be considered in addition to Chilaiditi syndrome[15]. In rare cases, other intestinal diseases may also occur at the same time as Chilaiditi syndrome. There are several reports of intestinal perforation caused by Chilaiditi syndrome[1,16,17]. Under such complicated conditions, further CT scan imaging of the abdomen is recommended if necessary and will help clinicians make correct diagnoses[18]. Our patient was initially treated in other hospitals and was diagnosed with enteritis and constipation. Luckily, the patient did not receive secondary damage during colonoscopy examination. It was revealed that the colonic mucosa was flaky, striate, linear, with reticulate white scars, slightly higher than normal mucosa. With 3 years of conservative treatment in the outside institute, the symptoms of the patient appeared ingravescence. With the intention to avoid potential complications as a result of invasive examination, abdominal CT and CT simulation endoscopy were arranged in our hospital. The imaging by CT simulation endoscopy identified a cystic dilatation in the colon hepatic flexure with the widest diameter of 8.2 cm, which seemed to be similar to volvulus. Based on the CT manifestations and the absence of severe abdominal pain, vomiting, and fever, we excluded the diagnosis of intestinal volvulus, and the patient was finally diagnosed with Chilaiditi syndrome.

Chilaiditi syndrome generally does not require surgical intervention[19]. Management strategies for Chilaiditi syndrome consist of conservative treatment and surgical intervention. Conservative treatment based on different clinical symptoms is always effective, and these measures include bed rest, fluid therapy, gastrointestinal decompression, enemas, and stool softeners[15]. For obese patients, losing weight, which gradually decreases the frequency and intensity of the patient's symptoms, is also a very important and effective method[7]. If conservative treatment is unsuitable or the patient has serious complications, such as intestinal obstruction, ischemia, volvulus and perforation[20], surgical intervention is recommended[21]. There are different operations for this syndrome, including transverse or right hemicolectomy, colopexy, and hepatopexy[22]. According to the literature, about 26% of all patients with Chilaiditi sign and Chilaiditi syndrome underwent surgical treatment, and stayed asymptomatic during different follow-up periods[14]. Recently, minimally-invasive surgery, such as laparoscopic surgery, is recommended[23], even to the extent that there is a report of robotic-assisted technique for the surgical management of Chilaiditi syndrome[24].

In the presented case, conservative treatment was first recommended because there were no symptoms of intestinal perforation, necrosis and volvulus. However, the patient complained that he could not tolerate long-term intermittent abdominal pain, distension and difficulty with defecation. He therefore demanded surgical treatment to resolve his symptoms. Based on the patient's preference and given the long course of his condition, the patient underwent laparoscopic-assisted right hemicolectomy. With the preexsisting abdominal distention, an artificial pneumoperitoneum was created through a small open incision to avoid secondary injury during surgery. As a result, the patient had a good recovery.

Chilaiditi sign and Chilaiditi syndrome are two different states of the same condition. Now that interposition can be found in all patients, why is it that some patients are asymptomatic, while others are symptomatic? We speculate that patients with asymptomatic Chilaiditi sign may become symptomatic for Chilaiditi syndrome in the following situations: (A) sudden increased activity of the redundant colon; (B) increased bowel movements; (C) sudden gas increase in the intestine; and (D) severe increased pressure in the chest with cough in patients with pulmonary tuberculosis or empyema. At present, the etiological classification and pathogenesis of Chilaiditi syndrome are not elaborated thoroughly; therefore, more research should be encouraged to reveal the specific etiology and pathogenesis of Chilaiditi syndrome.

In conclusion, we present a rare case and highlight the importance of proper diagnosis and treatment for subdiaphragmatic gas. When gas is presented under the diaphragm, surgeons and medical students need to consider this syndrome routinely instead of performing emergency surgery as conventional medical education suggests. This condition is typically conservatively treated, and surgery is only required when the conservative treatment is invalid.

ARTICLE HIGHLIGHTS

Case characteristics

A 59-year-old male patient was admitted to our hospital due to intermittent lower abdominal pain and distension accompanied by defecation difficulties for 3 years.

Clinical diagnosis

Chilaiditi syndrome.

Differential diagnosis

Renal or biliary colic, sub-phrenic abscess, pneumoperitoneum or congenital diaphragmatic hernia.

Laboratory diagnosis

Computed tomography (CT) scan of the abdomen confirmed right hepatic atrophy and interposition of the colon. CT simulation endoscopy identified a cystic dilatation in the colon hepatic flexure with the widest diameter of approximately 8.2 cm.

Imaging diagnosis

Chilaiditi syndrome.

Treatment

The patient underwent laparoscope-assisted right hemicolectomy.

Related reports

The incidence of Chilaiditi syndrome is very low. Imaging examination is very important for differential diagnosis and can avoid unnecessary emergency operation. The main treatment is conservative treatment.

Term explanation

Chilaiditi sign refers to the abnormal interposition of the colon or small bowel between the liver and right diaphragm, Once Chilaiditi sign is associated with a variety of clinical respiratory and digestive symptoms, the name is designated as Chilaiditi syndrome.

Experiences and lessons

Chilaiditi syndrome is rare. Due to its low incidence, Chilaiditi syndrome is easily misdiagnosed. Imaging examination is an important diagnostic technique in Chilaiditi syndrome.

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CASE REPORT

Endoscopic titanium clip closure of gastric fistula after splenectomy: A case report

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Author contributions: Yu J and Zhou CJ contributed equally to this work; Yu J, Zhou CJ, and Wang P wrote the manuscript; Yu J, Zhou CJ, Wang P, Wei SJ, He JS, and Tang J diagnosed and treated the patient; all authors discussed the results and commented on the manuscript.

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Abstract

This report describes a 52-year-old male patient with blunt abdominal traumatic rupture of the spleen due to injuries sustained in an automobile accident. Following splenectomy, the patient developed a gastric fistula. He underwent a long period of conservative treatment, including antibiotics and total parenteral nutrition, which was ineffective. The fistula could not be closed and titanium clip closure using a gastroscopy was then performed in order to close the fistula. After endoscopic therapy and clipping surgery, the patient's general condition improved significantly, and he had no post-procedural abdominal complications. On post-clipping day 6, the gastric fistula was completely closed as shown by X-ray examination of the upper digestive tract. The patient was discharged from hospital and no complications were observed during the six-month follow-up period. Our report suggests that titanium clip closure using endoscopy may be the choice of treatment in patients with a gastric fistula.

Key words: Titanium clipping; Endoscopy; Splenectomy;

Case report; Gastric fistula

Core tip: Gastric fistula after splenectomy is an uncommon complication, and is difficult to treat and cure. The current management of gastric fistula mainly includes conservative treatment and surgery. There are only a few reports concerning gastric fistula treatment using endoscopy. This is the first report of successful treatment of a gastric fistula after splenectomy using titanium endoscopic clipping.

Yu J, Zhou CJ, Wang P, Wei SJ, He JS, Tang J. Endoscopic titanium clip closure of gastric fistula after splenectomy: A case report. *World J Clin Cases* 2018; 6(15): 1047-1052 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1047.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1047

INTRODUCTION

Splenectomy is an important life-saving treatment in patients with massive hemorrhage due to splenic trauma[1]. However, post-splenectomy patients with gastric or pancreatic fistula and/or incomplete intestinal obstruction and other complications are very rare and these complications are difficult to cure[2,3]. At present, post-splenectomy patients with gastric fistula are usually treated with conservative or surgical treatment, whereas there are very few reports on endoscopic titanium clipping for the treatment of gastric fistula after splenectomy. To the best of our knowledge, this is the first report on successful titanium endoscopic clipping of a gastric fistula after splenectomy.

CASE REPORT

A 52-year-old male patient was admitted to our hospital in May 2017 due to post-splenectomy complications for 21 d. He reported abdominal pain and high fever lasting 19 d at a local hospital. Before admission to our hospital, he had undergone splenectomy and a peritoneal drainage tube was placed in the splenic recess due to traumatic rupture of the spleen with massive hemorrhage after an automobile accident. On post-operative days 1 and 2, the patient was almost normal, and the drainage tube outflow was a pale red liquid (approximately 300 mL/d). However, on post-operative day 3, the patient complained of moderate fever and obvious pain in the left upper quadrant of the abdomen. When the patient ate, he would feel severe abdominal pain and the food drained out of the drainage tube, so he had not been able to eat after splenectomy. In addition, the peritoneal drainage volume had increased to approximately 700 mL/d and the liquid had become purulent. Following conservative treatment at the local hospital for nearly 3 wk, the patient's condition showed no obvious improvement, and he was transferred to our hospital.

Physical examination revealed obvious tenderness and moderate rebound pain over the left upper quadrant of the abdomen, with a body temperature of 38.8 ℃, pulse frequency of 112 bpm, and blood pressure of 154/96 mmHg. Laboratory examination showed that the white blood cell count was 29500/mm^3 (normal range 4000-10000/mm^3), percentage of neutrophils was 86.90% (normal range 50%-70%), percentage of lymphocytes was 5.20% (normal range 20%-40%), and high sensitivity C-reactive protein level was 57.90 mg/L (normal range 0.068-8.20 mg/L). These results showed that the patient had a severe infection. An abdominal B-ultrasonography examination revealed a limited effusion (about 200 mL) in the splenic fossa area (Figure 1A). Chest X-ray examination showed a moderate amount of effusion in the left chest and intra-abdominal intestinal pneumatosis (Figure 1B). Furthermore, an upper abdominal computed tomography (CT) scan revealed that there was left abdominal wall swelling. A drainage tube and fluid were present in the left side of the abdomen, in addition to partial abdominal mesenteric edema and bowel wall thickening (Figure 2A).

An upper digestive tract ioversol angiography showed that contrast agent had overflowed from the greater curvature of the gastric body into the abdominal cavity, and had then entered the drainage tube (Figure 2B). Therefore, we considered that the patient had a gastric fistula and an abdominal infection. After more than a week of anti-infective treatment and nutritional support, the fistula did not heal, which was confirmed by oral methylene blue examination. Thus, we attempted to carry out endoscopic titanium clip closure of the gastric corpus fistula for approximately 30 min (Figure 3A and 3B). On post-clipping day 2, the patient's condition started to improve, his abdominal pain was significantly relieved, his body temperature returned to normal, and the drainage tube outflow volume (approximately 100 mL/d) was significantly reduced compared with previous days. On post-clipping day 6, an upper digestive tract ioversol angiography showed no contrast agent overflow into the abdominal cavity, suggesting that the gastric fistula had been closed (Figure 4A). On post-clipping day 7, the patient started a liquid diet, and no abdominal pain, fever, or other symptoms were observed. On post-clipping day 13, the drainage tube was removed as no liquid was observed in the tube, and CT examination showed almost no remaining liquid in the abdominal cavity (Figure 4B). The patient was then discharged, and no complications were detected during the six-month follow-up period (data not shown).

DISCUSSION

It is well known that splenectomy is necessary in patients with massive hemorrhage following rupture

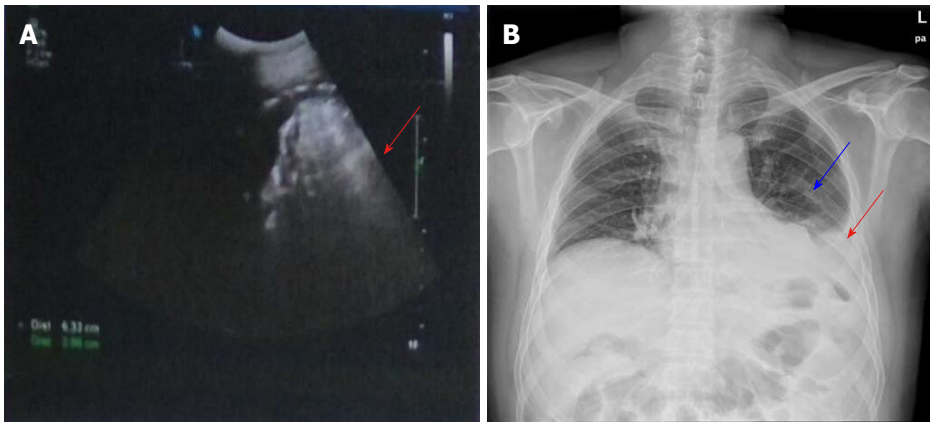

Figure 1 Abdominal B-ultrasonography findings. A: Abdominal B-ultrasonography showed a limited non-echo area (about 6.3 cm × 2.9 cm in diameter) in the splenic fossa area, which suggested effusion in this area (arrow); B: Chest x-ray revealed a high density in the left lower chest (blue arrow), the left diaphragm angle was unclear, and a moderate volume of pleural effusion was seen in the left side of the chest (red arrow).

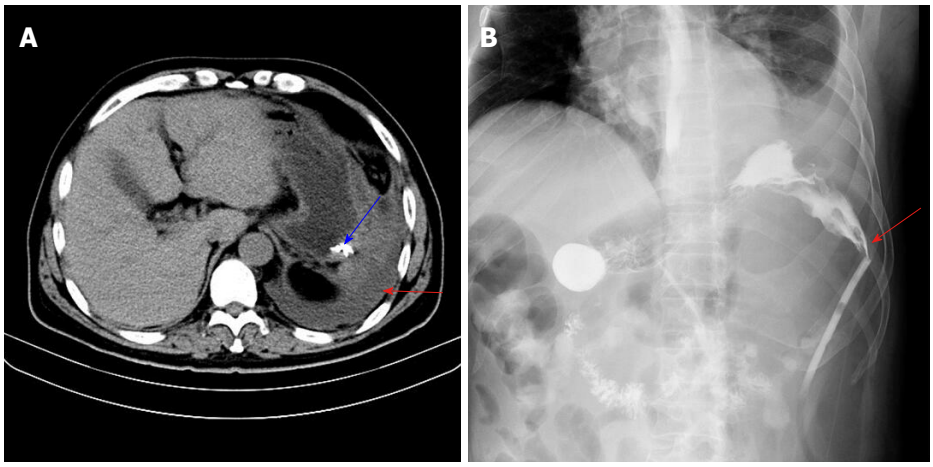

Figure 2 Upper abdominal computed tomography findings. A: Upper abdominal computed tomography examination indicated a large amount of effusion in the left upper abdominal cavity (red arrow), and enhanced lesions and a hematocele in the drainage tube (blue arrow); B: Upper digestive tract ioversol angiography showed contrast agent overflow from the greater curvature of the gastric body to the abdominal drainage tube (arrow).

of the spleen[1]. However, gastric or pancreatic fistula, pseudohyperkalemia, and other complications in post-splenectomy patients are difficult to treat[3-5]. Gastric fistula after splenectomy is often due to the condition and surgical factors caused by unfavorable anatomy. As the operative field during emergency splenectomy is usually filled with blood, it is easy to damage the splenic pedicle and short gastric vein in the gastric muscle layer. Poor visibility during surgery can result in gastric tissue being crushed by forceps, causing tissue ischemia and necrosis, and a post-operative gastric fistula can occur. Furthermore, poor post-operative gastric tube drainage and eating too early can aggravate the injured area, leading to the formation of a gastric fistula[6,7]. It has been reported that gastric contents can leak and cause local secondary infections, fever, left upper abdominal pain, and other symptoms; however, the diffusion of gastric contents into the abdominal cavity can result in peritonitis and aggravation of the infection[8]. Inappropriate or untimely treatment of the infection can lead to septic shock and multiple organ failure resulting in patient death[9].

Therefore, the choice of treatment in this situation is critical for patients with a gastric fistula. It has been documented that the current treatment of gastric fistula is as follows: (1) Non-surgical treatment: Full drainage is the key to the treatment of gastric fistula. Following splenectomy, the drainage tube is generally placed in the splenic fossa in patients with post-operative bleeding and gastric fistula, which can also guarantee drainage of stomach contents and prevent diffusion of gastric contents in the abdominal cavity[10,11]. Gastrointestinal decompression is also an important treatment for gastric fistula, and can greatly reduce the volume of gastric leakage[12]. It is known that supportive treatment can promote fistula healing, and supportive treatment should include fresh blood, plasma, and albumin. Good nutrition and vitamins are also necessary in these patients[13,14]; (2) Surgical repair should be performed if the gastric fistula is large, or a long period of conservative therapy was ineffective. However, this type of surgery is usually difficult due to severe adhesions in the abdominal

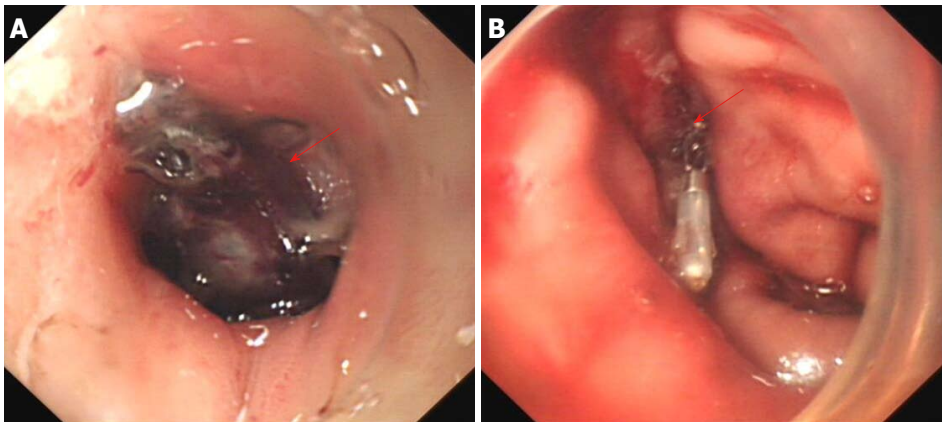

Figure 3 Gastroscopic findings. A: Gastroscopy showed a fistula (approximately 2.0 cm × 2.5 cm in diameter) with a black blood scab on the surface of the upper side of the greater curvature of the gastric body in which the surrounding mucosa was congestive and edematous (arrow); B: The gastric body fistula was fully closed using two titanium clips guided by gastroscopy (arrow).

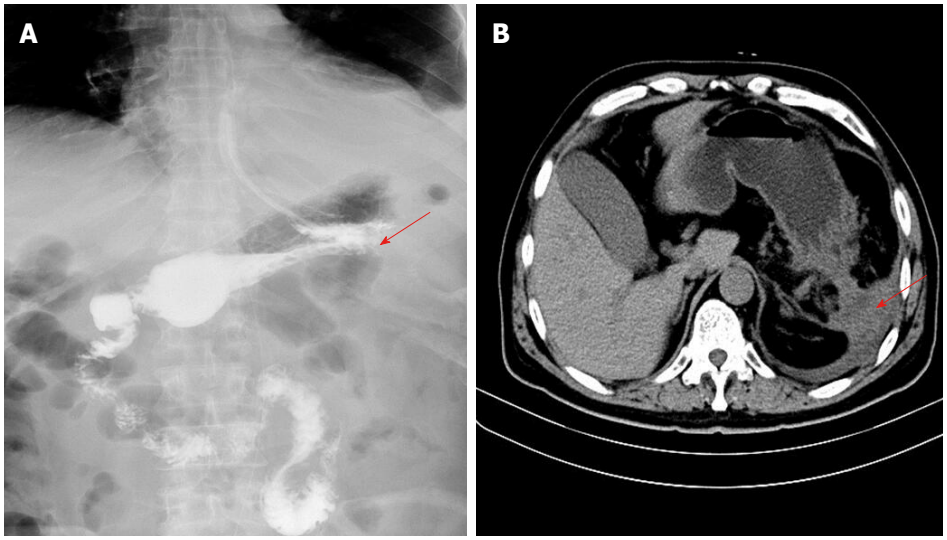

Figure 4 Upper digestive tract ioversol angiography findings. A: Upper digestive tract ioversol angiography showed that the gastric fistula was completely closed, and no leakage of contrast medium was observed (arrow); B: Abdominal computed tomography examination showed almost no liquid retained in the abdominal cavity, and the granulation tissue was organized (arrow).

cavity secondary to serious infection, and is also prone to causing new accessory injury of organs[15]; and (3) An over-the-scope clip has recently been used for endoscopic closure of perforations, leaks, fistulas, and endoscopic hemostasis[16].

In the present study, the patient experienced abdominal pain and high fever for approximately 3 wk during conservative treatment before admission to our hospital. Following physical and laboratory examinations, and taking into account the patient's mild and limited peritonitis signs, he received anti-infective treatment and nutritional support for 1 wk. However, the fistula did not heal, and the patient was unable to eat. Moreover, the patient may have had serious adhesions in the abdominal cavity, which was indicated by an abdominal enhanced CT scan (data not shown), and surgery would have been very difficult. Therefore, we attempted to perform endoscopy-assisted titanium clip closure of the fistula, which was successful. The patient recovered well after this treatment, and an X-ray examination of the upper digestive tract showed that the gastric fistula had completely closed.

Abdominal enhanced CT and both upper gastrointestinal radiography and endoscopy are important diagnostic methods for gastric fistula, and are of great significance in the assessment of fistula severity and treatment choice[17,18]. In this report, a patient with abdominal pain and high fever after splenectomy was admitted to our hospital, and ultrasound examination did not reveal the cause of peritoneal effusion. Further examinations, including abdominal CT, and gastrointestinal radiography and endoscopy were performed, and a definite diagnosis of gastric fistula was established. Gastroscopy showed that the fistula was of medium size (about 2.0 cm x 2.5 cm in diameter) and there was no obvious edema and necrosis in the surrounding tiss-

ues of the fistula; therefore, for the first time, we used titanium clips to treat this patient.

In review of the literature, there are very few reports on endoscopic closure of fistula. Uesato *et al*[19] reported endoscopic occlusion using an endobronchial Watanabe spigot was performed to close a long-term esophagobronchiole fistula after esophagectomy. Tsai *et al*[20] showed that gastrogastric fistula could be closed by using endoscopic Apollo Overstitch system. Our present report indicates that the key to successful endoscopic titanium clipping of the fistula is that the tissue around the fistula must be healthy enough to be held in place by the metal clip. If the tissue around the fistula is fragile or necrotic, the metal clip will not be able to achieve alignment of the tissue. Therefore, endoscopic closure can be performed for the long-term fistula.

In summary, our report indicates that if signs of peritonitis are mild, and a long period of conservative treatment for gastric fistula has been ineffective, endoscopic titanium clip closure may be a good treatment choice. This technique has the advantages of reduced trauma, shorter operative time, and fewer complications, and was effective in the treatment of gastric fistula.

ARTICLE HIGHLIGHTS

Case characteristics

A 52-year-old male patient with blunt abdominal traumatic rupture of the spleen developed a gastric fistula after splenectomy. Following conservative treatment in a local hospital for almost 3 wk that was ineffective, he was transferred to our hospital.

Clinical diagnosis

The patient was diagnosed with a gastric fistula and abdominal infection.

Differential diagnosis

Pancreatic fistula should be excluded.

Laboratory diagnosis

Laboratory examination showed that the white blood cell count, percentage of neutrophils, and high sensitivity C-reactive protein level were significantly increased.

Imaging diagnosis

A fistula of the greater curvature of the gastric body accompanied by abdominal infection was confirmed by upper digestive tract ioversol angiography and dynamic abdominal computed tomography scanning.

Treatment

Anti-infective treatment and nutritional support was ineffective for the fistula of the patient. Therefore, endoscopic titanium clip closure was performed and the gastric fistula was successfully closed.

Experiences and lessons

As conservative treatment may be ineffective for medium-sized gastric fistulas after splenectomy, endoscopic titanium clipping is a good and safe treatment choice, which avoids the risk of re-operation.

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CASE REPORT

Successful steroid treatment for acute fibrinous and organizing pneumonia: A case report

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Author contributions: Ning YJ, Ding PS and Ke ZY collected clinical data and wrote the paper; Zhang YB and Liu RY helped to design and revise the paper.

Informed consent statement: Informed consent was obtained from the patient before all procedures described in the report as well as for the use of the patient's clinical information and images for publication.

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Abstract

BACKGROUND

Since the acute fibrinous and organizing pneumonia (AFOP) was first described by Beasley in 2002, some case reports of patients aged from 38 d to 80 years have been published worldwide, but there is still no standard therapy for this disease and the treatment methods remain controversial. Both steroid and immunosuppressive agents, such as cyclophosphamide or mycophenolate mofetil, have been reported to be effective in some studies, but with many side effects, especially in patients of advanced age.

CASE SUMMARY

We herein report an 81-year-old female patient who was admitted to our hospital due to dry cough, and breathlessness for 1 mo. She was treated with broad-spectrum antibiotics and anti-fungal therapy, but without improvement in both symptoms and radiological findings, and her respiratory status worsened, and she required bed rest almost the whole day. Computed tomography-guided percutaneous needle lung biopsy was performed and histopathology examination confirmed the diagnosis of AFOP. She was then successfully treated with a steroid monotherapy, which resulted in a satisfactory clinical outcome without serious complications.

CONCLUSION

We conclude that complete remission of AFOP can be achieved by steroid monotherapy in patients of

advanced age.

Key words: Acute fibrinous and organizing pneumonia; Geriatric; Steroid; Computed tomography-guided percutaneous needle lung biopsy; Case report

Core tip: Acute fibrinous and organizing pneumonia is a rare histological pattern of acute lung injury. The age of the patients was diverse from infant to elderly, and there is still no specific therapy. Although treatments with steroids combined with immunosuppressants have been reported, none of them showed particular benefit, and these treatments always induce serious side effects, especially in patients of advanced age. We herein report an 81-year-old female patient, who was successfully treated with low-dose steroids, and only experienced some minor side-effects. This case report can add a new treatment choice for this disease.

Ning YJ, Ding PS, Ke ZY, Zhang YB, Liu RY. Successful steroid treatment for acute fibrinous and organizing pneumonia: A case report. *World J Clin Cases* 2018; 6(15): 1053-1058 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/1053.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.1053

INTRODUCTION

Acute fibrinous and organizing pneumonia (AFOP) was first described by Beasley in a pathologic study of 17 patients with acute/subacute lung injury in 2002[1]. It was defined as a rare type of the idiopathic interstitial pneumonia in 2013[2]. A few studies have reported the characteristics of AFOP in recent years, but the etiology is still not fully understood. AFOP may occur at any age, but usually presents in the elderly people. The clinical presentation of AFOP is nonspecific and often similar to common pneumonia, so it is easily misdiagnosed. The confirmation of AFOP diagnosis depends on pathological biopsy.

To date, the pathogenesis of AFOP remains unclear, and there is still no standard treatment. Steroid treatment was reported to be effective, but the information on dosage, duration and long-term side-effects is not available. We herein report a case of an 81-year-old female patient with AFOP, who was successfully treated with steroid monotherapy. We also report our observations of the dosage, duration and side-effects. This report can provide a new choice of AFOP treatment in geriatric patients.

CASE PRESENTATION

Chief complaints

An 81-year-old retired female doctor was admitted to our hospital with dry cough, and breathlessness for 1 mo.

History of present illness

She had taken Azithromycin for 2 d, but there was no improvement.

History of past illness

She denied any history of disease.

Physical examination

On examination, her temperature was 36.5 ℃, blood pressure was 108/72 mmHg, heart rate was 74 beats/min, oxygen saturation was 98% at room air, and respiratory rate was 19 breaths/min. Lung examination showed inspiratory crackles in the right lung base. The rest of her physical examinations were unremarkable.

Laboratory testing

Blood routine, liver function, renal function tests and serum sodium, potassium, creatinine, magnesium, calcium were all within normal limits. Blood tumor biomarker tests were negative. Serologic tests for antinuclear antibodies, rheumatoid factors and anti-neutrophil cytoplasmic antibodies were within normal limits. Tuberculin skin test, sputum stains for acid fast bacilli, and cultures of blood and sputum were all negative. Arterial blood gas analysis at room air revealed pH 7.4, PaO_2 63 mmHg and $PaCO_2$ 35 mmHg. The pulmonary function test revealed moderate restrictive ventilatory impairment and a moderate decrease in diffusing capacity.

Imaging examination

Computed tomography (CT) scan of the chest on admission showed bilateral lesions, multiple patchy, consolidation and ground-glass opacities, associated with air bronchogram (Figure 1), especially in the right lung and the upper lobe of the left lung. The patient was treated with broad-spectrum antibiotics and anti-fungal therapy in the following 2 wk. But her symptoms of cough and chest tightness, and shortness of breath were not relieved. The repeat CT scan of the chest 2 wk later (Figure 2) showed that her condition was significantly advanced, which means a previous misdiagnosis. CT-guided percutaneous needle lung biopsy was then performed after informed consent was obtained from the patient.

MULTIDISCIPLINARY EXPERT CONSULTATION

Fan-Qing Meng, MD, Professor, Department of Pathology

The pathologic consultation revealed prominent fibrinous exudation within most the alveolar spaces (Figure 3). No necrosis or granulomas were observed, neither any evidence of diffuse alveolar damage, alveolitis or eosinophilic infiltration. No evidence of special infections

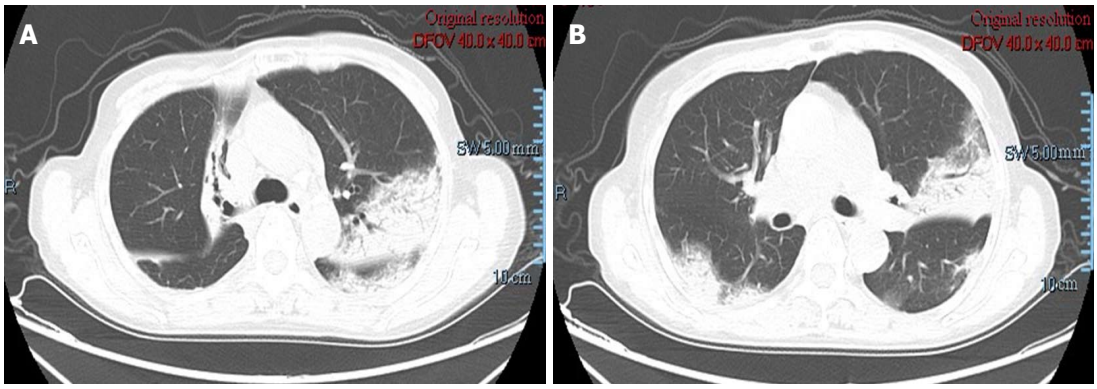

Figure 1 Chest computed tomography scan on admission showed bilateral lesions. The main findings were patchy, consolidation and ground-glass opacities, associated with air bronchogram.

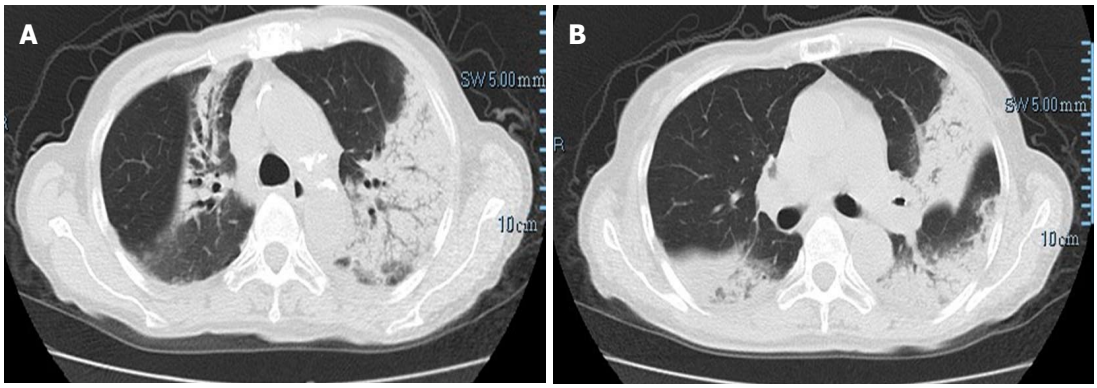

Figure 2 Repeat chest computed tomography scan showed an increase of the nodules and patchy infiltration after 2 wk antibacterial and antifungal treatment. Dyspnea deteriorated and no improvement was observed.

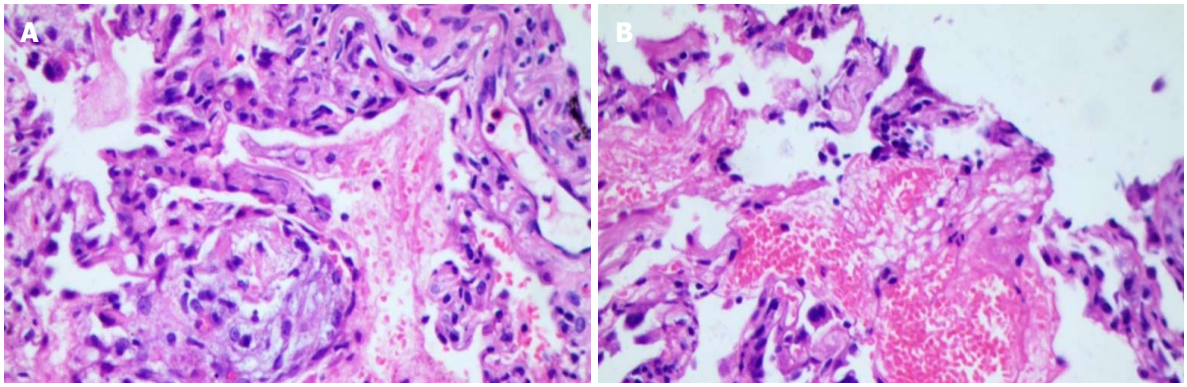

Figure 3 Pathological examinations revealed numerous fibrin and organizing tissue in the alveoli without pulmonary hyaline membrane, the fibrous tissue hyperplasia in the alveolar septum, which were consistent with acute fibrinous and organizing pneumonia (original magnification × 400).

was found. A diagnosis of AFOP was established.

FINAL DIAGNOSIS

AFOP.

TREATMENT

The patient was therefore started with intravenous methylprednisolone 40 mg/d for 1 wk. Considering the old age of the patient, and the considerable side effects of the drug, we then reduced the dosage to 12 mg twice daily taken orally for 1 wk. The patient discharged on a tapering schedule of methylprednisolone 20 mg/d for 10 d, then 16 mg/d for 10 d, 12 mg/d for 10 d, and 8 mg/d for 1 mo.

OUTCOME AND FOLLOW-UP

After 1 wk treatmengt of methylprednisolone 40

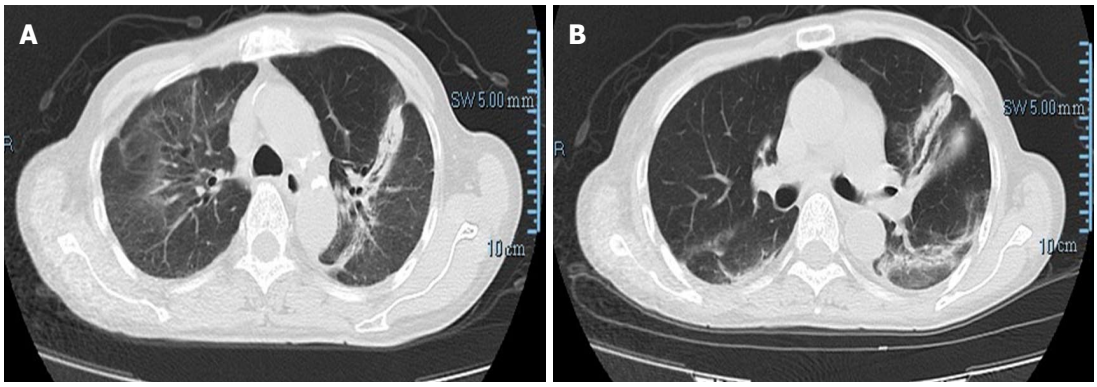

Figure 4 Repeat chest computed tomography scan after 1 wk steroid treatment showed significant improvement, and bilateral lesions resolved gradually.

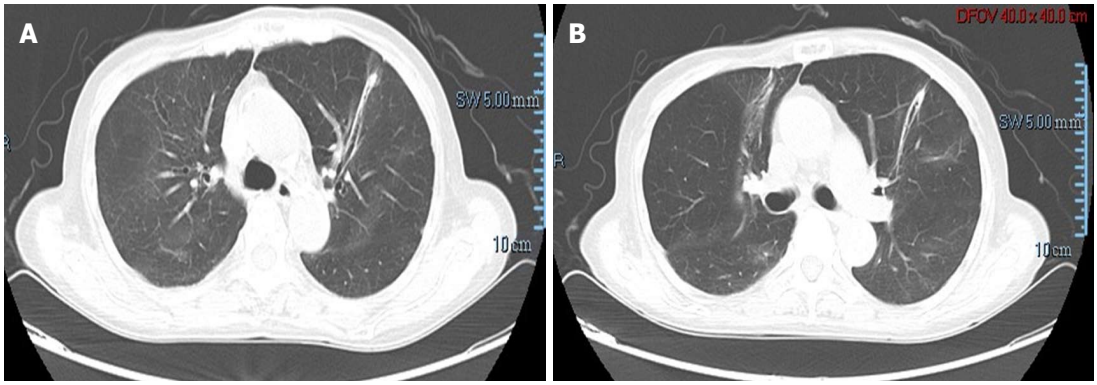

Figure 5 Repeat chest computed tomography scan after 3 wk steroid treatment showed significant improvement, and bilateral lesions almost disappeared.

mg/d, her symptom of cough was improved. CT scan also showed significant improvement (Figure 4), and bilateral lesions resolved gradually. During the treatment with steroids, the main side-effects were hypertension and hyperglycaemia, which were resolved by antihypertensives and dietary and lifestyle modifications. No significant adverse side-effects were noticed. The repeat chest CT scan revealed almost normal findings after 3 wk (Figure 5).

DISCUSSION

In 2002, Beasley[1] described a new histological pattern of lung injury named AFOP, which is characterized by intra-alveolar fibrin balls and organizing pneumonia with a patchy distribution. Sporadic case reports have been published on this newly recognized clinicopathological entity that is still underdiagnosed. In 2013, it was finally defined as a rare type of the idiopathic interstitial pneumonia by the American Thoracic Society/European Respiratory Society[2]. AFOP is rarely reported worldwide. We searched the PubMed using the keywords "AFOP" or "acute fibrinous and organizing pneumonia", and identified 74 relevant articles. The age of the patients was diverse from infant to elderly[3-5]. It is more common in males than in females[1]. Our patient was an 81-year-old female, who was the oldest one according to the literature.

Although the histopathological features are well described, the clinical manifestations, course, and treatment of AFOP are not characterized. Because the clinical manifestations are nonspecific, the pathogenesis of AFOP is not fully understood. It can be idiopathic or associated with a wide spectrum of clinical conditions, such as connective tissue diseases[4,6,7], bacterial infections or viral infections[3,8], specific etiologic agent like Chlamydophila pneumoniae[9], chronic renal insufficiency[10], drug reaction or drug-induced toxicity[11], hematologic disease[12,13], hematopoietic stem cell transplantation[14], and occupational or environmental exposures[1].

There is still no standard treatment for AFOP. Therapy with steroids alone or combined with immunosuppressants was attempted, but the dosage and duration of steroid treatment are still unclear. Usually 0.5-1 mg/kg daily of prednisone (or equivalent) are prescribed initially. A maximal dose of methylprednisolone was reported to be up to 1000 mg/d[4]. A pulse therapy of steroids was also administered in some fulminant patients[7,10,15,16]. Besides steroids, immunosuppressive agents such as cyclophosphamide, mycophenolate mofetil, cyclosporine and azathioprine have been tried in AFOP patients complicated with connective tissue diseases[4,6,7,17]. In addition, Zhou *et al*[18] reported that low-dose indomethacin combined with methylprednisolone was a new choice of treatment.

The role of anti-infective agents is not acknowledged, but in fact, most patients had been treated with sufficient anti-infective agents before a definite diagnosis could be established. We suggest that appropriate anti-infective agents should be given according to patient's condition.

There is no consensus on treatment duration, and relapse may occur during the period when the dosage of steroids is reduced. Sauter *et al*[17] reported a long duration of steroid treatment of nearly 24 mo. The major side-effects of steroids include hypertension, hyperglycaemia, immune suppression, electrolyte imbalance, and femoral head necrosis, especially in geriatric patients. The dosage and duration of steroids should be individualized according to the patient's condition, radiological evolution and the side-effects, and more studies on treatment of AFOP are required in order to reduce the complication and improve the survival rate and the patient's life quality.

In the present case, steroid was prescribed as soon as the diagnosis was established. Considering the old age of the patient, and to avoid potential severe side effects of high-dose steroids, an initial dose of methylprednisolone 40 mg/d was used. Fortunately, her symptoms were soon controlled. And when the dose of methylprednisolone was decreased to 24 mg/d, the improvement continued in patient's condition and radiological evolution, and the main side-effects included hypertension and hyperglycaemia, which were resolved by antihypertensives and dietary and lifestyle modifications.

AFOP is a rare lung disease with varying morbidity and mortality, and no definitive therapy is available. The successful use of steroids in this case indicates that the pulse therapy of steroids may not be necessary. This case report adds to the literature a new choice of treatment in terms of dosage of steroids for AFOP.

EXPERIENCES AND LESSONS

This case may serve as a reminder to respiratory physicians who encounter a suspected pulmonary infection case but unresponsive to optimum antibiotic therapy in their clinical practice. Although AFOP is a rare entity, it should be considered in the differential diagnosis of pulmonary infection unresponsive to optimum antibiotic therapy. On the other hand, AFOP might be under diagnosed and under reported especially in the developing countries due to the complicated means of obtaining a tissue diagnosis which are not routinely performed in the community and secondary hospitals. Our case is distinct. The patient was an 81-year-old woman and she had a good response to short-term steroid treatment. The last follow-up showed that no relapse occurred during tapering steroids. This case will contribute to a better understanding of the treatment of AFOP in geriatric patients, and provide a new choice of dosage and duration of it. Further more studies are needed to describe various clinical aspects of this rare disease.

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CASE REPORT

Sub-Tenon's urokinase injection-assisted vitrectomy in early treatment of suprachoroidal hemorrhage: Four cases report

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Abstract

BACKGROUND

Suprachoroidal hemorrhage (SCH) is a rare but potentially catastrophic ocular event. Surgery for SCH is often challenging because of the difficulty in resolving the retinal and choroidal detachment. Here, we describe a novel surgical technique in which urokinase is administered by sub-Tenon's injection to target an organized clot in SCH prior to drainage.

CASE SUMMARY

A consecutive case series of four eyes with serous and hemorrhagic choroidal detachments secondary to cataract surgery or trauma was documented to evaluate the feasibility of using a sub-Tenon's urokinase injection-assisted 23-gauge and 20-gauge incision to drain choroidal detachments. Urokinase (2000 IU) was given by sub-Tenon's injection one day before surgery for clot liquefaction. A 23-gauge infusion line was placed in the anterior chamber. A 20-gauge incision was created in the suprachoroidal space 3.5 mm from

the limbus. After drainage, pars plana vitrectomy was performed because of concomitant pathology that demanded this additional procedure. Visual acuity, ocular findings, the timing of surgical interventions, surgical procedures, and outcomes were retrospectively reviewed in four patients. Postoperative follow-up of the patients ranged from 6 to 24 mo (mean, 13 mo). After the treatment, all patients achieved excellent anatomical recovery.

CONCLUSION

Sub-Tenon's urokinase injection-assisted vitrectomy makes clot liquefaction happen in the early treatment stage, resulting in marked stability during the procedure.

Key words: Urokinase; Suprachoroidal hemorrhage; Choroidal detachments; Vitrectomy; Case report

Core tip: We report a consecutive case series of four eyes with serous and hemorrhagic choroidal detachments secondary to cataract surgery or trauma to evaluate the feasibility of using a sub-Tenon's urokinase injection-assisted 23-gauge and 20-gauge incision to drain choroidal detachments. The primary advantage of this technique is that it makes clot liquefaction happen in the early treatment stage and allows a slower and semiautomated controlled mechanism to be achieved, resulting in marked stability during the procedure.

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INTRODUCTION

Suprachoroidal hemorrhage (SCH) is a vision-threatening complication associated with ocular trauma or certain surgical procedures, such as cataract extraction, glaucoma filtering surgery, penetrating keratoplasty, and vitreoretinal surgery[1-5]. It has also been reported to occur spontaneously[6-8]. Sudden reductions in intraoperative and postoperative intraocular pressure (IOP) and/or sustained low IOP due to various causes are important causes of fulminant SCH. Risk factors such as advanced age, hypertension, arteriosclerosis, diabetes and hemorrhagic disorders, glaucoma, and high myopia are all predisposing factors for SCH[9-13]. Although Verhoeff reported treatment by scleral incision in 1915, the effect was poor, and eventually many patients needed eye-excavation. The advance of vitreous surgery in recent years, especially the application of heavy water and silicone oil, has made the treatment of SCH possible. Through eyeball reconstruction, it not only effectively reduces the chance of eyeball atrophy, but even retains certain visual functions. However, what treatment is most appropriate for choroidal detachment and SCH remains largely controversial[14-16].

To improve therapeutic effects, we developed a novel method of sub-Tenon's urokinase injection-assisted vitrectomy drainage for serous and hemorrhagic choroidal detachments. We sought to prospectively evaluate this method for safety and efficacy in patients treated for massive SCH and choroidal detachment. In this study, we describe a novel surgical technique in which urokinase is administered sub-Tenon's to target an organized clot in SCH prior to drainage. After drainage, pars plana vitrectomy (PPV) was performed because concomitant pathology demanded this additional procedure.

CASES PRESENTATION

All cases who underwent sub-Tenon's urokinase injection-assisted vitrectomy in our institution between April 2016 and December 2017 were collected. The surgical treatments were performed by the same surgeon (Dr. Xi-Quan Zhao) to minimize bias due to different procedures and levels of experience. Informed consent was obtained from all individual participants included in the study. All patients are female, and the other details of the patient characteristics are given in Table 1.

Imaging examination

Details of the physical examination and imaging examination are given in Figures 1-4.

FINAL DIAGNOSIS

With the clear history, eye examination, and ultrasound findings, all the four patients in this group were diagnosed with SCH.

TREATMENT

The urokinase was supplied fresh in ampoules as a lyophilized powder. A 10000-unit urokinase solution was made by mixing the powder with 1 mL of sterile saline. A sub-Tenon's injection was performed for clot liquefaction with 0.2 mL of urokinase solution and 0.05 mL of 2% lidocaine. The next day, PPV was performed using 20G and 23G vitrectomy cannulas that were placed 3.5 mm from the limbus (Figure 5A). The 20G cannula was left open, and the infusion line was placed in the anterior chamber through a clear corneal paracentesis with a bottle height of 40 mmHg. As soon as the infusion line was opened, a copious, thick flux of blood flowed out of the 20G cannula. As the blood flow continued, the choroidal detachment visibly regressed.

Table 1 Preoperative clinical characteristics

Patient No.	Age (yr)	Chief complaints	History of present illness	History of past illness	Physical examination	Laboratory testing
1	73	Vision loss for 10 d (L)	Phaco 10 d before	Glucoma for more than 30 yr	VA: LP IOP: 6.7 mmHg Aphakia Retinal detachment	(-)
2	56	Vision loss for 5 d (L)	ECCE 5 d before	Hypertension	VA: HM IOP: 9.6 mmHg Aphakia Iridocoloboma Aphakia Vitreous hemorrhage	(-)
3	61	Vision loss for 7 d (R)	Phaco 8 d before	High myopia	VA: HM IOP: 9.2 mmHg Vitreous incarceration Aphakia Choroidal detachment	(-)
4	52	Vision loss for 12 d (R)	Trauma 12 d before, and the wound was sutured	Trauma	VA: LP IOP: 6.7 mmHg Hyphema Vitreous incarceration Aphakia Vitreous hemorrhage	(-)

L: Left eye; R: Right eye; Phaco: Phacoemulsification; ECCE: Extracapsular cataract extraction; VA: Vision acuity; LP: Light perception; HM: Hand motion; IOP: Intraocular pressure.

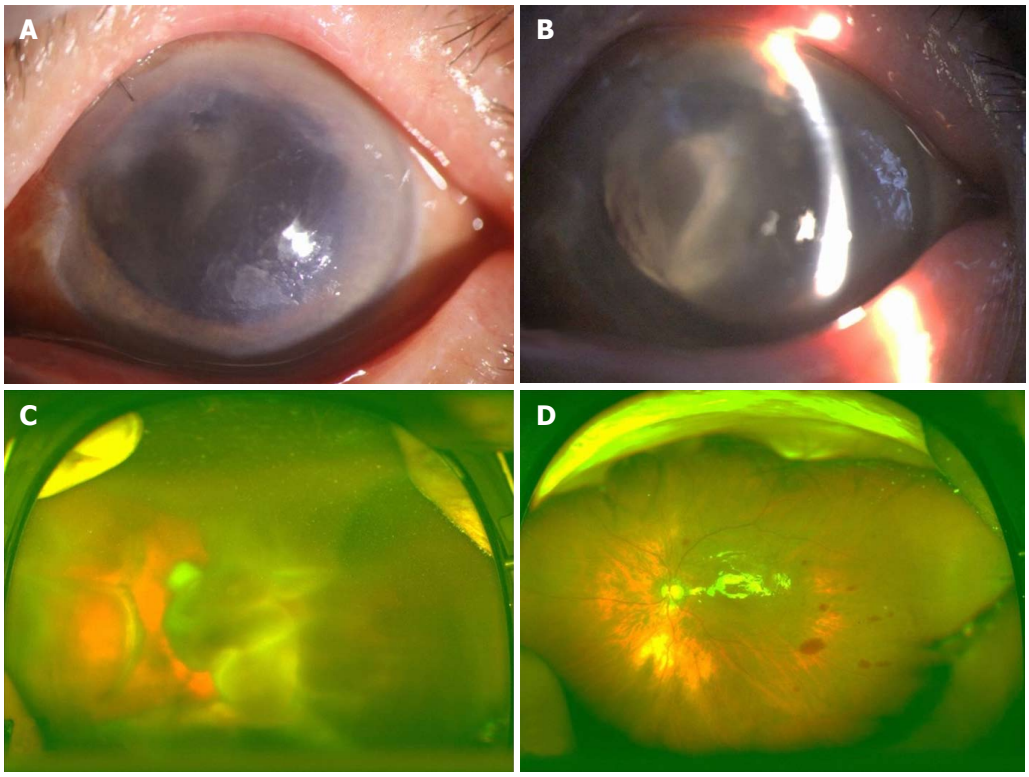

Figure 1 Clinical findings in patient 1. A: The cornea exhibited edema with local epithelial defect; B: The left eye was aphakic, and a prominent retinal detachment was visible through the pupil; C: A fundus examination revealed retinal detachment with choroidal detachment; D: Postoperatively, the retinal and choroidal detachment was completely reduced.

Vitrectomy, fibrovascular membrane peeling, and liquid gas exchange combined with silicone oil tamponade were performed later. During infusion and vitrectomy, the sclerotomies remained functional and permitted continuous blood flow out of the suprachoroidal space (Figure 5B). The drainage during surgery went smoothly and resulted in excellent final anatomical results. We performed PPV and tamponade with silicone oil instillation in three cases and no tamponade in one case (Table 2).

Table 2 Intraoperative clinical characteristics

Patient No.	1	2	3	4
Lens status at the time of intervention	Aphakia	Aphakia	Aphakia	Aphakia
Preoperative findings	Retinal detachment	Vitreous hemorrhage	Vitreous incarceration, subretinal hemorrhage	Hyphema, vitreous hemorrhage
Drainage during surgery	Good drainage of blood	Partial drainage of blood	Good drainage of blood	Good drainage of blood
Instillation of PFCL	No	No	No	No
Tamponade	Silicone oil	Silicone oil	None	Silicone oil
Anatomic success	Retinal and choroidal reattachment	Choroidal reattachment	Choroidal reattachment	Choroidal reattachment

PFCL: Perfluorocarbon liquids.

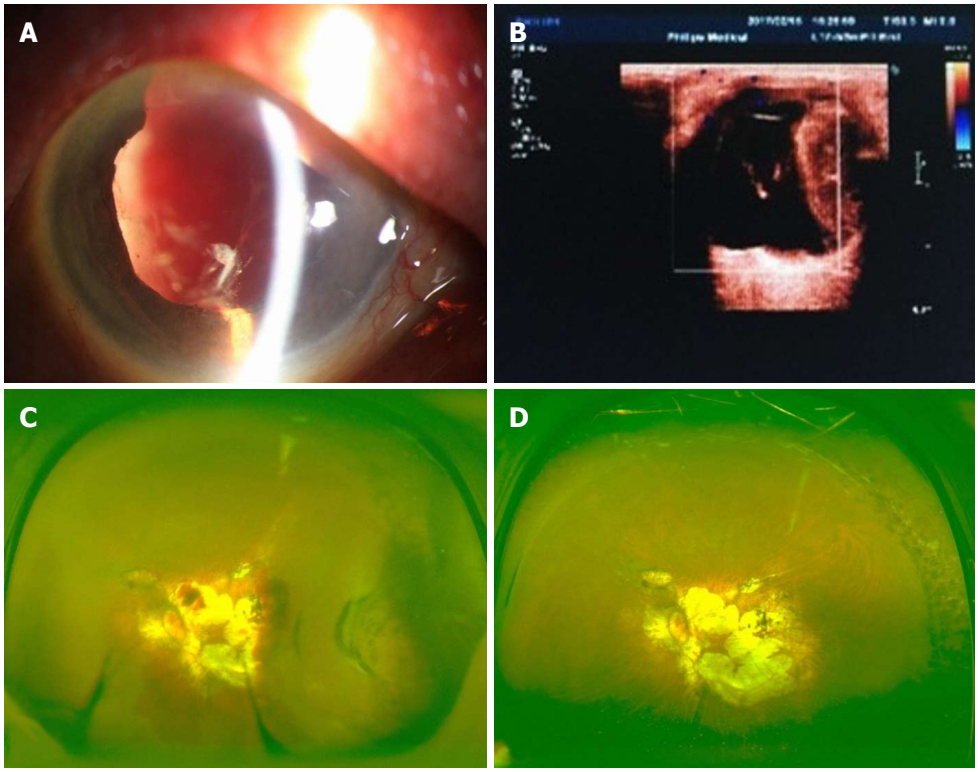

Figure 2 Clinical findings in patient 2. A: An examination showed a deep anterior chamber with blood and cells, iridocoloboma, aphakia, capsule remnants, and a massive vitreous hemorrhage; B: A color ultrasound showed choroidal detachment; C: The day after PPV, a globular elevation of the choroidal detachment was clearly visible in the temporal quadrant; D: At 1 year later, the fundus was flat without any signs of choroidal detachment.

OUTCOME AND FOLLOW-UP

Two cases of SCH were completely discharged during operation, and two cases of hemorrhage were absorbed in 7-12 mo after operation. The patients were followed for 6-24 mo, and excellent final anatomical results were achieved in all four cases. Preoperative visual acuity (VA) was light perception in two eyes and hand motion in two eyes. At final presentation, VA improved in two cases and remained the same in case 4, whereas in case 1, light perception was lost (Table 3). In this group, two patients had low IOP (average IOP, 5.9 mmHg), and the IOP was normal after 3 mo of follow-up. The silicone oil tamponade was removed in case 1 and case 3 at 2 mo postoperatively, at which time the IOP was increased while the retina was in place. Proliferative vitreoretinopathy occurred 3 mo postoperatively in case 4, and vitrectomy combined with intraoperative injection of silicone oil was performed. The retina was attached and no complications occurred.

DISCUSSION

Although the incidence of SCH is very low, sudden bleeding can force the eye content to escape from the open wound, and the blood can seep into the subretinal, vitreous, and anterior chambers. In the later stage, intraocular blood mechanization causes retinal and ciliary body detachment, which can cause complete loss of vision and even atrophy of the eyeball[1-5]. In our study, the patients had one to three systemic or ocular risk factors for developing SCH, including hypertension,

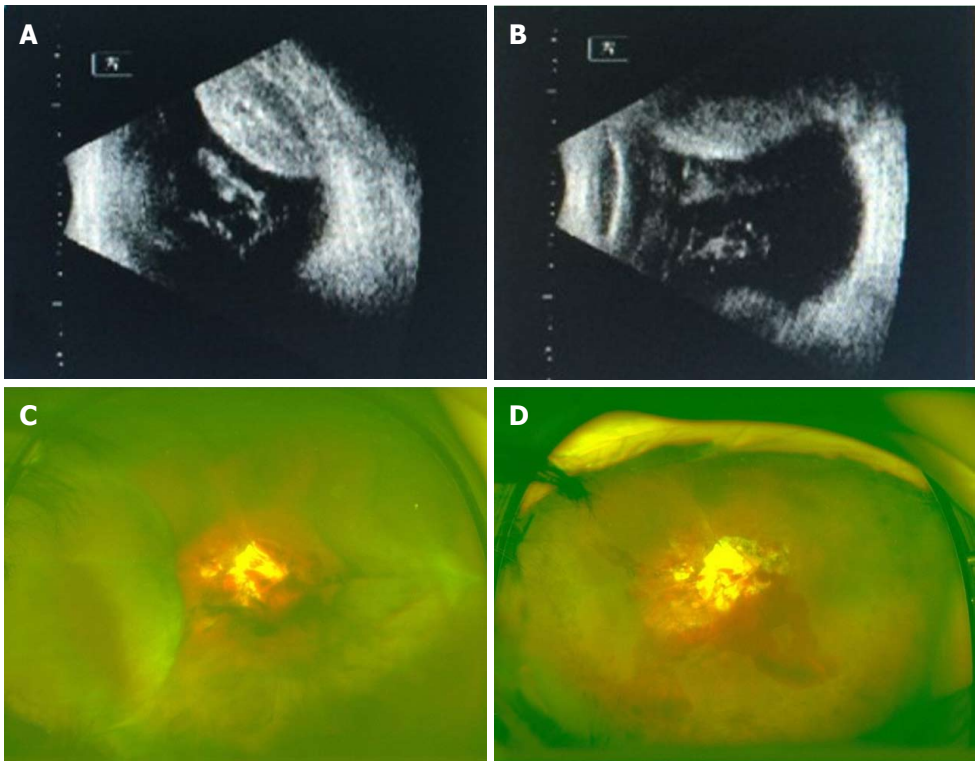

Figure 3 Clinical findings in patient 3. A, B: An ultrasound showed choroidal detachment; C: A fundus examination revealed prominent choroidal detachment in four quadrants; D: Complete drainage of the suprachoroidal hemorrhage and flat retina was observed after vitrectomy was finished.

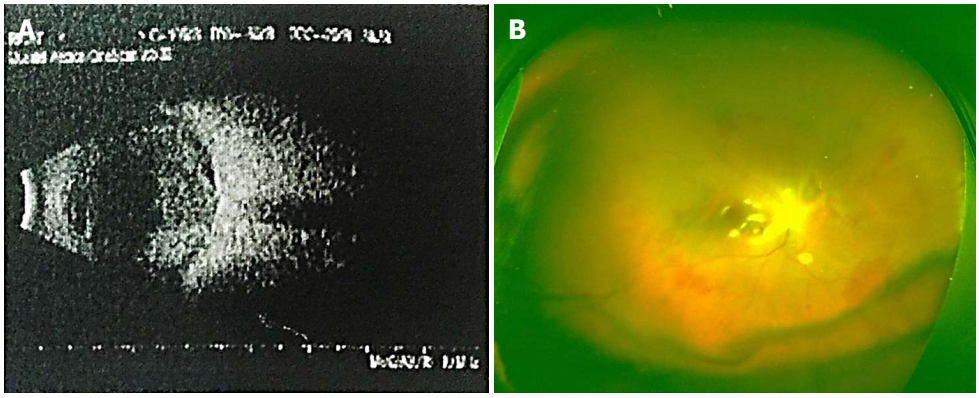

Figure 4 Clinical findings in patient 4. A: An ultrasound showed massive suprachoroidal hemorrhage with choroidal detachment; B: The choroidal detachment was completely reduced after surgery.

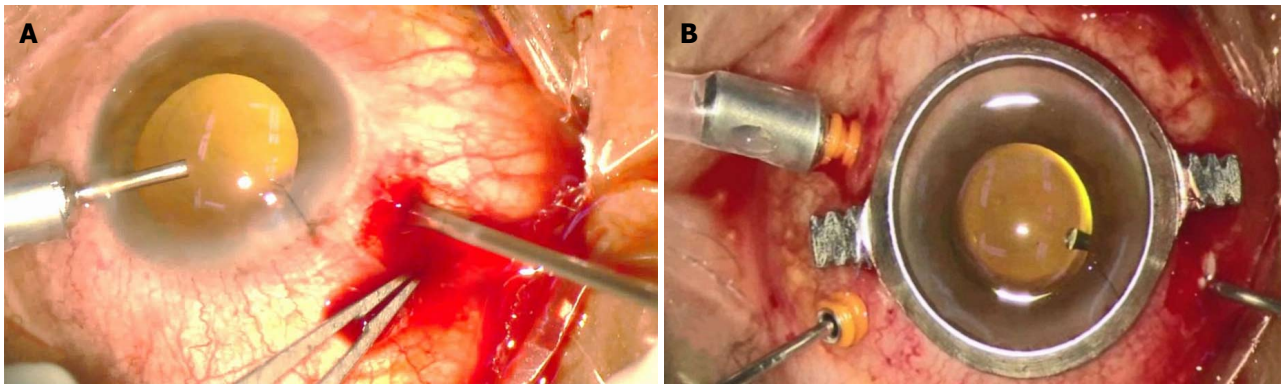

Figure 5 The drainage process during surgery. A: As soon as the infusion line was opened, a copious, thick flux of blood flowed out of the 20G cannula; B: The 20G cannula was left open throughout the surgery.

Table 3 Best corrected visual acuity

Patient No.	Prior to SCD	1 mo follow-up	Last follow-up (mo)
1	LP	NLP	NLP (7)
2	HM	CF	20/1000 (14)
3	HM	CF	20/1000 (6)
4	LP	LP	LP (24)

SCD: Suprachoroidal hemorrhage drainage; LP: Light perception; NLP: No light perception; HM: Hand motion; CF: Counting fingers.

glaucoma, and aphakia, which are consistent with other studies[10-13,17]. For such patients, the systemic condition should be actively improved before surgery, such as controlling blood pressure and blood sugar, improving cardiopulmonary function, stopping oral anticoagulant drugs, *etc*. It may be safer to perform surgery after the general condition is improved.

In the event of SCH during surgery, the incision should be quickly closed to control IOP. Local or systemic application of corticosteroids to reduce intraocular inflammation, and the use of carbonic anhydrase inhibitors, sedatives, *etc*., can be applied according to systemic conditions. Surgical treatment should be taken in the cases with a large amount of bleeding in the suprachoroidal space, especially the generation of kiss signs, difficult to control high IOP, persistent pain, and patients with other vitreoretinal complications (such as a large amount of vitreous hemorrhage, retinal detachment, or retinal incarceration)[18,19].

The timing of surgery is important when performing a sclerectomy. Some authors believe that the time of liquefaction is 7-14 d after bleeding. If the operation time is too early, the blood is not fully liquefied, and drainage is difficult. If the delay is too long, the blood clot will cause retinal proliferation, and the success rate of surgery is low. Therefore, if the blood clot can liquefy earlier, the success rate of operation and surgical effect may be better. Some authors have also used suprachoroidal cavity injection of tissue plasminogen activator 4-5 d after SCH to liquefy the clot[20-22]. Suprachoroidal cavity injection is an intraocular operation which can be performed in some complications, such as retinal detachment, vitreoretinal traction, and vitreous hemorrhage. However, sub-Tennon's injection is much more easy and safe to perform. Urokinase catalyzes the cleavage of plasminogen to plasmin and may degrade fibrin clots by thrombolysis, producing rapid and positive results. It has a short half-life of approximately 16 min, improves vascular adenosine diphosphate (ADP) activity, inhibits ADP-induced platelet aggregation, and prevents thrombosis. Urokinase has been reported in the successful treatment of various vitreoretinal diseases, including traumatic hyphema[23], vitreous hemorrhage[17], branch retinal artery occlusion[24], and central retinal artery occlusion[25]. At the same time, urokinase is a common clinical drug, and the price is appropriate, which is more suitable for clinical treatment in developing countries.

We took advantage of 20G and 23G vitrectomy cannulas to ensure sclerotomies of known and reliable diameter and consistent patency throughout all surgical maneuvers. The cannulas also allow the very quick, safe, and easy closure of the sclerotomy when needed, and this method has also been described in other studies that used 23G or 25G cannulas[15,16]. The advantage of vitrectomy for SCH is that its closed surgical system maintains a stable IOP. Surgery can remove the incarcerated anterior vitreous body and relieve the pulling action, thereby reducing the vitreous hemorrhage. When the vitreous body is removed, the perfusate is injected into the eyeball, which forces the SCH to be further discharged through the scleral incision. We performed PPV and tamponade with silicone oil instillation in three cases and no tamponade in one case. A silicone oil tamponade has been shown provide advantages over a balanced salt solution or gas filling because it protects against choroidal re-bleeding and prevents the development of chronic hypotony[3,26]. While none of our patients developed postoperative hypotony, other studies have reported a frequency for hypotony ranging from 24% to 71%[1,13,27]. The reduction in aqueous humor production followed by low IOP may be the cause of rebleeding. The injection of silicone oil prevents this from happening and avoids reoperation. Silicone oil can be removed if the patient's vision is well recovered or silicone oil-related complications occur.

There are important points during surgery that require our attention. The first is the location of drainage. The traditional suprachoroidal effusion is usually performed by 5-11 mm scleral puncture after the limbus[9,28], and in this study, patients were cut from the flat part of the ciliary body. This method can avoid unnecessary surgical incision and reduce tissue damage. The second is intraocular perfusion. Neither is it IOP during drainage nor intraocular perfusion during vitrectomy, the most important thing is to ensure that the perfusion needle is located in the vitreous cavity. Otherwise it will only increase the retinal and choroidal detachment, leading to surgery failure. Third, there are many reports of heavy water, intraocular laser and silicone oil filling. It is necessary to flexibly apply various filling materials and techniques during surgery to restore the retina as much as possible and close the retinal tear. Finally, retinal proliferative lesions will occur in some patients after surgery. Close follow-up is needed to select the appropriate surgical timing for re-operation to achieve therapeutic goals. In our study, the mean time from the occurrence of SCH to surgical intervention was 8.5 d (range, 5-12 d). In other studies, the mean time interval was 11 d with a similar range (6-20 d)[3,9]. Generally, a longer duration of appositional SCH has been shown to result in poorer visual outcomes[24].

The recovery of vision is mainly related to the amount of bleeding and the range and height of bleeding choroidal detachment. And also, the prognosis is related to whether the treatment after the bleeding is

correct. Rapid closure of the incision during surgery, selection of appropriate surgical timing, and reasonable surgical procedures are useful to preserve the optimal vision. A face-up posture, the disappearance of the anterior chamber, increasing IOP and, finally, optic nerve atrophy were the underlying causes of the poor visual outcome achieved in this patient. While the VA of case 4 remained light perception with a large central chorioretinal scar, cases 2 and 3 had better results, including a final VA of 20/1000. Patient 1 was the only case of intraoperative SCH included in our study, and an immediate tamponade was performed by quickly suturing all surgical incisions. Despite the poor visual outcome (no light perception) achieved in case 1, the anatomical outcome at the final presentation (7 mo postoperatively) was good and showed a reattached choroidea and retina. Excellent final anatomical results were also achieved in cases 1 and 3, and good choroidal reattachment following absorption of the hemorrhage 1 year postoperatively was observed in case 2. Anatomical recovery reduces the eyeball from being phthisical or eviscerated/enucleated, which were a considerable proportion of events in the literature reported[29].

The primary advantage of this technique is that it makes clot liquefaction happen in the early treatment stage and allows a slower and semiautomated controlled mechanism to be achieved, resulting in marked stability during the procedure. At the same time, this study is a pilot study that was undertaken to examine the use of sub-Tenon's urokinase injection-assisted vitrectomy in the timely treatment of massive SCH complicating cataract surgery or trauma, and the absence of a control group is a limitation of this study. In the future, more cases will be included, according to the preliminary data obtained in the present study.

CONCLUSION

It is important to ensure that the perfusion needle is located in the vitreous cavity. Otherwise, it will only aggravate the retinal and choroidal detachment, leading to surgery failure. It is necessary to flexibly apply various filling materials and techniques during surgery to restore the retina as much as possible and close the retinal tear. Close follow-up is needed to select the appropriate surgical timing for re-operation to achieve therapeutic goals.

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CASE REPORT

Plexiform fibromyxoma of the small bowel: A case report

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Abstract

BACKGROUND

Plexiform fibromyxoma is a rare, special type of mesenchymal tumor. The most common presenting symptoms are anemia, hematemesis, and hematochezia, without sex or age predilection. The reported cases have mainly occurred in the gastric antrum and pylorus region, with some cases in the duodenum.

CASE SUMMARY

We report here a case of plexiform fibromyxoma in the upper segment of the jejunum, which was continuously followed up for 3 years after surgical removal. Plexiform fibromyxoma showed multinodular or plexiform growth. The cells in the tumor node were spindle-shaped but few in number and mitotic figures. Small blood vessels and mucous matrix were found among the tumor cells. Immunohistochemistry revealed that the plexiform fibromyxoma cells were positive for smooth muscle actin, focally positive for CD10, and negative for cytokeratin, CD117, DOG-1 (discovered on GIST-1) desmin, S-100, epithelial membrane antigen, and CD34. Ki-67 labeling index was < 5%. Plexiform fibromyxoma showed benign biological behavior. After 3 years of consecutive postoperative follow-up, no obvious signs of metastasis or recurrence were found by imaging examination.

CONCLUSION

Plexiform fibromyxoma is a rare type of mesenchymal tumor. The diagnosis mainly depends on pathological

examination, and it should be distinguished from other gastrointestinal mesenchymal tumors.

Key words: Plexiform fibromyxoma; Gastrointestinal stromal tumor; Plexiform angiomyxoid myofibroblastic tumor; Small bowel; Benign tumor; Case report

Core tip: Plexiform fibromyxoma is a rare, special type of mesenchymal tumor. It is reported to occur mainly in the gastric antrum and pylorus region, but it may also occur in the duodenum. We here report a case of plexiform fibromyxoma in the upper segment of the jejunum, which was continuously followed up for 3 years after surgical removal. No obvious signs of metastasis or recurrence were found by imaging examination.

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INTRODUCTION

Plexiform fibromyxoma is a rare type of mesenchymal tumor. It was known as plexiform angiomyxoid myofibroblastic tumor (PAMT), which was first described by Takahashi *et al*[1] in 2007. In 2009, Miettinen *et al*[2] reported benign gastric antral fibromyxoid tumors and designated them as plexiform fibromyxoma. It was classified as a gastrointestinal mesenchymal tumor in the 2010 World Health Organization Classification of Digestive System Neoplasms[3] and was termed plexiform fibromyxoma. Many scholars, however, still prefer using PAMT rather than plexiform fibromyxoma[4,5].

Plexiform fibromyxoma has a wide range of onset age, without sex or age predilection. So far, > 60 cases of PAMT or plexiform fibromyxoma have been reported worldwide[5]. The most common presenting symptoms are anemia, hematemesis, and hematochezia. The reported cases have mainly occurred in the gastric antrum and pylorus region, with some cases in the duodenum[6]. We here report a case of plexiform fibromyxoma in the upper segment of the jejunum, which was continuously followed up for 3 years after surgical removal.

CASE PRESENTATION

A 31-year-old woman with repeated hematochezia and syncope without obvious cause for 20 d presented to a local hospital for treatment in 2013. No discomfort, such as hematemesis or abdominal pain, was found at disease onset. Gastroscopic examinations performed in the local hospital showed no evidence of upper gastrointestinal hemorrhage. However, her condition was not improved after inpatient care, so she was transferred to our hospital after 2 d. Physical examination on admission showed no abnormal signs except for pale appearance. Routine blood examination indicated anemia (red blood cell count 2.18 T/L, hemoglobin 51.0 g/L, and mean cell hemoglobin 22.90 pg). One gastroscopic examination and one colonoscopic examination performed on the same day failed to find the hemorrhagic focus. In order to avoid more severe gastrointestinal bleeding, the patient was not prepared for intestinal cleaning.

FINAL DIAGNOSIS

No abnormalities were found by B-ultrasound examination of the upper abdomen, enhanced computed tomography (CT) of the abdomen, and CT angiography (CTA) of the small intestine. The patient stopped bleeding after 3 d in the hospital. We suspected that the hemorrhage was caused by small intestinal disease. Therefore, we performed capsule endoscopic examination after cleaning the intestinal tract after 2 d. Capsule endoscopic examination revealed one protuberant lesion about 1.2 cm × 1.0 cm in the upper segment of the jejunum; the margin of which was unclear. Ulceration was found at the top, which was covered with uneven white necrotic substance (Figure 1). Single balloon enteroscopy was performed to determine further the position of the lesion. This indicated that the protuberant lesion was located about 100 cm away from the duodenal papilla, and its size and morphology were consistent with the findings of capsule endoscopic examination (Figure 2).

TREATMENT

The patient underwent surgical exploratory laparotomy and resection of the upper jejunal tumor, including local intestinal resection. The size of the resected tumor was about 1.2 × 1.0 cm. Postoperative pathological examination confirmed the presence of proliferative spindle cells in the mucosal and submucosal layers of the small intestine. Immunohistochemical staining indicated spindle cells that were positive for smooth muscle actin (SMA) and CD10 (few cells) and negative for cytokeratin, CD117, DOG-1 (discovered on GIST-1), desmin, S-100, epithelial membrane antigen, and CD34. The Ki-67 labeling index was < 5%, and no vascular invasion was observed. The results supported the diagnosis of small intestinal plexiform fibromyxoma (Figure 3).

OUTCOME AND FOLLOW-UP

Seven days after surgery, the patient's condition im-

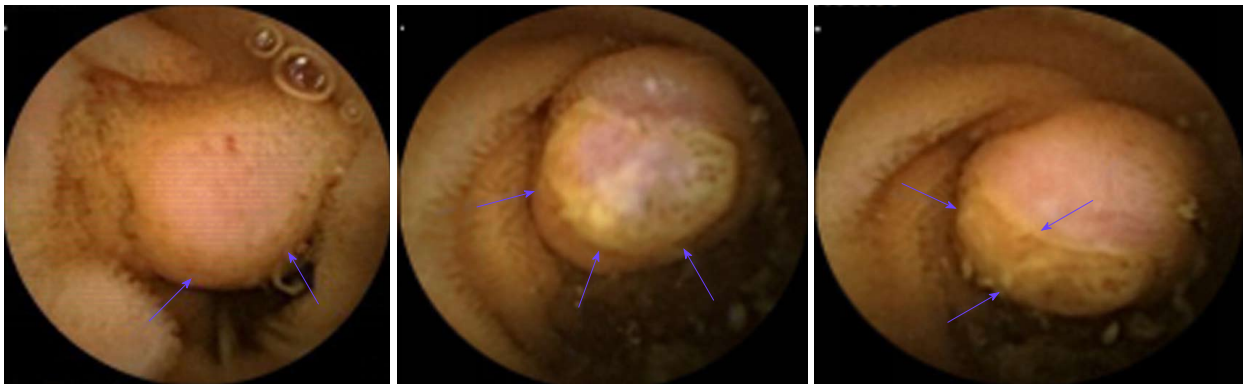

Figure 1 Capsule endoscopy revealed a protuberant lesion in the upper segment of the jejunum; the margin of which was unclear. Ulceration was found at the top (arrow).

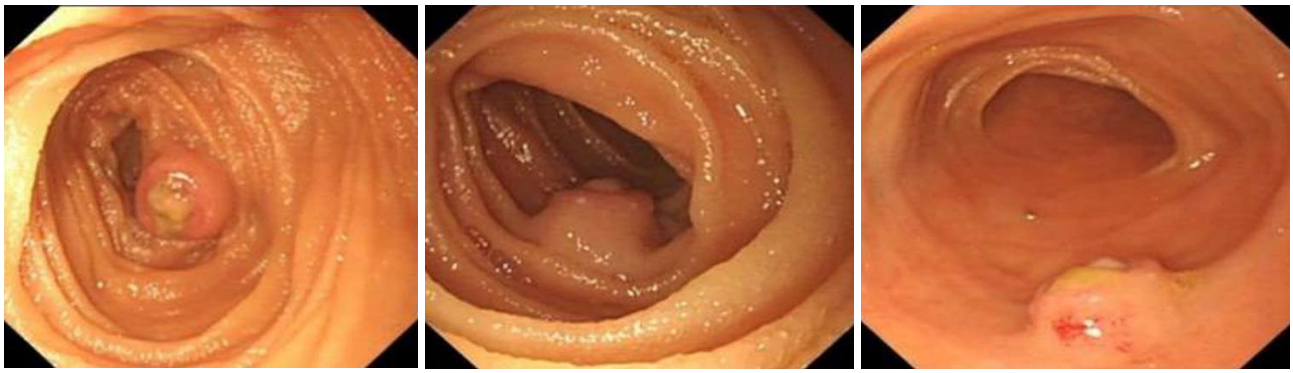

Figure 2 Results of single balloon colonoscopy. A protuberant lesion in the upper segment of the jejunum. Ulceration was found at the top.

proved, and she was discharged from hospital. No gastrointestinal hemorrhage was found during 3 years consecutive follow-up. No signs of tumor recurrence and metastasis were found by imaging examination (enhanced CT and CTA of the abdomen) at 6 mo and 1, 2, and 3 years after surgery.

DISCUSSION

Plexiform fibromyxoma is a rare mesenchymal tumor. It was previously reported[2,7] to occur in the gastric antrum and was thought to be derived from cells in this location. However, as the number of reported cases has increased, this is no longer thought to be the case. So far, > 60 cases of PAMT or plexiform fibromyxoma have been reported worldwide[5]. The published literature suggests that plexiform fibromyxoma is mainly located in the gastric antrum and prepyloric area, but some reports indicate that the tumor originates from the gastric fundus[8], gastric body[9], the duodenum, and even the cecum[10] and posterior mediastinum may be involved[11]. Takahashi *et al*[7] reported six cases of plexiform fibromyxoma that originated from the pyloric area but extended into the duodenal bulb, and one of those cases came from the duodenal stump[12]. In the present case, plexiform fibromyxoma originated from the upper segment of the jejunum. There are no previous reports of plexiform fibromyxoma originating from the jejunum or ileum, and the present case may be the first jejunal plexiform fibromyxoma.

Plexiform fibromyxoma has a wide range of onset age, from 7 to 75 years[7]. It also has a balanced gender distribution. The clinical symptoms of patients with plexiform fibromyxoma are atypical, so patients often present to a hospital for treatment due to upper gastrointestinal symptoms, including hematemesis, melena, anemia, vomiting, abdominal pain, abdominal distension, abdominal mass, and other abdominal discomfort. There are also individual reports of gastrointestinal perforation[13]. The majority of patients attend hospital for treatment for gastrointestinal hemorrhage, which is induced by ulceration that forms on the surface of the tumor.

In the present case, the patient presented with hematochezia as the initial symptom. At the local hospital and our hospital, gastroscopy, colonoscopy, ultrasound examination of the upper abdomen, and enhanced abdominal CT were suspicious for gastrointestinal hemorrhage induced by small intestinal disease. Further CT and CTA of the small intestine still did not detect any lesions that could reasonably explain the gastrointestinal hemorrhage. A gastrointestinal hemorrhage due to small intestinal disease was suspected and capsule endoscopy was perfor-

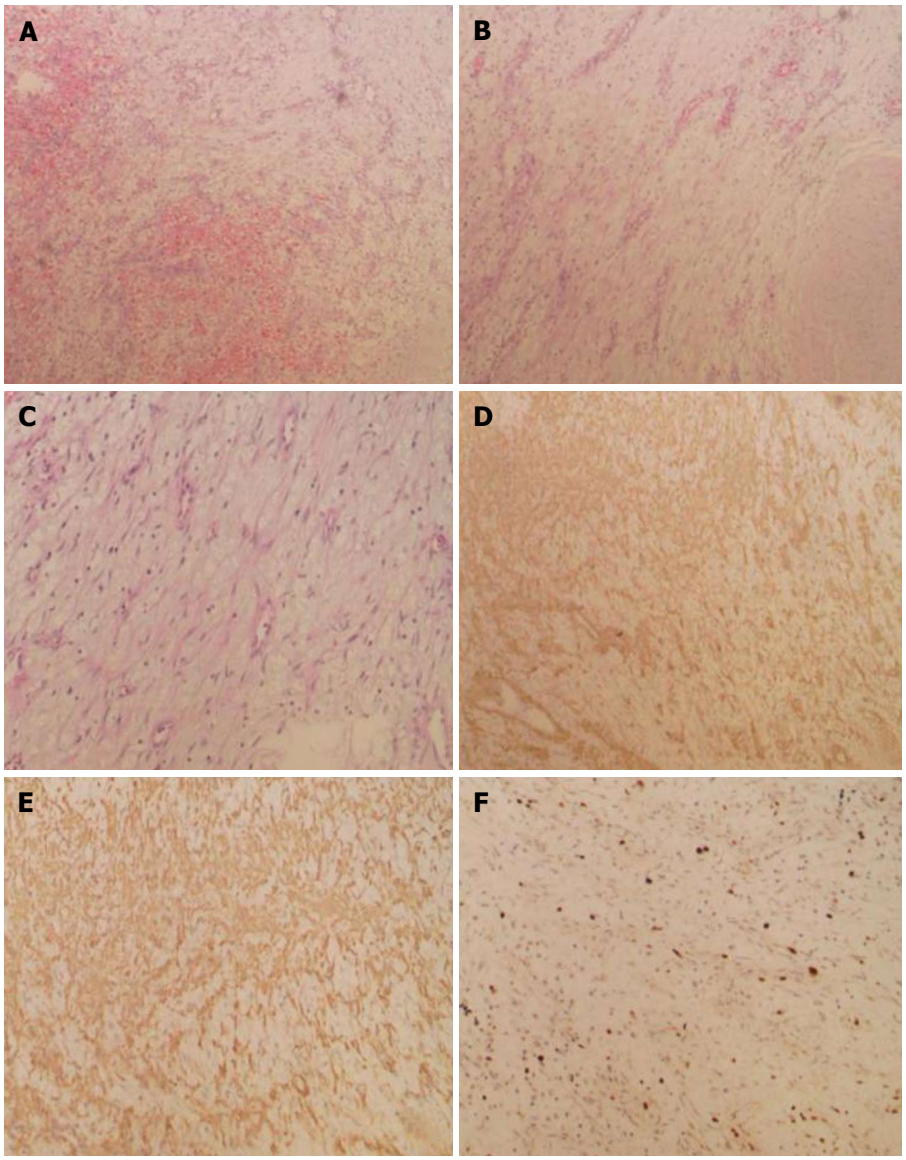

Figure 3 The diagnosis of small intestinal plexiform fibromyxoma. A: Myxoid nodules and extensive hemorrhagic areas. The stroma was rich in small vessels (HE × 40); B: Tumor showed multinodular or plexiform growth, paucicellular nodules with blunt spindle cells and myxoid stroma (HE, × 40); C: Spindle-shaped bland tumor cells were separated by an abundant intercellular myxoid or fibromyxoid matrix (HE, × 100); D: Tumor SMA(+) (× 40); E: Tumor SMA(+) (× 100); F: Ki-67 labeling index < 5% (× 100). HE: Hematoxylin and eosin; SMA: Smooth muscle actin.

med. One protuberant lesion was found in the small intestine, which was coupled with ulceration on its surface. Initially, we considered that it may have been a small intestinal stromal tumor, so we performed peroral single balloon enteroscopy again to assist with tumor orientation and resected the lesion completely. Surprisingly, the results of final pathological examination indicated plexiform fibromyxoma.

Plexiform fibromyxoma has been described as subserosal nodules[4] and polypoid projections, and it has smooth mucosal surface or ulceration[14]. The tumor size is 1.5 cm-15.0 cm[15]. Plexiform fibromyxoma and other subserosal nodules are indistinguishable macroscopically. The diagnosis of plexiform fibromyxoma mainly depends on pathological examination. The gross findings are characterized by a lobulated or nodular solid mass, accompanied by ulcer, erosion, and even cystic changes[16]. Histologically, plexiform fibromyxoma shows multinodular or plexiform growth. The cells in the tumor node are spindle-shaped but few in number and mitotic figures. Rich small vessels and mucous matrix can be found among the tumor cells. In most areas, the tumor cells are arranged loosely. Immunohistochemical staining shows that plexiform fibromyxoma cells are positive for SMA[17], focally positive for CD10, and negative for cytokeratin, CD117, DOG-1, desmin, S-100, epithelial membrane antigen, and CD34[1,2,6,7]. Mitoses are rare (up to 7/50 HPF). The positive expression rate of Ki-67 is low[2,3].

Small intestinal plexiform fibromyxoma has a unique histological appearance, which is easy to distinguish from other mesenchymal tumors in the small

intestine: (1) Gastrointestinal stromal tumor (GIST): Plexiform fibromyxoma shows plexiform or nodular growth, with few cells. The capillary vessels proliferate obviously. Histologically, few small intestinal stromal tumors show plexiform or nodular growth, while they are positive for DOG-1 and CD117. Plexiform or nodular growth can be seen in succinate-dehydrogenase-deficient GIST. Genetic detection can reveal mutation of *kit* or *PDGFR-α* genes, which can contribute to the identification of plexiform fibromyxoma and GIST; (2) Small intestinal leiomyoma: A rare tumor that mainly occurs in the esophagus, and leiomyomas derived from the stomach and colorectum are even rarer. Leiomyomas comprise irregular fascicular smooth muscle cells. Except for SMA(+), immunohistochemical staining shows desmin(+) and h-caldesmom(+) as well as CD117(+) and CD34(+), which can distinguish leiomyoma from plexiform fibromyxoma; (3) Small intestinal schwannoma: A rare disease that is similar to gastric schwannoma. It has benign biological behavior. The tumor comprises diversely arranged tumor cells that often form a microtrabecular structure against a background of collagen. Immunohistochemical staining is S-100(+) and vimentin(+), which can distinguish schwannoma from plexiform fibromyxoma; and (4) Inflammatory myofibroblastic tumor: A rare tumor that is composed of spindle myofibroblasts, lymphocytes, and plasma cells. Immunohistochemical staining indicates anaplastic lymphoma kinase[18], which can contribute to the identification of inflammatory myofibroblastic tumor and plexiform fibromyxoma.

Plexiform fibromyxoma has benign biological behavior[1,6,7-18], and tumor resection is considered to be effective. To date, no cases with local recurrence or distal metastasis after resection have been reported, except for abdominal dilatation and vascular invasion. In the present case, imaging showed no obvious signs of metastasis or recurrence during 3 years consecutive follow-up. Currently, there are few reports on plexiform fibromyxoma, so more cases and close follow-up observation are needed. Obscure gastrointestinal bleeding occurs in approximately 5% of all patients with gastrointestinal bleeding. In 41%–75% of patients with obscure gastrointestinal bleeding, further evaluation can confirm the lesions that cause bleeding in the small intestine[19]. Capsule endoscopy is preferred for patients with high suspicion of small intestinal disease. In particular, capsule endoscopy should be performed for initial screening in patients with gastrointestinal hemorrhage caused by suspicious small intestinal disease. After finding the lesion by capsule endoscopy, enteroscopy can be considered to assist with orientation if the location of the lesion is inaccurate. Small intestinal disease or postoperative follow-up needs imaging examination as well as capsule endoscopic or enteroscopic re-examination, which could be used for direct observation of small intestinal disease or postoperative anastomosis.

Plexiform fibromyxoma is a rare, special type of mesenchymal tumor. The diagnosis mainly depends on pathological examination, and it should be distinguished from other gastrointestinal mesenchymal tumors. At present, plexiform fibromyxoma is reported to occur in the stomach, duodenum, cecum, and small intestine. According to the existing literature, plexiform fibromyxoma has benign biological behavior. Currently, there are few reports on plexiform fibromyxoma, so more cases and close follow-up observation are needed.

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