ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2019 June 30; 7(6): 259-338

Published by Baishideng Publishing Group Inc

WJMA World Journal of Meta-Analysis

Contents

Irregular Volume 7 Number 6 June 30, 2019

MINIREVIEWS

259 Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis using pancreatic stents: A review of efficacy, diameter and length
Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Takasumi M, Hashimoto M, Hikichi T, Ohira H

SYSTEMATIC REVIEW

269 Significance of multivisceral resections in oncologic surgery: A systematic review of the literature
Nadiradze G, Yurttas C, Königsrainer A, Horvath P

290 Relationship between perioperative anaemia and outcomes in older people with hip fractures: A systematic review and meta-analysis protocol
Khow KS, Kee MW, Shibu PN, Yu SC, Chehade MJ, Visvanathan R

297 Treatment options for rumination syndrome: A systematic review
Ong AML, Tay SW, Wang YT

309 Surgery with adjuvant or neoadjuvant treatment *vs* surgery alone for resectable pancreatic cancer: A network meta-analysis
Shen P, Huang KJ, Zhang CZ, Xiao L, Zhang T

META-ANALYSIS

323 Single strain probiotics for dyslipidemia, fatty liver, and obesity: A systematic review and meta-analysis
Pongpirul K, Janchot K, Dai Y

Contents

World Journal of Meta-Analysis

Volume 7 Number 6 June 30, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Meta-Analysis*, Małgorzata Kujawska, MSc, PhD, Associate Professor, Department of Toxicology, Poznan University of Medical Sciences, Poznań 60-631, Poland

AIMS AND SCOPE

The *World Journal of Meta-Analysis* (*WJMA*) is an online, open-access, single-blind peer-reviewed journal that is published by Baishideng Publishing Group. Accepting both solicited and unsolicited manuscripts, the *WJMA* mainly publishes high quality meta-analysis and systematic review articles to lead the development of various fields of clinical medicine. The type of articles published in the *WJMA* include the editorial, minireview, review, meta-analysis, meta-regression, systematic review, and evidence-based practice.

The primary aim of the *WJMA* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high quality meta-analysis and systematic review articles and communicate their research findings online.

The *WJMA* mainly publishes research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

INDEXING/ABSTRACTING

The *WJMA* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Giuseppe Biondi-Zoccai

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
June 30, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 259-268

DOI: 10.13105/wjma.v7.i6.259

ISSN 2308-3840 (online)

MINIREVIEWS

Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis using pancreatic stents: A review of efficacy, diameter and length

Mitsuru Sugimoto, Tadayuki Takagi, Rei Suzuki, Naoki Konno, Hiroyuki Asama, Yuki Sato, Hiroki Irie, Ko Watanabe, Jun Nakamura, Hitomi Kikuchi, Mika Takasumi, Minami Hashimoto, Takuto Hikichi, Hiromasa Ohira

ORCID number: Mitsuru Sugimoto (0000-0002-4223-613X); Tadayuki Takagi (0000-0003-0696-5973); Rei Suzuki (0000-0002-4049-0484); Naoki Konno (0000-0001-9830-4317); Hiroyuki Asama (0000-0002-0102-0404); Yuki Sato (0000-0001-8000-0972); Hiroki Irie (0000-0002-4805-6244); Ko Watanabe (0000-0003-3895-7636); Jun Nakamura (0000-0001-6006-1778); Hitomi Kikuchi (0000-0003-0583-1623); Mika Takasumi (0000-0002-6025-8084); Minami Hashimoto (0000-0002-5750-7182); Takuto Hikichi (0000-0002-9815-1557); Hiromasa Ohira (0000-0003-4331-0634).

Author contributions: Sugimoto M designed and performed the study; Sugimoto M, Takag T, and Ohira H analyzed the data; Sugimoto M, Takag T, and Ohira H wrote the paper; Suzuki R, Konno N, Asama H, Hikichi T, Watanabe K, Nakamura J, Kikuchi H, Takasumi M, Sato Y, Hashimoto M, and Irie H provided clinical advice; and Hikichi T and Ohira H supervised the study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Mitsuru Sugimoto, Tadayuki Takagi, Rei Suzuki, Naoki Konno, Hiroyuki Asama, Yuki Sato, Hiroki Irie, Ko Watanabe, Jun Nakamura, Hitomi Kikuchi, Mika Takasumi, Minami Hashimoto, Hiromasa Ohira, Department of Gastroenterology, Fukushima Medical University, School of Medicine, Fukushima 9601247, Japan

Ko Watanabe, Jun Nakamura, Hitomi Kikuchi, Minami Hashimoto, Takuto Hikichi, Department of Endoscopy, Fukushima Medical University Hospital, Fukushima 9601295, Japan

Corresponding author: Tadayuki Takagi, MD, PhD, Assistant Professor, Doctor, Department of Gastroenterology, Fukushima Medical University, 1 Hikarigaoka, Fukushima 9601247, Japan. daccho@fmu.ac.jp
Telephone: +81-24-5471202
Fax: +81-24-5472055

Abstract

Although endoscopic retrograde cholangiopancreatography (ERCP) is an important procedure for the diagnosis and treatment of pancreaticobiliary diseases, post-ERCP pancreatitis (PEP) is the most frequent adverse event that can sometimes be fatal. However, prophylactic pancreatic stent (PS) insertion has been performed to prevent PEP in high-risk patients. In some randomized controlled trials (RCTs) and meta-analyses, the efficacy of prophylactic PS insertion has been shown to prevent PEP. In addition, several types of stents have been used to decrease PEP. In this review, we introduce the details of these RCTs and meta-analyses and reveal the specifications for stent placement, for example, the stent diameter and length and the pancreatic region into which the stent should be inserted.

Key words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Prophylactic pancreatic stent

Core tip: Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most frequent adverse event that can sometimes be fatal. Pancreatic stent (PS) insertion is recommended to prevent PEP based on some randomized controlled trials (RCTs) and

Manuscript source: Invited manuscript

Received: April 15, 2019
Peer-review started: April 15, 2019
First decision: May 8, 2019
Revised: June 2, 2019
Accepted: June 10, 2019
Article in press: June 10, 2019
Published online: June 30, 2019

P-Reviewer: Isik A, Barret M
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu JH

meta-analyses. Currently, several types of PS have been used. In this review, we introduce these RCTs and meta-analyses and reveal what stent should be used.

Citation: Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Takasumi M, Hashimoto M, Hikichi T, Ohira H. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis using pancreatic stents: A review of efficacy, diameter and length. *World J Meta-Anal* 2019; 7(6): 259-268
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/259.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.259

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important procedure for the diagnosis and treatment of pancreaticobiliary diseases but is sometimes a dangerous procedure. Several adverse events related to ERCP have been reported (duodenal perforation, bleeding, *etc*)[1-4]. Among them, post-ERCP pancreatitis (PEP) is the most frequent adverse event and is sometimes fatal. According to past reports, PEP occurs in 0.4%-5.6% of patients[5-12], and the mortality rate of PEP is 0-0.1%[8,10-12]. The risk factors of PEP that have been specified in past reports were history of previous PEP, more than two contrast injections into the pancreatic duct, sphincter of Oddi dysfunction (SOD), age less than 50 years, female gender, difficult biliary duct cannulation, biliary sphincter balloon dilation, precut sphincterotomy, and a history of previous pancreatitis[11-19]. As prophylaxis for PEP in high-risk patients with these risk factors, pancreatic stent (PS) insertion is a preventative option. In this review, we present our investigations on the efficacy of PS placement for preventing PEP, and we disclose what stent should be selected and how the PS should be inserted.

SEARCH STRATEGY

The studies included in this review were retrieved from PubMed using the following keywords: "Post-ERCP pancreatitis" and "pancreatic stent". Furthermore, studies written in English were selected. Only randomized controlled trials (RCTs) and meta-analyses that examined the efficacy of PS for preventing PEP were selected for further analysis. Studies that compared different stents (flanged or unflanged, diameter, length) were analyzed to determine which PSs should be used.

ADAPTATION OF PROPHYLACTIC PS INSERTION

As mentioned above, patients with high risk factors become candidates for prophylactic PS insertion. The patients recommended PS insertion had a history of previous PEP, SOD, difficult biliary duct cannulation, biliary sphincter balloon dilation, precut sphincterotomy or sphincterotomy, pancreatic duct cannulation or contrast agent injection to the pancreatic duct, or endoscopic ampullectomy[20].

RCTs

In an RCT in 1993, Smithline *et al*[21] reported first prophylactic PS insertion for preventing PEP. In the report, the risk factors of PEP were acinarization, precutting, and a history of pancreatitis. The report could not prove the efficacy of PS insertion and did not recommend PS for PEP (PEP rate: Stent group 14% (6/43) *vs* 18% (9/50), $P = 0.299$). However, several additional RCTs were performed, and the total number of RCTs on this topic increased to eleven from 1993 to 2016[21-31] (Table 1). Except for the first report written by Smithline, all reports indicated the efficacy of PS insertion for preventing PEP, and severe PEP did not occur in patients who received a PS[22-31]. Although a significant difference was not observed, the PEP rate was lower in the stent group than in the no stent group in the report written by Tsuchiya *et al*[25] [stent group 1/32 (3.1%) *vs* no stent group 4/32 (12.5%), $P > 0.05$].

Table 1 Randomized controlled trials of prophylactic pancreatic stent insertion for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

Author	Yr	Country	Sample number		Risk factors	PEP *n* (%)	Criteria for PEP
			Stent	No stent		Stent/no stent	
Smithline *et al*[21]	1993	United States	43	50	Acinarization, pre-cutting, history of pancreatitis	Total 6 (14)/9 (18), *P* = 0.299; Mild 5 (12)/5 (10), *P* = NA; Moderate 1 (2)/2 (4) *P* = NA; Severe 0 (0)/2 (4), *P* = 0.264	Cotton
Tarnasky *et al*[22]	1998	United States	41	39	SOD	Total 1 (2)/10 (26), *P* = 0.003; Mild 0 (0)/5 (13), *P* = NA; Moderate 0 (0)/5 (13), *P* = NA; Severe 0 (0)/0 (0), *P* = NA	Cotton
Fazel *et al*[23]	2003	United States	38	36	Difficult cannulation SOD	Total 2 (5.3)/10 (28), *P* < 0.05; Mild 2 (5.3)/5 (14), *P* = NA; Moderate 0 (0)/2(6), *P* = NA; Severe 0 (0)/3 (8), *P* = NA	Cotton
Sofuni *et al*[24]	2007	Japan	98	103	IDUS, biopsy, EPBD, SOD, POCS, Duodenal diverticulum, acinarization, initial pancreato-graphy, difficulty of cannulation	Total 3 (3)/14 (13.6), *P* = 0.019; Mild 2 (2)/8 (7.8), *P* = 0.139; Moderate 1 (1)/6 (4.6), *P* = 0.156; Severe 0 (0)/0(0), *P* = NA	Cotton
Tsuchiya *et al*[25]	2007	Japan	32	32	EST, IDUS, EPBD, SOD, pancreatic duct cannulation	Total 1 (3.1)/4 (12.5), *P* > 0.05; Mild 1 (3.1)/2 (6.3), *P* = NA; Moderate 0 (0)/1 (3.1), *P* = NA; Severe 0 (0)/1 (3.1), *P* = NA	Cotton
Ito *et al*[26]	2010	Japan	35	35	History of pancreatitis, history of PEP, pancreatic duct opacification, EST, IDUS, EPBD, cytology of pancreatic juice, biopsy of pancreatic duct	Total 1 (2.9)/8 (23) (per-protocol) 0 (0)/9 (24), *P* = 0.0096; Mild 1 (2.9)/8 (23); Moderate and severe 0	Cotton

Sofuni *et al*[28]	2011	Japan	213	213	History of pancreatitis, SOD, pancreato-graphy, EST, precut sphincter-otomy, EPBD, CBD tissue sampling, pancreatic duct tissue sampling, biliary drainage without EST, ENBD without EST, IDUS, difficulty of cannulation, long procedural time	(Intention to treat) Total 20 (9.4)/31 (14.6), *P* = 0.076; Mild 16 (7.5)/22 (10.3), *P* = 0.24; Moderate 4 (1.9)/8 (3.8), *P* = 389; Severe 0 (0)/1 (0.5), *P* = 1.00; (Full analysis set) Total 16 (7.9)/31 (15.2), *P* = 0.021; Moderate 12 (5.9)/22 (10.8), *P* = 0.77; Mild 4 (1.97)/8 (3.92), *P* = 0.952; Severe 0 (0)/1 (0.5), *P* = 1.00	Cotton
Pan *et al*[27]	2011	China	20	20	History of pancreatitis, pancreatic duct cannulation, pancreato-graphy, difficult cannulation, hyperamyla-semia	Total 4 (20)/14 (70), *P* < 0.01; Mild, moderate, severe NA	Cotton
Kawaguchi *et al*[29]	2012	Japan	60	60	History of PEP, SOD, difficult cannulation, pre-cutting, pancreatic duct biopsy, IDUS of pancreatic duct	Total 1 (1.7)/8 (13.3), *P* = 0.032; Mild 1 (1.7)/8 (13.3), *P* = 0.032	Modified Cotton
Lee *et al*[30]	2012	Korea	50	51	Difficult biliary cannulation, pancreatic cannulation	Total 6 (12)/15 (29.4), *P* = 0.031; Mild 5 (10)/12 (23.5), *P* = NA; Moderate 1 (2)/2 (3.9), *P* = NA; Severe 0 (0)/1 (2), *P* = NA	Cotton
Yin *et al*[31]	2016	China	104	102	History of PEP, cannulation difficulty, periampullary diverticulum	Total 8 (7.7)/18 (17.7), *P* = 0.031, Mild, Moderate, severe NA	NA

RCT: Randomized controlled trial; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; SOD: Sphincter of Oddi dysfunction; IDUS: Intraductal ultrasonography; EPBD: Endoscopic papillary balloon dilation; POCS: Peroral cholangioscopy; EST: Endoscopic sphincterotomy; CBD: Common bile duct; ENBD: Endoscopic nasobiliary drainage; NA: Not available.

PS FOR AMPULLECTOMY

In 2005, Harewood *et al*[32] reported on prophylactic PS placement for endoscopic snare excision of the duodenal ampulla. In this study, 19 patients were enrolled, and 10 received a PS. Although the number of participants was small, postprocedure pancreatitis was significantly higher in patients without PS than in patients with PS [33% (3/9) *vs* 0% (0/10), *P* = 0.02].

META-ANALYSES

Among the eleven RCTs, PEP occurred more in patients without PS than in patients with PS. PS insertion was recommended for preventing PEP. Additionally, severe PEP did not occur in any patient who received a PS in all eleven RCTs. However, the frequency of severe PEP was not significantly different between the stent group and

the no stent group in any of the RCTs. The results of severe PEP referred to the small sample size in each RCT and far fewer patients with severe PEP. These facts indicated that prophylactic PS might prevent not only total PEP but also severe PEP.

The usefulness of prophylactic PS placement for preventing severe PEP was not statistically recognized within each RCT. However, six meta-analyses were previously performed on prophylactic PS placement to prevent PEP[33-38] (Table 2). Among them, two of the six meta-analyses reported that prophylactic PS insertion did not statistically prevent severe PEP[33,35]. As more cases of prophylactic PS were reported, the second-most recent meta-analysis was conducted by Shi *et al*[37]; however, the efficacy of prophylactic PS for preventing severe PEP could not be proven. As a cause, the meta-analysis involved only full text articles and excluded articles with only abstracts, and the number of cases became small. On the other hand, two meta-analyses written by Mazaki *et al*[34,36] involved both full-text articles and articles with only abstracts; therefore, the number of cases was large. In the two meta-analyses written by Mazaki *et al*[34,36], the efficacy of prophylactic PS insertion for preventing severe PEP was indicated (2010: Stent group 0/336 *vs* no stent group 7/344, $P < 0.04$, 2014: Stent group 0/694 *vs* no stent group 13/718, $P = 0.01$). Furthermore, in the most recent meta-analysis written by Fan *et al*[38], severe PEP was significantly lower in patients with a PS than in patients without a PS (stent group 0/493 *vs* no stent group 13/516, $P < 0.01$).

From a meta-analysis, it became apparent that prophylactic PS might be efficient for preventing not only PEP but also severe PEP.

WHAT STENT SHOULD BE USED?

As described above, PEP is reduced by PS insertion. However, several forms, diameters, and lengths of PSs exist. What stent should we use (Table 3)?

Internal flanged or unflanged

In 2018, He *et al*[39] compared 5-Fr 3 cm internal unflanged stents with a single pigtail on the duodenal side and 5-Fr 3 cm internal flanged stents with a single pigtail on the duodenal side. The PEP rates were not different between the two types of stents [unflanged stents 5.07% (7/138) *vs* flanged stents 7.97% (11/138), $P = 0.329$]. However, spontaneous PS displacement at 5 d was significantly higher in the internal unflanged stent group than in the internal flanged stent group [unflanged stent 47.72% (63/138) *vs* flanged stent 15.67% (21/134), $P < 0.001$]. Furthermore, spontaneous PS displacement at 14 d was significantly higher in the internal unflanged stent group than in the internal flanged stent group [unflanged stent 84.21% (112/133) *vs* flanged stent 42.65% (58/136), $P < 0.001$]. When the internal unflanged stent with a single pigtail on the duodenal side was used, an additional endoscope insertion to remove the PS was avoided.

PS diameter

In past reports, the diameter of the PS makes a difference not only in the occurrence of PEP but also in usability. In 2004, Rashdan *et al*[40] wrote a retrospective study about prophylactic PS placement in 2940 cases. They described that small-diameter stents (*i.e*., 3-4-Fr) were more effective than were 5-Fr or 6-Fr stents in preventing PEP [PEP rate: 3-4-Fr stent 8.7% (213/2447) *vs* 5-6-Fr stent 11.0 % (54/493), $P = 0.0471$]. However, Zolotarevsky *et al*[42] reported that there was no significant difference in the PEP rate between patients who received a 3-Fr PS and patients who received a 5-Fr PS. However, insertion of a 5-Fr stent was faster (9.2 min *vs* 11.1 min, $P = 0.355$), easier [mean modified 5-point Likert scale[41,42]: 1.8 (5-Fr) *vs* 3.4 (3-Fr), $P < 0.01$], and required fewer wires [1.5 (5-Fr) *vs* 1.9 (6-Fr), $P = 0.002$] than insertion of a 3-Fr PS[43]. Pahk *et al*[44] reported that spontaneous passage was more frequent with 4-Fr PSs than with 5-Fr PSs [95.8% (115/137) *vs* 68.7% (134/209), $P < 0.001$ (by log-rank test)]; therefore, the need for additional endoscopy to retrieve the PS was reduced by using a 4-Fr PS. However, the incidence of PEP was not significantly different between the 4-Fr PS group and the 5-Fr PS group. An additional report stated that insertion of a PS with a diameter > 5-Fr was effective in preventing PEP (PEP rate: > 5-Fr > 5 cm 1.4% *vs* ≤ 5-Fr ≤ 5 cm 9.4%, $P = 0.0252$)[45].

Based on the above results, whether the diameter of PS influences the occurrence of PEP remains controversial. According to past reports, thin stents (*i.e*., 3-Fr or 4-Fr) should be used with the expectation of spontaneous dislodgment, and a 5-Fr stent should be used in cases that were difficult to insert PS.

PS length

Few reports have described the length of PSs (Table 3). In 2009, Chahal *et al*[46]

Table 2 Meta-analyses of prophylactic pancreatic stent insertion for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

Author	Yr	Number of included studies	Type of included studies	PEP rateStent/no stent	PS insertion for preventing PEP
Singh *et al*[33]	2004	5	Full text	*n* = 206/275	Recommended
			Abstract	Total 12/43, *P* = 0.001 Mild to moderate 12/36, *P* = 0.001; Severe 0/7, *P* = 0.15	
Mazaki *et al*[34]	2010	8	Full text	*n* = 336/344	Recommended
			Abstract	Total 19/64, *P* < 0.001; Mild to moderate 19/55, *P* < 0.001; Severe 0/7, *P* < 0.04	
Choudhary *et al*[35]	2011	8	Full text	*n* = 322/334	Recommended
			Abstract	Total 16/66, *P* < 0.00001	
Mazaki *et al*[36]	2014	14	Full text	*n* = 751/781	Recommended
			Abstract	Total 49/133, *P* < 0.001; Mild to moderate 49/120, *P* < 0.001; Severe 0/13, *P* = 0.01	
Shi *et al*[37]	2014	10	Full text	*n* = 561/584; Total 34/117, *P* < 0.001; Mild 24/70, *P* < 0.001; Moderate 6/24, *P* = 0.004; Severe 0/6, *P* = 0.077	Recommended
Fan *et al*[38]	2015	15	Full text	*n* = 1233/1277	Recommended
			Abstract	Total 49/133, *P* < 0.00001; Mild 49/120, *P* < 0.00001; Severe 0/13, *P* < 0.00001	

PS: Pancreatic stent; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis.

compared the occurrence of PEP between 5-Fr, 3 cm long unflanged PSs and 3-Fr, 8 cm or longer unflanged PSs. PEP was less frequent in the 5-Fr, 3 cm stent group than in the 3-Fr, long-stent group [PEP rate: 3-Fr 8 cm 14% (18/133) *vs* 5-Fr 3 cm 9% (11/116), *P* = 0.30]. However, significant differences between these two groups were not observed. Fujisawa *et al*[47] compared PS lengths (unflanged straight stent, 5-Fr at 3 cm *vs* 5-Fr at 5 cm) and reported that the PEP rate and the median time until stent dislodgement were both lower in the 3 cm group than in the 5 cm group (PEP rate: 3 cm 2.0% *vs* 5 cm 8.8%, *P* = 0.035, median period until spontaneous PS dislodgement: 3 cm 2 d *vs* 5 cm 4 d, *P* < 0.001). In this report, earlier stent dislodgement of the 3 cm PS might contribute to preventing PS obstruction-induced PEP. However, Olsson *et al*[45] reported that a PS with a length > 5 cm and a diameter > 5 Fr is the most effective in preventing PEP. In this report, the frequency of PEP was not significantly different between patients who received a PS ≤ 5 cm and patients who received a PS > 5 cm.

These results regarding the influence of PS length on PEP varied, and we propose two explanations for these inconsistencies. Perhaps the diameters of PS were not matched, except for in the second report written by Fujisawa *et al*[47]; although in this report the pancreatic region into which the PS was inserted was not investigated, and only PS length was investigated. Pancreas size differs among people; therefore, both a 3 cm and 5 cm stent can be inserted into the pancreatic head depending on the patient. However, spontaneous dislodgement could contribute to preventing PEP if both a 3 cm and 5 cm PS were inserted in or near to the pancreatic head.

Location in the pancreas of PS insertion

As described in the previous section, the PEP rate was compared between patients who received a PS ≤ 5 cm and patients who received a PS > 5 cm in a report written by Olsson *et al*[45]. In comparison, the PEP rate was not significantly different between the two groups. In patients who received a PS > 5 cm, the stent might reach the pancreatic body or the tail. However, the pancreatic regions into which the stents were inserted were not described.

However, Sugimoto *et al*[48] compared hyperamylasemia and the PEP rate between

Table 3 Comparison of stent type

Author, yr	Stent type	*n*	Results
Flanged or unflanged			
He *et al*[39], 2018	Internal unflanged 5-Fr 3 cm stent with a single pigtail on the duodenal side *vs* internal flanged 5-Fr 3 cm stent with a single pigtail on the duodenal side	138/138	Spontaneous migration was more frequent with the internal unflanged stent (migration at five days: 47.72% *vs* 15.67%, $P < 0.001$, migration at 14 d 84.21% *vs* 42.65%, $P < 0.001$)
Comparison of stent diameter			
Rashdan *et al*[40], 2004	3-4-Fr, 3-8 cm without internal flange *vs* 5-6-Fr, NA, with internal flange	2447/493	The 3-4-Fr stent was more effective in preventing PEP than the 5-6-Fr stent (PEP rate: 3-4-Fr stent 8.7% (213/2447) *vs* 5-6Fr 11.0% (54/493), $P = 0.0471$)
Zolotarevsky *et al*[43], 2011	5-Fr 5 cm *vs* 3-Fr 6 cm	38/40	PEP rates did not differ. 5-Fr PS placement was easier [mean modified 5-point Likert scale[40,41]: 1.8 (5-Fr) *vs* 3.4 (3-Fr), $P < 0.01$)], faster [9.2 (5-Fr) *vs* 11.1 minutes (3-Fr), $P = 0.355$], and required fewer wires [1.5 (5-Fr) *vs* 1.9 (6-Fr), $P = 0.002$]
Pahk *et al*[44], 2011	4-Fr *vs* 5-Fr, both stents were 2 to 11 cm, unflanged	137/209	PEP rates did not differ. Spontaneous migration was more frequent with the 4-Fr stent [95.8% (115/137) *vs* 68.7% (134/209), $P < 0.001$ (by log-rank test)]
Olsson *et al*[45], 2016	≤ 5-Fr, ≤ 5 cm *vs* > 5-Fr, > 5 cm	241 (≤ 5-Fr)/135 (> 5-Fr)	The > 5-Fr, > 5 cm stent was more effective in preventing PEP (> 5-Fr, > 5 cm 1.4% *vs* ≤ 5-Fr, ≤ 5 cm 9.4%, $P = 0.0252$)
Comparison of stent length			
Chahal *et al*[46], 2009	5-Fr 3 cm, unflanged *vs* 3-Fr 8 cm or longer, unflanged	116/133	Spontaneous migration was more frequent with the 5-Fr 3 cm stent (5-Fr 98% *vs* 3-Fr 88%, $P = 0.0001$). Failure of PS placement was observed more often in the longer 3-Fr stent group (5-Fr 0/116 *vs* 3-Fr 11/133, $P = 0.0003$). PEP rates did not differ
Fujisawa *et al*[47], 2016	5-Fr 3 cm *vs* 5-Fr 5 cm, both stents were unflanged and straight	98/102	The 5-Fr 3 cm stent was more efficient for preventing PEP (3 cm 2.0% *vs* 5 cm 8.8%, $P = 0.035$). The period until spontaneous dislodgement was significantly shorter for the 3 cm stent than for the 5 cm stent (3 cm 2 d *vs* 5 cm 4 d, $P < 0.001$)
Part of the pancreas in which the stent was inserted			
Sugimoto *et al*[48], 2018	Pancreatic head *vs* pancreatic body or tail	131/16	After ERCP, the level of the pancreatic isozyme of serum amylase was higher in the head group than in the body/tail group [head group 138.5 (7.0-2086) IU/L *vs* body/tail group 78.5 (5.0-1266.5) IU/L, $P < 0.03$]

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post-ERCP pancreatitis.

patients who had a PS inserted into the pancreatic head (the head group) and patients who had a PS inserted into the pancreatic body or tail (the body/tail group). Although a significant difference was not observed, the PEP rate was lower in the body/tail group than in the head group [0% (0/16) *vs* 9.2% (12/131), $P = 0.363$]; PEP was not observed in the body/tail group. Furthermore, after ERCP, the level of the pancreatic isozyme of serum amylase was significantly higher in the head group than in the body/tail group [138.5 (7.0-2086) IU/L *vs* 78.5 (5.0-1266.5) IU/L, $P = 0.03$]. Proteinase activation, which exacerbates pancreatitis, is induced by difficult pancreatic duct drainage[49]; therefore, stent placement up to the pancreatic body or tail contributes to greater pancreatic drainage than stent placement in the pancreatic

head does.

CONCLUSION

The results of several RCTs and meta-analyses have revealed that PS is efficient for preventing PEP. However, PEP can occur in patients who underwent stent placement. Currently, the main argument is which PS should be used. Additional endoscopic insertion to remove the PS could be avoided by using an internal unflanged PS. The diameter of PS is controversial because thin stents easily migrate, and thick stents are easily inserted in some cases. With respect to the length of the stent, a 3 cm stent may be more efficient than a 5 cm stent in preventing PEP. However, the risk of PEP may be altered according to the pancreatic region into which the PS is inserted.

Overall, there remain few cases in which a prophylactic PS was utilized; therefore, the accumulation of additional cases is necessary.

REFERENCES

1 **Bergman JJ**, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, Tytgat GN, Huibregtse K. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bileduct stones. *Lancet* 1997; **349**: 1124-1129 [PMID: 9113010 DOI: 10.1016/s0140-6736(96)11026-6]

2 **Howard TJ**, Tan T, Lehman GA, Sherman S, Madura JA, Fogel E, Swack ML, Kopecky KK. Classification and management of perforations complicating endoscopic sphincterotomy. *Surgery* 1999; **126**: 658-63; discussion 664-5 [PMID: 10520912 DOI: 10.1016/S0039-6060(99)70119-4]

3 **Stapfer M**, Selby RR, Stain SC, Katkhouda N, Parekh D, Jabbour N, Garry D. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. *Ann Surg* 2000; **232**: 191-198 [PMID: 10903596 DOI: 10.1097/00000658-200008000-00007]

4 **Baron TH**, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *Am J Gastroenterol* 2004; **99**: 1455-1460 [PMID: 15307859 DOI: 10.1111/j.1572-0241.2004.30151.x]

5 **Reiertsen O**, Skjøtø J, Jacobsen CD, Rosseland AR. Complications of fiberoptic gastrointestinal endoscopy--five years' experience in a central hospital. *Endoscopy* 1987; **19**: 1-6 [PMID: 3493897 DOI: 10.1055/s-2007-1013011]

6 **Sherman S**, Hawes RH, Rathgaber SW, Uzer MF, Smith MT, Khusro QE, Silverman WB, Earle DT, Lehman GA. Post-ERCP pancreatitis: randomized, prospective study comparing a low- and high-osmolality contrast agent. *Gastrointest Endosc* 1994; **40**: 422-427 [PMID: 7926531 DOI: 10.1016/S0016-5107(94)70204-7]

7 **Johnson GK**, Geenen JE, Bedford RA, Johanson J, Cass O, Sherman S, Hogan WJ, Ryan M, Silverman W, Edmundowicz S. A comparison of nonionic versus ionic contrast media: results of a prospective, multicenter study. Midwest Pancreaticobiliary Study Group. *Gastrointest Endosc* 1995; **42**: 312-316 [PMID: 8536898 DOI: 10.1016/S0016-5107(95)70128-1]

8 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/nejm199609263351301]

9 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10 [PMID: 9684657 DOI: 10.1016/S0016-5107(98)70121-X]

10 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]

11 **Glomsaker T**, Hoff G, Kvaløy JT, Søreide K, Aabakken L, Søreide JA; Norwegian Gastronet ERCP Group. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. *Br J Surg* 2013; **100**: 373-380 [PMID: 23225493 DOI: 10.1002/bjs.8992]

12 **Katsinelos P**, Lazaraki G, Chatzimavroudis G, Gkagkalis S, Vasiliadis I, Papaeuthimiou A, Terzoudis S, Pilpilidis I, Zavos C, Kountouras J. Risk factors for therapeutic ERCP-related complications: an analysis of 2,715 cases performed by a single endoscopist. *Ann Gastroenterol* 2014; **27**: 65-72 [PMID: 24714755 DOI: 10.1097/SLE.0000000000000012]

13 **Chen JJ**, Wang XM, Liu XQ, Li W, Dong M, Suo ZW, Ding P, Li Y. Risk factors for post-ERCP pancreatitis: a systematic review of clinical trials with a large sample size in the past 10 years. *Eur J Med Res* 2014; **19**: 26 [PMID: 24886445 DOI: 10.1186/2047-783X-19-26]

14 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88 [PMID: 19286178 DOI: 10.1016/j.gie.2008.10.039]

15 **Leghari A**, Ghazanfar S, Qureshi S, Taj MA, Niaz SK, Quraishy MS. Frequency and risk factors in the post-ERCP pancreatitis in a tertiary care centre. *J Coll Physicians Surg Pak* 2013; **23**: 620-624 [PMID: 24034184 DOI: 09.2013/JCPSP.620624]

16 **Liu Y**, Su P, Lin S, Xiao K, Chen P, An S, Zhi F, Bai Y. Endoscopic papillary balloon dilatation versus endoscopic sphincterotomy in the treatment for choledocholithiasis: a meta-analysis. *J Gastroenterol Hepatol* 2012; **27**: 464-471 [PMID: 21913984 DOI: 10.1111/j.1440-1746.2011.06912.x]

17 **Masci E**, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy* 2003; **35**: 830-834 [PMID: 14551860 DOI: 10.1055/s-2003-42614]

18 **Weinberg BM**, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. *Cochrane Database Syst Rev* 2006; CD004890 [PMID:

17054222 DOI: 10.1002/14651858.CD004890.pub2]
19 **Zhao HC**, He L, Zhou DC, Geng XP, Pan FM. Meta-analysis comparison of endoscopic papillary balloon dilatation and endoscopic sphincteropapillotomy. *World J Gastroenterol* 2013; **19**: 3883-3891 [PMID: 23840129 DOI: 10.3748/wjg.v19.i24.3883]
20 **Freeman ML**. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 1354-1365 [PMID: 17981248 DOI: 10.1016/j.cgh.2007.09.007]
21 **Smithline A**, Silverman W, Rogers D, Nisi R, Wiersema M, Jamidar P, Hawes R, Lehman G. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. *Gastrointest Endosc* 1993; **39**: 652-657 [PMID: 8224687 DOI: 10.1016/S0016-5107(93)70217-5]
22 **Tarnasky PR**, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **115**: 1518-1524 [PMID: 9834280 DOI: 10.1016/S0016-5085(98)70031-9]
23 **Fazel A**, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. *Gastrointest Endosc* 2003; **57**: 291-294 [PMID: 12612504 DOI: 10.1067/mge.2003.124]
24 **Sofuni A**, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, Toyota M, Fujii T, Harada Y, Takada T. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol* 2007; **5**: 1339-1346 [PMID: 17981247 DOI: 10.1016/j.cgh.2007.07.008]
25 **Tsuchiya T**, Itoi T, Sofuni A, Itokawa F, Kurihara T, Ishii K, Tsuji S, Kawai T, Moriyasu F. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. *J Hepatobiliary Pancreat Surg* 2007; **14**: 302-307 [PMID: 17520207 DOI: 10.1007/s00534-006-1147-8]
26 **Ito K**, Fujita N, Noda Y, Kobayashi G, Obana T, Horaguchi J, Takasawa O, Koshita S, Kanno Y, Ogawa T. Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial. *J Gastroenterol* 2010; **45**: 1183-1191 [PMID: 20607310 DOI: 10.1007/s00535-010-0268-7]
27 **Pan XP**, Dang T, Meng XM, Xue KC, Chang ZH, Zhang YP. Clinical study on the prevention of post-ERCP pancreatitis by pancreatic duct stenting. *Cell Biochem Biophys* 2011; **61**: 473-479 [PMID: 21739262 DOI: 10.1007/s12013-011-9230-4]
28 **Sofuni A**, Maguchi H, Mukai T, Kawakami H, Irisawa A, Kubota K, Okaniwa S, Kikuyama M, Kutsumi H, Hanada K, Ueki T, Itoi T. Endoscopic pancreatic duct stents reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. *Clin Gastroenterol Hepatol* 2011; **9**: 851-8; quiz e110 [PMID: 21749851 DOI: 10.1016/j.cgh.2011.06.033]
29 **Kawaguchi Y**, Ogawa M, Omata F, Ito H, Shimosegawa T, Mine T. Randomized controlled trial of pancreatic stenting to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. *World J Gastroenterol* 2012; **18**: 1635-1641 [PMID: 22529693 DOI: 10.3748/wjg.v18.i14.1635]
30 **Lee TH**, Moon JH, Choi HJ, Han SH, Cheon YK, Cho YD, Park SH, Kim SJ. Prophylactic temporary 3F pancreatic duct stent to prevent post-ERCP pancreatitis in patients with a difficult biliary cannulation: a multicenter, prospective, randomized study. *Gastrointest Endosc* 2012; **76**: 578-585 [PMID: 22771100 DOI: 10.1016/j.gie.2012.05.001]
31 **Yin HK**, Wu HE, Li QX, Wang W, Ou WL, Xia HH. Pancreatic Stenting Reduces Post-ERCP Pancreatitis and Biliary Sepsis in High-Risk Patients: A Randomized, Controlled Study. *Gastroenterol Res Pract* 2016; **2016**: 9687052 [PMID: 27057161 DOI: 10.1155/2016/9687052]
32 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370 [PMID: 16111953 DOI: 10.1016/j.gie.2005.04.020]
33 **Singh P**, Das A, Isenberg G, Wong RC, Sivak MV, Agrawal D, Chak A. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc* 2004; **60**: 544-550 [PMID: 15472676 DOI: 10.1016/S0016-5107(04)02013-9]
34 **Mazaki T**, Masuda H, Takayama T. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. *Endoscopy* 2010; **42**: 842-853 [PMID: 20886403 DOI: 10.1055/s-0030-1255781]
35 **Choudhary A**, Bechtold ML, Arif M, Szary NM, Puli SR, Othman MO, Pais WP, Antillon MR, Roy PK. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. *Gastrointest Endosc* 2011; **73**: 275-282 [PMID: 21295641 DOI: 10.1016/j.gie.2010.10.039]
36 **Mazaki T**, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. *J Gastroenterol* 2014; **49**: 343-355 [PMID: 23612857 DOI: 10.1007/s00535-013-0806-1]
37 **Shi QQ**, Ning XY, Zhan LL, Tang GD, Lv XP. Placement of prophylactic pancreatic stents to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a meta-analysis. *World J Gastroenterol* 2014; **20**: 7040-7048 [PMID: 24944500 DOI: 10.3748/wjg.v20.i22.7040]
38 **Fan JH**, Qian JB, Wang YM, Shi RH, Zhao CJ. Updated meta-analysis of pancreatic stent placement in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastroenterol* 2015; **21**: 7577-7583 [PMID: 26140006 DOI: 10.3748/wjg.v21.i24.7577]
39 **He Q**, Wang L, Peng C, Zou X, Zhan Q, Xu Y, Liu Q, Qian J, Gong L, Shen Y, Chen J. Modified prophylactic 5-fr pancreatic duct stent enhances the rate of spontaneous dislodgement: A multicenter randomized controlled trial. *United European Gastroenterol J* 2018; **6**: 1519-1526 [PMID: 30574322 DOI: 10.1177/2050640618804729]
40 **Rashdan A**, Fogel EL, McHenry L, Sherman S, Temkit M, Lehman GA. Improved stent characteristics for prophylaxis of post-ERCP pancreatitis. *Clin Gastroenterol Hepatol* 2004; **2**: 322-329 [PMID: 15067627 DOI: 10.1016/S1542-3565(04)00062-X]
41 **Komorita SS**. Attitude Content, Intensity, And The Neutral Point On A Likert Scale. *J Soc Psychol* 1963; **61**: 327-334 [PMID: 14084811 DOI: 10.1080/00224545.1963.9919489]
42 **Likert R**. A technique for the measurement of attitudes. *Archives of psychology* 1932; **140**: 5-55
43 **Zolotarevsky E**, Fehmi SM, Anderson MA, Schoenfeld PS, Elmunzer BJ, Kwon RS, Piraka CR, Wamsteker EJ, Scheiman JM, Korsnes SJ, Normolle DP, Kim HM, Elta GH. Prophylactic 5-Fr pancreatic duct stents are superior to 3-Fr stents: a randomized controlled trial. *Endoscopy* 2011; **43**: 325-330 [PMID: 21455872 DOI: 10.1055/s-0030-1256305]

44 **Pahk A**, Rigaux J, Poreddy V, Smith J, Al-Kawas F. Prophylactic pancreatic stents: does size matter? A comparison of 4-Fr and 5-Fr stents in reference to post-ERCP pancreatitis and migration rate. *Dig Dis Sci* 2011; **56**: 3058-3064 [PMID: 21487771 DOI: 10.1007/s10620-011-1695-x]

45 **Olsson G**, Lübbe J, Arnelo U, Jonas E, Törnqvist B, Lundell L, Enochsson L. The impact of prophylactic pancreatic stenting on post-ERCP pancreatitis: A nationwide, register-based study. *United European Gastroenterol J* 2017; **5**: 111-118 [PMID: 28405329 DOI: 10.1177/2050640616645434]

46 **Chahal P**, Tarnasky PR, Petersen BT, Topazian MD, Levy MJ, Gostout CJ, Baron TH. Short 5Fr vs long 3Fr pancreatic stents in patients at risk for post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2009; **7**: 834-839 [PMID: 19447196 DOI: 10.1016/j.cgh.2009.05.002]

47 **Fujisawa T**, Kagawa K, Ochiai K, Hisatomi K, Kubota K, Sato H, Nakajima A, Matsuhashi N. Prophylactic Efficacy of 3- or 5-cm Pancreatic Stents for Preventing Post-ERCP Pancreatitis: A Prospective, Randomized Trial. *J Clin Gastroenterol* 2016; **50**: e30-e34 [PMID: 26280707 DOI: 10.1097/MCG.0000000000000397]

48 **Sugimoto M**, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Waragai Y, Takasumi M, Hikichi T, Ohira H. Pancreatic stents for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis should be inserted up to the pancreatic body or tail. *World J Gastroenterol* 2018; **24**: 2392-2399 [PMID: 29904246 DOI: 10.3748/wjg.v24.i22.2392]

49 **Kingsnorth A**. Role of cytokines and their inhibitors in acute pancreatitis. *Gut* 1997; **40**: 1-4 [PMID: 9155566 DOI: 10.1136/gut.40.1.1]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 269-289

DOI: 10.13105/wjma.v7.i6.269

ISSN 2308-3840 (online)

SYSTEMATIC REVIEW

Significance of multivisceral resections in oncologic surgery: A systematic review of the literature

Giorgi Nadiradze, Can Yurttas, Alfred Königsrainer, Philipp Horvath

ORCID number: Giorgi Nadiradze (0000-0001-6374-8778); Can Yurttas (0000-0001-9720-8243); Alfred Koenigsrainer (0000-0002-2301-4080); Philipp Horvath (0000-0002-2008-3267).

Author contributions: Nadiradze G and Yurttas C contributed equally to this work. Königsrainer A initiated the study and approved the final version of the manuscript; Nadiradze G and Yurttas C participated in developing the manuscript and approved the final version of the manuscript. Horvath P led the literature research, abstracted and analyzed the data and developed the manuscript.

Conflict-of-interest statement: We declare that we have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared according to the PRISMA 2009 checklist.

Giorgi Nadiradze, Can Yurttas, Alfred Königsrainer, Philipp Horvath, Department of General, Visceral and Transplant Surgery, University of Tübingen, Comprehensive Cancer Center, Tübingen 72076, Germany

Philipp Horvath, National Center for Pleura and Peritoneum, Tübingen 72076, Germany

Corresponding author: Philipp Horvath, MD, Surgeon, Surgical Oncologist, Department of General, Visceral and Transplant Surgery, University of Tübingen, Comprehensive Cancer Center, Hoppe-Seyler-Strasse 3, Tübingen 72076, Germany. philipp.horvath@med.uni-tuebingen.de
Telephone: +49-7071-2986620
Fax: +49-7071-295588

Abstract

BACKGROUND

Multivisceral resections (MVR) are often necessary to reach clear resections margins but are associated with relevant morbidity and mortality. Factors associated with favorable oncologic outcomes and elevated morbidity rates are not clearly defined.

AIM

To systematically review the literature on oncologic long-term outcomes and morbidity and mortality in cancer surgery a systematic review of the literature was performed.

METHODS

PubMed was searched for relevant articles (published from 2000 to 2018). Retrieved abstracts were independently screened for relevance and data were extracted from selected studies by two researchers.

RESULTS

Included were 37 studies with 3112 patients receiving MVR for colorectal cancer (1095 for colon cancer, 1357 for rectal cancer, and in 660 patients origin was not specified). The most common resected organs were the small intestine, bladder and reproductive organs. Median postoperative morbidity rate was 37.9% (range: 7% to 76.6%) and median postoperative mortality rate was 1.3% (range: 0% to 10%). The median conversion rate for laparoscopic MVR was 7.9% (range: 4.5% to 33%). The median blood loss was lower after laparoscopic MVR compared to the open approach (60 mL *vs* 638 mL). Lymph-node harvest after laparoscopic MVR was comparable. Report on survival rates was heterogeneous, but the 5-year overall-survival rate ranged from 36.7% to 90%, being worst in recurrent rectal

Manuscript source: Invited manuscript

Received: March 20, 2019
Peer-review started: March 20, 2019
First decision: May 16, 2019
Revised: June 7, 2019
Accepted: June 16, 2019
Article in press: June 17, 2019
Published online: June 30, 2019

P-Reviewer: Kitai C
S-Editor: Dou Y
L-Editor: A
E-Editor: Ma YJ

cancer patients with a median 5-year overall survival of 23%. R0 -resection, primary disease setting and no lymph-node or lymphovascular involvement were the strongest predictors for long-term survival. The presence of true malignant adhesions was not exclusively associated with poorer prognosis. Included were 16 studies with 1.600 patients receiving MVR for gastric cancer. The rate of morbidity ranged from 11.8% to 59.8%, and the main postoperative complications were pancreatic fistulas and pancreatitis, anastomotic leakage, cardiopulmonary events and post-operative bleedings. Total mortality was between 0% and 13.6% with an R0 -resection achieved in 38.4% to 100% of patients. Patients after R0 resection had 5-year overall survival rates of 24.1% to 37.8%.

CONCLUSION
MVR provides, in a selected subset of patients, the possibility for good long-term results with acceptable morbidity rates. Unlikelihood of achieving R0 -status, lymphovascular- and lymph -node involvement, recurrent disease setting and the presence of metastatic disease should be regarded as relative contraindications for MVR.

Key words: Colorectal cancer; Gastric cancer; Primary; Recurrent; Multivisceral resection; Hyperthermic intraperitoneal chemotherapy; Morbidity

Core tip: Multivisceral resections constitute a huge challenge for an interdisciplinary team. Proper patient selection, combined perioperative systemic treatment and en-bloc resection of adherent organs can provide acceptable morbidity-, mortality- and long-term survival rates.

Citation: Nadiradze G, Yurttas C, Königsrainer A, Horvath P. Significance of multivisceral resections in oncologic surgery: A systematic review of the literature. *World J Meta-Anal* 2019; 7(6): 269-289
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/269.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.269

INTRODUCTION

Patients with locally advanced primary and recurrent cancers constitute a challenge for the interdisciplinary treatment team because the only chance for cure and prolonged survival is complete resection of the tumor with clear margins. Invasion of adjacent organs occurs in 10%-20% of patients suffering from colorectal cancer and gastric cancer. The prerequisite for long- and short-term results is completeness of surgical resection. This aggressive surgical concept is accompanied by pre- and postoperative systemic treatment schedules, consisting of chemotherapy, radiotherapy and chemoradiotherapy. Due to the lack of sufficient and reliable preoperative data the decision in favor of multivisceral resections (MVR) is often made intraoperatively. MVR is defined as the *en-bloc* resection of the tumor and the adjacent organs including reproductive organs and organs of the urinary tract. MVR should therefore always be taken into account if macroscopic complete resection is achievable. Adherence of the primary or recurrent tumor to adjacent structures does not necessarily predict true malignant invasion. Winter *et al*[1] stated that up to two-third of cases are postoperatively classified as inflammatory adhesions rather than true malignant invasion. Furthermore, lysis of adhesions or separation of the adjacent organ from the tumor dramatically increases the risk of recurrence and should be avoided. The significance of palliative MVR for patients with obstruction, fistula and pain is not clearly defined but the data presented in this review suggest that non-curative MVR does not improve patient outcome. Leijssen *et al*[2] showed that patients with a T4 -tumor not undergoing MVR had a poorer outcome regarding overall-, disease-free-, and cancer-specific survival. The indication in favor of MVR for patients with metastatic disease is also common in the current literature but the true benefit of MVR for stage IV disease is unclear.

This review aims to systematically evaluate the current literature on outcomes following MVR for colorectal and gastric cancer and for patients undergoing MVR and HIPEC for peritoneal metastasis of gastrointestinal, especially colorectal, origin.

MATERIALS AND METHODS

A systematic review was conducted with reference to the PRISMA statement and the current methodological literature[3,4]. Electronic medical literature databases were screened for appropriate publications from 2000 to 2018. Databases were searched using the following terms: "multivisceral" AND "colon cancer", "multivisceral" AND "rectal cancer", "multivisceral" AND "gastric cancer", "multivisceral AND "cytoreductive surgery", and "multivisceral" AND "hyperthermic intraperitoneal chemotherapy". Comments and case reports were excluded. Furthermore, publications that did not report performance of MVR, morbidity and mortality rates, oncologic outcome and publications that included unspecified cancer types were also not included in this systematic review.

For the search terms "multivisceral" AND "colon cancer" and "multivisceral" AND "rectal cancer" 211 records were provided. After the abstracts were screened (level 1 screening) independently by two reviewers 165 publications excluded (Figure 1).

For the search terms "multivisceral" AND "gastric cancer" 93 records were provided. After the abstracts were screened (level 1 screening) independently by two reviewers 71 publications excluded.

After level 2 screening, 37 publications for "Multivisceral resection for colon cancer and rectal cancer", 16 publications for "Multivisceral resection for gastric cancer and 3 publications for "Multivisceral resections with hyperthermic intraperitoneal chemotherapy" were included.

MVR were defined as resection of more than two organs.

RESULTS

MVR for colon cancer and rectal cancer (n = 37).

Study design

After full-text screening 37 studies were selected that met the inclusion criteria. Of these 37 included studies, 36 were retrospective.

Demographics

In total 3112 patients underwent MVR for colon and rectal cancer (1095 for colon cancer, 1357 for rectal cancer and in 660 patient's origin of primary tumor was not specified (Table 1). Of the 36 studies ten included patients with recurrent colon and rectal cancer. The remainder dealt only with primary colon and rectal cancer. Included studies were published after 1999 to the present time and all but one was retrospective. In total five publications presented patient- and treatment-related data after minimally-invasive MVR. The decision for or against suspected MVR, according to preoperative imaging modalities like CT, MRI, EUS and PET-CT, was made intraoperatively. Every verified adhesion of the primary tumor to adjacent structures was classified as a cT4b -situation. All but seven publications did not report the true pT4b -rate. There were 17 studies that included patient with Stage IV disease. Another seven studies did not specify whether or not patients with metastatic disease were included.

Pathological features

In the event of adhesion of adjacent structures to the primary tumor, these adhesions should definitely not be separated intraoperatively. For the surgeon it is not possible to distinguish between inflammatory and malignant adhesions. Hunter *et al*[5] showed that patients with adherent colon cancer and lysis of adhesion, had a local recurrence rate of 69% and a 5-year overall survival rate of only 23%. Of the included studies, 30 publications report the histopathologically confirmed malignant invasion rate. The true pT4b -rate varied from 23% to 77%. Three publications performed multivariate analysis in order to determine whether true malignant invasion into adjacent structures is of predictive value for overall- and progression-free survival[6-8]. Rosander *et al*[7] and Lehnert *et al*[8] did not find malignant invasion to be a predictive factor in multivariate analysis. Rosander *et al*[7] found female sex, adjuvant chemotherapy, low tumor stage and R0-resection to be associated with better overall survival. On the other hand, Lehnert *et al*[8] found intraoperative blood loss, age older

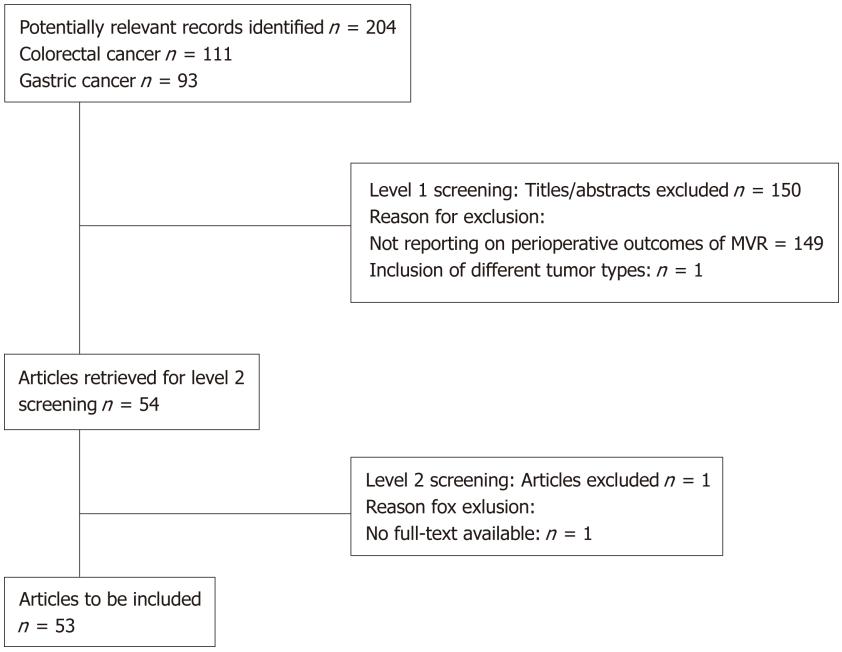

Figure 1 Preferred reporting items for systematic reviews and meta-analyses diagram.

than 64 years and UICC stage to be predictive. Contrary to the aforementioned results Chen *et al*[6] found adhesion pattern (inflammatory *vs* malignant) to be highly significantly associated with reduced overall survival for both, colon and rectal cancer patients.

Concerning resection status, 27 studies report R0 rates, ranging from 65% to 100%. In the vast majority of publications R0 *vs* R1 -status was of significant prognostic impact (Table 2). Data show a trend towards decreased R0 -rates in patients undergoing MVR for recurrent cancers, especially rectal cancer. Nielsen *et al*[9], Rottoli *et al*[10] and Vermaas *et al*[11] reported resection status in primary and recurrent rectal cancers and showed decreased R0 -rates for recurrent rectal cancer without being statistically significant (66% *vs* 38%; 71% *vs* 56% and 82% *vs* 58%).

Morbidity and mortality

There was heterogeneity in reporting total complication rate, degree of complications and specification of different complications, so that the focus was set on complications, which were reported in the vast majority of publications. The postoperative morbidity rates ranged from 7%[12] to 76.6%[13]. Only one study reported that the occurrence of perioperative complications was an independent predictor of shorter overall survival (HR 3.53)[14].

Anastomotic insufficiency: Twelve studies did not report occurrence of anastomotic insufficiency (AI). The remainder reported AI-rates ranging from 0.8%[15] to 19%[16]. There was no structured report on management of AI in the studies included.

Surgical site infection: Surgical site infections (SSI) were one of the most common complications ranging from 2.5%[15] to 53%[13]. The differentiation into superficial and deep SSI was inconsistently used in the studies included. Kumamoto *et al*[15] reported the lowest rate of SSI including 118 patients undergoing minimally-invasive MVR. The other studies, looking at minimal-invasive MVR, reported SSI -rates ranging from 12%-17%. The study by Kim *et al*[17] found no statistically significant difference in the occurrence of SSI between the open and the minimally-invasive group.

Intraabdominal abscess: Intraabdominal abscess (IAA) formation was not reported in 17 studies. The remainder reported IAA rates ranging from 1%[18] to 21%[19]. Documentation of IAA management was again inconsistently reported in the included studies.

Re-operation: The rate of necessary surgical re-intervention was again not reported in 17 studies. In the remaining studies the re-operation rate ranged from 0%[14] to 20%[19].

Mortality: In total 15 studies reported mortality rates of 0% and the median mortality rate was 1.3%. The highest reported perioperative mortality rate, namely 10% was

Table 1 Patient demographics

Study/Yr	*n*	Disease	Site
Cukier *et al*[24], 2012	33	Primary	Colon
Hallet *et al*[20], 2014	15	Recurrent	Colon
Kumamoto *et al*[15], 2017	118	Primary	Colon
Leijssen *et al*[2], 2018	103	Primary	Colon
López-Cano *et al*[49], 2010	113	Primary	Colon
Rosander *et al*[7], 2018	121	Primary	Colon
Takahashi *et al*[12], 2017	84	Primary	Colon
Tei *et al*[23], 2018	29	Primary	Colon
Chen *et al*[6], 2011	287; Colon (152); Rectum (135)	Primary recurrent	Colorectal
Eveno *et al*[58], 2014	152; Colon (81); Rectum (71)	Primary	Colorectal
Fujisawa *et al*[29], 2002	35; Colon (19); Rectum (17)	Primary recurrent	Colorectal
Hoffmann *et al*[21], 2012	78; Colon (52); Rectum (26)	Primary	Colorectal
Gezen *et al*[18], 2012	90; Colon (43); Rectum (47)	Primary	Colorectal
Kim *et al*[17], 2012	54; Colon (32); Rectum (22)	Primary	Colorectal
Laurence *et al*[56], 2017	660; Colon/Rectum not specified	Primary	Colorectal
Lehnert *et al*[8], 2002	201; Colon (139); Rectum (62)	Primary	Colorectal
Li *et al*[16], 2011	72; Colon (28); Rectum (44)	Primary	Colorectal
Park *et al*[53], 2011	54; Colon (23); Rectum (31)	Primary	Colorectal
Rizzuto *et al*[57], 2016	22; Colon (16); Rectum (6)	Primary	Colorectal
Winter *et al*[1], 2007	63; Colon (46); Rectum (17)	Primary	Colorectal
Bannura *et al*[55], 2006	30	Primary	Rectal
Crawshaw *et al*[25], 2015	61	Primary recurrent	Rectal
Derici *et al*[48], 2008	57	Primary	Rectal
Dinaux *et al*[50], 2018	29	Primary	Rectal
Dosokey *et al*[30], 2017	34	Primary	Rectal
Gannon *et al*[28], 2007	72	Primary recurrent	Rectal
Harris *et al*[19], 2011	42	Primary	Rectal
Ishiguro *et al*[54], 2009	93	Primary	Rectal
Mañas *et al*[13], 2014	30	Primary	Rectal
Nielsen *et al*[9], 2012	90	Primary recurrent	Rectal
Pellino *et al*[14], 2018	82	Primary	Rectal
Rottoli *et al*[10], 2017	46	Primary recurrent	Rectal
Sanfilippo *et al*[51], 2001	32	Primary	Rectal
Shin *et al*[22], 2016	22	Primary	Rectal
Smith *et al*[47], 2012	124	Primary	Rectal
Vermaas *et al*[11], 2007	35	Primary recurrent	Rectal

reported in the study by Manas *et al*[13].

Long-term outcomes

Table 3 shows overall (OS)- and disease-free survival (DFS) rates and depicts factors associated with decreased OS and DFS after MVR for rectal and colon cancers. 5-year OS rate ranged from 36.7%[13] to 90%[20], but the proportion of included patients with metastatic disease differed between those two studies (20% *vs* 0%).

Local and distant recurrences: The local control rate expressed by the local recurrence rate were reported in 27 publications and ranged from 1.8% to 66.7%[15]. The aforementioned study and Rosander *et al*[7] showed higher rates of local recurrences after R1 -resection. Distant recurrence rates varied from 10.9%[2] to 45.5%[17]. Patients with metastatic disease, receiving MVR, were also included in the vast majority of publications and the rate of patients with Stage-IV disease varied from 0% to 49%[21].

Operative approach

Laparoscopic *vs* open surgery: Five publications focused on the perioperative und long-term results of minimally-invasive (laparoscopic and/or robotic) MVR (Table 4).

Table 2 Patient- and treatment- associated parameters after multivisceral resection for colon and rectal cancers

Study	Resection margin (R0 *vs* R1)	Local and distant recurrence	Most common resected organs	Lymph node involvement	Age	Blood loss(mL)	Pre-operative (Chemo)-radiation	Complica-tions (AI;SSI;IAA) (Re-OP)	Prognostic factors/con-clusions
Cukier *et al*[24]	R0: 100%	LR: 6%; DR: 18%	Small bowel (56%); Bladder/ Ureter (54%)	N0: 79% N1: 21%	64	NR	RCTX:100%	6%; 18%; NR (9%)	No statistical difference in terms of disease-free survival when analyzing subgroups stratified by nodal-status ypN0 *vs* ypN1: (P = 0.29)
Hallet *et al*[20]	R0: 87%	LR: 13%; DR: 13%	Colon (87%) Small bowel (47%) Bladder (40%)	N0: 70% N1: 30%	60.2	1500	RCTX:100%	NR	Neoadjuvant RCTX for recurrent colon cancer is feasible; no addition of toxicity (radiation plus MVR)
Kumamoto *et al*[15]	R0: 95%	LR: R0: 1.8% R1: 66.7%; DR: NR	Small bowel (14%) Bladder (12%) Colorectum (11%)	N0: 62% N1: 28% N2: 10%	64	48	CTX: 4.4%	(0.8%; 2.5%; 0.8%) (0%)	R1-resection and N+ status predictors of poor prognosis Laparoscopic approach: Feasible, low conversion, low R1-rate
Leijssen *et al*[2]	R0: 89%	LR: 14.5%; DR: 10.9%	Small intestine (31%); Reproductive organs (9%); Bladder (7%)	NR	69	NR	NR	(1.8%; 3.6%; NR) (2%)	Patients with T4-cancer not undergoing MVR had a significantly poorer outcome regarding overall-, disease-free and cancer-specific survival
López-Cano *et al*[49]	R0: 85%	LR: 23%; DR: 19%	Small intestine (42%) Oophorec-tomy (28%) Bladder (19%)	N0: 35% N1: 32% N2: 34%	71	NR	0%	(NR; 10%; NR) (8%)	Poorly differentiated tumors and stage IV were associated with a poor survival; significant predictors of disease progression: Venous invasion (RR 2.34) and four or more positive lymph nodes (RR 3.99)

Rosander *et al*[7]	R0: 93%	LR: R0: 7% R1: 33% DR: 14%	Bowel (45%) Ovaries (24%) Bladder (partial/total) : 22%/19% Uterus/Vagina (17%)	N0: 71% N1: 19% N2: 10%	67	NR	CTX: 27% RT: 1% RCTX: 5%	(8%; 7%; 7%) (14%)	Female sex, low tumor stage, and adjuvant CTX, and N - but not tumor infiltration per se, were independently associated with better overall survival
Takahashi *et al*[12]	R0: 96%	LR: 2%	Bowel (38%); Uterus/Ovari-es (5%); Bladder (11%)	NR	68.5- 71.5	Lap. completion: 50; Conversion: 366; Lap overall: 57.5; open: 321	CTX: open: 25% lap: 6%	(4%; NR; NR) (NR)	Overall- and disease-free survival (multivariate) was shorter in the males; operative approach did not affect overall- and disease-free survival
Tei *et al*[23]	R0: 93%-100%	LR: NR; DR: 24%	Small intestine (38%); Bladder (17%); Ovaries (14%)	N0: 48% N1: 24% N2: 28%	70	60-220	NR	(3%; 17%; 10%) (3%)	S-MVR and M-MVR do not differ significantly in terms of blood loss, operative time and number of harvested lymph nodes. No difference in occurrence of complications
Chen *et al*[6]	NR	NR	Colon cancer: small bowel (40%); Rectal cancer: Bladder (36%)	NR	NR	NR	NR	NR	Multivariate analysis showed that adhesion pattern was independently associated with overall survival among both colon (P = 0.00001) and rectal (P = 0.0002) cancer patients
Eveno *et al*[58]	R0: 90%	NR	Vagina (25%); Small bowel (23%); Bladder (20%); Ovaries/Uterus (each 19%)	N0: 55% N1: 25% N2: 19%	63	NR	RT: 8%; CT: 2%; RCTX: 27%	(3%, 4%; NR) (9%)	Patients with resection of multiple organs had a better survival rate than patients with single organ resection (P = 0.0469)
Fujisawa *et al*[29]	NR	NR	Bladder (partial/total) : 54%/34%	NR	59	NR	0%	NR	Complication rate was higher in pat; undergoing cystectomy *vs* partial cystectomy (58.3% *vs* 10.5%)

Hoffmann *et al*[21]	R0: 95%	LR: 2%	53%: 1 add. Organ 27%: 2 add; organs	NR	69	NR	RCTX (rectal): 35%	(9%; 9%; NR) (19%)	No significant differences in overall survial: Colon *vs* rectal cancer (P = 0839); lap *vs* open (P = 0.610); emergency *vs* planned (P = 0.674), pN0 *vs* pN1 (P = 0.658)
Gezen *et al*[18]	R0: 91%	NR	Ovaries: 27%; Bladder: 26%; Small bowel: 21%; Uterus: 19%	NR	59	450 (non-MVR: 250)	NR	(2%; 3%; 1%) (2%)	MVR do not alter the rates of sphincter-saving procedures, morbidity and 30-d mortality
Kim *et al*[17]	R0: 71%	LR: 7.7% (lap) and 27.3% (open) P = 0.144) DR: 15.4% (lap) *vs* 45.5% (open) P = 0.091)	Small bowel: 10%; Bladder: 10%; Seminal vesicle: 13%; Prostate: 6%	NR	68	lap: 269; open: 638	RCTX: 50% of rectal cancer patients	(12%; 8%; NR) (NR)	No adverse long-term oncologic outcomes of laparoscopic MVR were observed
Laurence *et al*[56]	NR	NR	NR	NR	64	NR	RT: 62%	NR	Female gender, tumor grade 2, MVR were significant protective factors of mortality
Lehnert *et al*[8]	R0: 65% R1: 9% R2: 26%	LR: 7% DR: 13% Both: 4%	Small bowel: 29%; Bladder: 24%; Uterus: 13%	NR	64	< 1000 mL: 37%; 1000-2000 mL: 13%; > 2000 mL: 10%	RT/CT/RCTX: 40% of R0 resected patients	(5%; 9%; 1%)	Intraoperative blood loss, age older than 64 and UICC stage but not histologic tumor infiltration *vs* inflammation were prognostic factors
Li *et al*[16]	NR	LR at 5 years: 15% DR: 14%	Bladder (partial/total) : 56%/19%	NR	67	Partial cystectomy: 0; Urologic recon-struction: 1700	0%	(19%; 25; 6%) (4%)	Negative prognostic factors: Age older than 70 years; receiving palliative resection and not involvement of the bladder dome
Park *et al*[53]	NR	NR	Small bowel: 24%; Ovary: 17%; Bladder 14%	NR	64	NR	NR	(6%; 11%; 9%) (NR)	MVR was associated with a two times higher complications rate compared to standard resections
Rizzuto *et al*[57]	R0: 91%	NR	Small bowel: 36%; Bladder: 27%; Vagina/Uter-us/Ovaries: Each 22%	N0: 50% N+: 50%	62	NR	RCTX: 28%	(11%; 14%; 5%) (NR)	Patients with rectal cancer and occlusive disease had worse prognosis

Winter *et al*[1]	R0: 89%	LR: 14%	Bladder (partial): 84%	N0: 65% N1: 35%	63	NR	RCTX: 37%	(3%; NR; NR) (NR)	Bladder reconstruction is achievable in most patients; margin- and node-negative patients benefit the most
Banamura *et al*[56]	NR	LR: 13%; DR. 23%: Both: 20%	APR: 30%; PPE: 70%	NR	57	NR	RCTX: 20%	(3%; 27%; NR) (NR)	PPE showed prolonged operative time, higher postoperative complications, a trend towards a poor prognosis in recurrence and survival
Crawshaw *et al*[25]	R0: 87%	LR: 16%	Bladder: 49%; Vagina: 38%; Prostate: 31%; Uterus: 31%; Ovaries: 20%; Small bowel: 10%	NR	62	800	RCTX: 90%	(NR; 7%; 12%) (NR)	Sphincter perseveration did not affect oncologic outcomes
Derici *et al*[48]	R0: 75%	LR: 18%	Adnexa: 47%; Uterus: 32%; Bladder: 30%	NR	60	NR	RCTX: 51%	(7%; 19%; NR) (NR)	Lymph node status pN0 (P = 0.007) and R0 resection (P = 0.005) were independently significant factors in the multivariate analysis for overall survival
Dinaux *et al*[50]	R0: 100%	LR. 3%; DR: 21%	Bladder: 28%; Prostate: 21%; Ovaries: 20%; Uterus: 20%	NR	55	NR	CTX. 100%; RCTX: 97%	(3%; 14%; 3%) (NR)	Chance of overall mortality significantly increased for patients; who underwent MVR, for administration of adjuvant CTX, for Pn+ and ypN+ status
Dosokey *et al*[30]	NR	LR. 3% DR: 11%	Vagina: 50%; Prostate: 30%; Bladder: 33%	NR	66	549	CTX: 97% RT: 92%	(16%; NR; NR) (NR)	Patients with APR only had a longer 5 yr overall survival and a longer disease-free survival compared to patients undergoing MVR

Gannon *et al*[28]	R0: 90%	Primary: LR: 9%, LR + DR: 13%, DR: 22%; Recurrent: LR: 4%, LR + DR: 48%, DR:15%	TPE: 47% SLE: 47% PPE: 33%	NR	52	NR	RCTX: 85%	(NR; 4%; 11%) (4%)	A significant difference in 5-yr disease-free survival was found between primary and recurrent tumors (52% *vs* 13%, $P < 0.01$)
Harris *et al*[19]	R0: 93%	LR: 7%	Bladder+ Prostate: 55% Uterus: 24%	N0: 52% N1: 29% N2: 17% N3: 2%	62	NR	RCTX: 74%	(5%; 5%; 21%) (20%)	Association with worse overall survival in multivariate analysis: Metastatic disease, pT4N1 stage, vascular invasion
Ishiguro *et al*[54]	R0: 98%	LR: 9% DR: 25%	Uterus+ Bladder+ Rectum: 89%	N0: 57% N+: 43%	55	NR	RCTX: 14%	(4%; 23%; 8%) (9%)	Patients with positive lateral pelvic lymph node had a higher probability to recur and a decreased 5-yr over all survival
Mañas *et al*[13]	R0: 73%	LR: 37% DR: 35%	Uterus/Ovari-es (each): 53%; Vagina; 27%; Seminal vesicle: 23%	N0: 40% N1: 27% N2: 34%	68	NR	RCTX: 20%	(13%; 53%; 10%) (NR)	Multivariate analysis showed that nodal involvement was independent predictor of poor survival (> 4 pos; nodes RR: 9.06 (P = 0.006)
Nielsen *et al*[9]	Primary:R0: 66% Recurrent: R0: 38%	NR	TPE with sacrectomy: 22%	NR	63	NR	RT: 65%	(4%; 20%; 7%) (NR)	There was no statistically significant difference in overall survival between primary and recurrent disease when comparing R0 resections
Pellino *et al*[14]	R0: 77%	LR: 16% DR: 22%	Not clearly specified	N0: 13% N1: 29% N2: 43%	62	NR	RT: 54%	(NR; 37%; 10%) (10%)	Perioperative complications were independent predictors of shorter survival (HR 3.53)

Rottoli *et al*[10]	Primary: R0 71%, Recurrent: R0: 56%	Primary: LR: 18% DR: 29% Both: 7%; Recurrent: LR: 22% DR: 33% Both: 17%	Sacrectomy: Primary: 18% Recurrent: 22%)	N0: 41% N1: 15% N2: 37%	57	Primary: 600 Recurrent: 750	65% (not specified)	NR	The long-term disease-free survival of patients undergoing pelvic exenteration is significantly worse when the procedure is performed for recurrent rectal cancer, regardless of the tumor involvement of the resection margins
Sanfilippo *et al*[51]	NR	LR: 20% DR: 44%	Vagina: 66%; Bladder/Pros -tate: 14%; Bladder/Vagi -na: 6%; Vagi-na/Uterus/O -varies: 6%	N0: 72% N1: 9% N2: 9%	55	NR	RCTX: 100%	(NR; 19%; 6%) (9%)	No significant association with pelvic control rate and age, sex, cN-stage, tumor distance from the anal verge, clinical tumor length, tumor circumference , tumor mobility, obstruction, grade, neoadjuvant CTX, and MVR
Shin *et al*[22]	R0: 100%	LR: 4%	Prostate: 36%; Vagina: 23%; Small bowel: 14%; Bladder wall: 14%	N0: 41% N1: 46% N2: 14%	54	225	RCTX: 82%	(NR; 17%; 17%) (13%)	Robotic MVR including resection of lateral pelvic lymph nodes is feasible with acceptable morbidity and no conversion
Smith *et al*[47]	R0: 85%	LR: 19%	Vagina: 52%; Uterus: 23%; Bladder: 11%	N0: 60% N+: 40%	63	NR	RCTX: 73% RT: 2%	(6%; 19%; 6%) (at least 1%)	5-yr overall survival in stage I-III: Tumor category (T3-4 *vs* T0-2: HR 2.80), Node category (N1-2 *vs* N0: HR 1.75), Involved resection margin: HR = 2.19), lymphovascu-lar invasion (L0 *vs* L1: HR 1.56)

Vermaas *et al*[11]	Primary:R0: 82%; Recurrent: R0: 58%	LR at 5-yr: Primary: 12%; Recurrent: 40%	TPE: 83% TPE an sacral bone: 11%; TPE with coccygeal bone: 6%	N0: 37% N1: 6% N2: 6%	58	NR	RT: 97%	(NR; 26%; NR) (9%)	Patients with recurrent rectal cancers have a higher rate of complications, a high distant metastasis rate and a poor overall survival

CTX: Chemotherapy; MVR: Multivisceral resection; S-MVR: Single-port MVR; M-MVR: Multi-port MVR; HR: Hazard ratio; RR: Relative risk; APR: Abdominoperioneal resection; PPE: Posterior pelvic exenteration; RCTX: Chemoradiotherapy; TPE: Total pelvic exenteration; LR: Local recurrence; DR: Distant recurrence; AI: Anastomotic insufficiency; SSI: Surgical site infections; IAA: Intraabdominal abscess; RT: Radiotherapy; NR: Not reported.

Completeness of surgical resection was not impaired by minimally-invasive MVR and the included studies showed no reduction in lymph -node harvest as compared to open surgery. The conversion rate to open surgery varied from 4.5%[22] to 33%[23]. The most common reasons for conversion were involvement of the small intestine, intraperitoneal adhesions and the need for urologic reconstructive procedures. The minimally-invasive approach offered a reduced length of stay, significantly reduced blood loss but prolonged operative time.

Chemoradiotherapy

The number of patients receiving any kind of preoperative therapy, including chemotherapy, radiotherapy and combined chemoradiotherapy, was mentioned in 31 studies. Preoperative chemotherapy was received by 129 (4%) patients, 591 (19%) patients underwent preoperative radiotherapy and 423 (14%) patients were given preoperative combined chemoradiotherapy. Two studies reported on applications of chemoradiotherapy in primary and recurrent colon cancers[20,24]. Cukier *et al*[24] reported that perioperative complication rates were not negatively impacted by chemoradiotherapy. The same results were obtained by Hallet *et al*[20] who stated that the addition of neoadjuvant chemoradiotherapy prior to MVR for recurrent adherent colon cancer did not elevate toxicity-or complication rates.

Six studies reported on patients receiving intraoperative radiotherapy (IORT)[11,22,24-27]. All studies exclusively included patients with primary and or recurrent rectal cancer. Indications for application of IORT were a minimal circumferential free resection margin equal to or less than 2 mm in the study from Vermaas *et al*[11] and the concern for close and/or involved radial margins in the study by Gannon *et al*[28] Only 12 patients in the study by Vermaas *et al*[11] received IORT but no improvement in overall survival was seen.

Primary vs recurrent rectal cancer

In total seven publications included primary as well as recurrent rectal cancers[6,9-11,26,28,29]. The studies by Gannon *et al*[28] Nielsen *et al*[9] and Vermaas *et al*[11] included 197 patients and only Gannon *et al*[28] reported that the disease setting was the only significant prognostic factor in favor of primary rectal cancers. This is in line with the results published by Rottoli *et al*[10] who also found the recurrent disease setting to be a negative prognostic factor.

MVR for gastric cancer (n = 16).

Study design

A total of 93 articles were identified using the aforementioned search algorithm (Figure 1). After full-text screening 16 studies were selected that met the inclusion criteria.

Demographics

We identified 16 studies published between 1998 and 2019 describing MVR for a total of 1600 patients with locally advanced gastric cancer (Table 5). One publication reported patient- and treatment-related data after minimally-invasive MVR, whereas the other authors either performed open surgery or did not mention whether an open or laparoscopic approach was chosen[31]. The decision for or against suspected MVR, according to preoperative imaging modalities like CT, MRI, EUS and PET-CT, was made intraoperatively. Every verified adhesion of the primary tumor to adjacent structures was classified as a cT4b -situation. Together with a gastrectomy, mainly surrounding organs like spleen, pancreas or colon were resected. More rarely, the gallbladder or parts of the small bowel or the liver had to be removed.

Table 3 Morbidity, mortality and survival rates after multivisceral resection for colon and rectal cancer

Study	Follow-up (mo)	Morbidity (%)	Mortality (%)	Survival[1]	Stage IV disease (%)	True pT4b (%)
Cukier *et al*[24]	36	36	0	3-yr OS: 85.9%; 3-yr DFS: 73.7%	0	67
Hallet *et al*[20]	54	33.3	0	90%; 5-yr DFS: 63.5%	0	50
Kumamoto *et al*[15]	32	17.8	0.8	87%	12	45
Leijssen *et al*[2]	48.5	25	0	5-yr OS (pT3): 63%; 5-yr OS (pT4): 70%	0	24
López-Cano *et al*[49]	74.9	47.8	7.1	48%; 5-yr DFS: 46.3 mo	20	65
Rosander *et al*[7]	28	37% (≥ Grade III)	5	60.8% for the infiltration group; 86.9% for the inflammation group	0	63
Takahashi *et al*[12]	48.4	LAP: 7 OPEN: 36	0	3-ys OS (open): 79.8%; (lap): 92.8%	25	50
Tei *et al*[23]	34	37.9	0	3-yr OS Stage II-III (S-MVR/M-MVR): 81.8%/80.0% 3-yr DFS Stage II-III (S-MVR/M-MVR: 58.3%/70.0%	28	34
Chen *et al*[6]	NR	11.5	NR	59% (Colon/inflammation) 39% (Colon/invasion) 63% (Rectum/inflammation); 42% (Rectum/invasion)	54	55
Eveno *et al*[58]	48	12	1.3	77%; 3-yr OS (without stage IV disease): 89%; 5-yr DFS: 58%	13	65
Fujisawa *et al*[29]	42 (mean)	NR	NR	3-yr OS (colon/bladder sparing): 90%; (colon/nonsparing): 67%; 3 yr OS (rectal/bladder sparing): 50%; (rectal/nonsparing): 67%	NR	NR
Hoffmann *et al*[21]	NR	34.6	7.7	55% (if curative)	49	63
Gezen *et al*[18]	25 (mean)	24.4	4.4	69.4%	12	34
Kim *et al*[17]	35/40 (mean)	LAP: 21 OPEN: 44	0	LAP: 60.5%; OPEN 48%	33	44
Laurence *et al*[56]	NR	NR	NR	52.7%	3	NR
Lehnert *et al*[8]	71	33	7.5	51%	5	50
Li *et al*[16]	64.3	61	5.6	50%; 59%: if curative	21	47
Park *et al*[53]	NR	35.2	3.1	58%	0	44
Rizzuto *et al*[57]	NR	55	0	3-yr OS (non-occlusive): 58.4%; (occlusive): 33.3%	0	77
Winter *et al*[1]	84	18	1.5	57%; 61% (R0); 17% (R1) 77% (R0, N0); 28% (R0, N+)	NR	54
Banmura *et al*[56]	32	50	0	Local recurrence rate: 30%	33	63
Crawshaw *et al*[25]	27.8	57.4	0	49.2%; 5-yr DFS: 45.3%	0	39
Derici *et al*[48]	40.4 (mean)	38.6	3.5	49%; 3-yr OS: 81.6%	0	58
Dinaux *et al*[50]	38.2	72.4	0	OS: 45 mo	0	24
Dosokey *et al*[30]	32 (mean)	39	0	67%; 5-yr DFS: 79%	0	NR

Gannon *et al*[28]	40	43	0	48%; Primary: 65% Recurrent: 22%; 5-yr DFS. 38%; Primary: 52% Recurrent: 13%	NR	NR
Harris *et al*[19]	30	50	0	5-yr OS (R0): 48%; R1/R2: 33%	14	52
Ishiguro *et al*[54]	40	39.8	2.2	52%; 5-yr DFS: 46%	NR	49
Mañas *et al*[13]	28.8	76.6	10	36.7%	20	67
Nielsen *et al*[9]	12	51	2.2	5-yr OS (primary): 46%; (recurrent):17%	0	NR
Pellino *et al*[14]	NR	54.9	2.4	67%	NR	70
Rottoli *et al*[10]	32.5/56.6	33 Primary: 32% Recurrent: 33%	4	5-yr DFS (primary): 46% (recurrent): 24%	NR	NR
Sanfilippo *et al*[51]	NR	25	NR	4-yr OS: 69%	0	44
Shin *et al*[22]	30	41.7	0	80%	27	23
Smith *et al*[47]	NR	47.6	0.8	53.3%; M0: 59%	20	44
Vermaas *et al*[11]	28 (mean)	69; Primary: 61; Recurrent: 83	3	52% (primary); 3-yr OS (recurrent): 32%	NR	43

[1]if not specified 5-yr OS is reported. S-MVR: Single-port laparoscopic multivisceral resection; M-MVR: Multi-port laparoscopic multivisceral resection; NR: Not reported.

Pathological features

Prior clinically suspected T4-tumor was confirmed in 14%[32]-89.0%[33] of histopathological samples. Involvement of lymph nodes was described in 38.8%[33]-89.3%[34]) of patients.

Morbidity and mortality

The rate of morbidity ranged from 11.8%[35] to 59.8%[31] of patients who underwent gastrectomy and MVR (Table 6). Main postoperative complications were pancreatic fistulas and pancreatitis, anastomotic leakage, cardiopulmonary events and postoperative bleedings. Total mortality lay between 0%[35] and 13.6%[33]. R0-resections were achieved in 38.4%[34]-100%[36] of patients.

Anastomotic insufficiency: Ten studies did not report the occurrence of anastomotic insufficiency (AI). The remainder reported AI -rates ranging from 0%[37,38] to 19.4%[31]. There was no structured report on management of AI in the studies included.

Re-operation: The rate of re-operation was only mentioned in 4 publications and ranged from 0%[37,38] to 13.8%[31].

Long-term outcomes

Patients after R0 resection had 5 year overall survival rates of 24.1%[38] to 37.8%[35]. In the multivariate analysis, mostly incomplete resection status[34,39-42] as well as lymph node involvement[31,34,36,39,40,42-45] were found to be negative prognostic factors for survival. Further negative prognostic factors were metastasized stage[35,39], advanced age[44] the number of resected organs[31,42,44,46], no adjuvant chemotherapy[31] and white race[31].

DISCUSSION

MVR for locally advanced and adherent colorectal and gastric cancers seems to be a feasible approach that is associated with an acceptable morbidity - and mortality -rate and in a subset of patients good oncologic long-term results can be obtained[15,20,25,42,44,47]. Due to the reduced sensitivity and specificity of preoperative imaging for prediction of true malignant adhesion, the decision in favor of performing MVR is made intraoperatively in the vast majority of cases[1]. It is virtually impossible for the surgeon to differentiate between inflammatory and true malignant adhesions, so that every adherence to the tumor must be considered malignant and the appropriate operative strategy has to be applied. Data on intraoperative lysis of adhesions to the primary tumor, which were proven malignant by histopathological examination, revealed devastating overall survival rates and high local recurrence rates (Hunter *et al*[5]). In this review the true pT4b -rate varied from 23% to 77% and data on the impact of malignant invasion are heterogeneous with two studies[7,8] reporting no impact on overall-survival if malignant adhesions were detected and one

Table 4 Patient- and treatment- associated parameters of minimal-invasive multivisceral resection for colon and rectal cancer

Study	Resection margin (R0 *vs* R1)	Lymph-node harvest (*n*)	Conversion rate	Reason for conversion	Blood loss (mL)	Operative time (min)	LOS (d)
Kumamoto *et al*[15]	R0: 95%	26	6.8%	Excessive tumor fixation (*n* = 4); Suspicion of invasion to the duodenum (*n* = 2); Intraperitoneal adhesion (*n* = 2)	49	254	11
Takahashi *et al*[12]	R0: 96%	34 Open: 33	12%	The conversion rate was highest in cases involving the urinary tract (40%)	50; Open: 321	279; Open: 255	14; Open: 22.5
Tei *et al*[23]	R0: S-MVR: 100%; M-MVR: 93%	S-MVR: 30; M-MVR: 25	S-MVR M-MVR: 14%; M-MVR Open: 33%	Small intestine involvement	S-MVR: 60; M-MVR: 220	S-MVR: 222; M-MVR: 255	S-MVR: 11; M-MVR: 18
Kim *et al*[17]	R0: 71%	34; Open: 40	7.9%	NR	268; Open: 637	330; Open: 257	21.9; Open: 21
Shin *et al*[22]	R0: 100%	20	4.5%	Unable to tolerate Trendelenburg position and intraperitoneal adhesions	225	421	4.5

LOS: Length of hospital stay; S-MVR: Single-port multivisceral resection; M-MVR: Multi-port MVR.

study reporting the opposite[6]. It seems it is not the presence of proven malignant infiltration into adherent adjacent organs but the presence other tumor- and treatment-associated factors that are of prognostic importance. This review emphasized the importance of microscopic complete surgical resection, as one of the most predictive factors for overall- and recurrence-free survival[15,48]. These results are further highlighted by the results presented by Nielsen *et al*[9] comparing primary and recurrent rectal cancers. The authors stated that no statistically significant difference in overall survival was seen regarding the disease setting when comparing R0-resections. The remaining studies dealing with primary versus recurrent rectal cancer found the disease setting to be of significant prognostic impact[10,28]. Patient selection for MVR in the recurrent disease setting should be made on a case-by-case basis, because achievement of R0 -resection in these patients can also produce acceptable long-term results. The intraoperative assessment of truly preventing an R1 -resection is virtually not possible, but nevertheless palliative MVR should not be performed as shown by the data from Leijssen *et al*[2]. Authors reported for patients with proven T4 -cancers not undergoing MVR the highest local recurrence rate, namely 21.5% (compared to patients undergoing MVR: 14.5%) and the worst 5-year OS-and DFS rates (46.3% *vs* 52.7% *vs* 70% and 74.1%, respectively).

Apart from the completeness of surgical resection factors like lymph -node and lymphovascular involvement seem to be predictive for survival. López-Cano *et al*[49], Smith *et al*[47] and Harris *et al*[19] showed that lymphatic spread was associated with worse prognosis. Cukier *et al*[24] and Dinaux *et al*[50] discussed the significance of the ypN -stage. Cukier *et al*[24] reported no statistical difference in terms of DFS when comparing ypN0 and ypN1 patients. Contrarily, Dinaux *et al*[50] showed that ypN+ status was significantly associated with overall mortality. Hoffmann *et al*[21] found no difference in terms of OS for pN0 versus pN1 patients after MVR for primary co-lorectal cancers.

The role of neoadjuvant and adjuvant chemo- (radio-) therapy in short- and long-term results was hardly assessable due to the heterogeneity of data provided. The study by Sanfilippo *et al*[26] showed no significant association between application of neoadjuvant chemotherapy and local pelvic control rate. Dinaux *et al*[50] even found the performance of adjuvant chemotherapy to be significantly associated with overall mortality.

The significance of minimally-invasive MVR was highlighted in a couple of studies (Table 4). The laparoscopic approach for standard -resections for colon - and gastric cancer has already become accepted with low morbidity rates and comparable oncologic long-term results. The acceptance of laparoscopic or robotic MVR is low but the minimally-invasive approach seems to harbor some advantages over the open

Table 5 Patient- and treatment- associated parameters after multivisceral resection for gastric cancer

Study	Resection margin (R0 *vs* R1)	Most common resected organs	Lymph node involvement	Age	Blood transfusion	Complications (AI) (Re-OP)	Other prognostic factors
Carboni *et al*[39], 2005	R0 61.5%; R1 27.7%; R2 10.8%	Spleen: 48%; Pancreas: 43%; Colon: 25%	86.2%	61	NR	(1.5%) (1.5%)	Lymph-node involvement and metastatic disease
Colen *et al*[37], 2004	NR	Spleen: 62%; Pancreas 57%; Colon: 24%	NR	67.5	NR	0% (NR)	NR
D'Amato *et al*[38], 2004	R0: 69%	Pancreas: 62%; Colon: 12%	NR	NR	NR	(0%) (NR)	NR
Jeong *et al*[43], 2009	R0: 78.3%; R+: 21.7%	Spleen: 47%; Pancreas: 61%; Colon: 24%	N+: 90.1%	59	NR	(6.7%) (11%)	Lymph-node and lymphovascular involvement
Kim *et al*[35], 2009	R0: 43%; R1: 15%; R2: 74%	Spleen: 38%; Pancreas: 29%; Colon: 56%	NR	NR	NR	(2.9%) (0%)	histologic type, M stage, peritoneal metastasis, curability and treatment groups
Martin *et al*[36], 2002	R0: 100%	Spleen: 67%; Pancreas: 19%; Colon: 6%; Liver: 4% Gallbladder: 7%	N0: 35% N+: 65%	66	NR	(NR) (NR)	Lymph-node involvement and > pT3
Oñate-Ocaña *et al*[32], 2008	R0: 58.1%; R1: 18.9%; R2: 23%	Spleen: 68%; Pancreas: 26%; Colon: 12%; Liver: 9%	NR	NR	NR	(NR) (NR)	NR
Ozer *et al*[44], 2009	NR	Pancreas: 54%; Colon: 32%; Liver: 18%	NR	58	NR	(8.9%) (NR)	Advanced age, lymph node involvement, and resection of more than 1 additional organ were significant prognostic factors for survival.
Persiani *et al*[46], 2008	R0: 320; R1: 39; R2: 29%	Spleen: 84%; Pancreas: 25%; Colon: 10%	NR	63.4	NR	(NR) (NR)	Splenectomy, D2 lymphadenectomy, and age greater than 64 yr were the only factors predictive of overall morbidity
Shchepotin *et al*[33], 1998	NR	Spleen: 43%; Pancreas: 69%; Colon: 45% Liver: 29%	N+: 38.8%	NR	NR	(3.7%) (NR)	NR
Isozaki *et al*[45], 2000	NR	Pancreas + Spleen: 36%; Pancreatoduodenectomy: 7%	N0 = 13%; N1 = 36%; N2 = 25%; N3 = 12%	NR	NR	(NR) (NR)	Location of the tumor, lymph node metastasis, histological depth of invasion, and extent of lymph node dissection
Molina *et al*[40], 2019	R0: 94%	Pancreas (49%); Spleen (34%) Liver (29%).	N+: 80%	64,5	NR	(NR) (NR)	Lymph-node involvement and R1-status
Mita *et al*[42], 2017	R0: 82.5%; R1: 17.5%	Spleen 29.1%; Pancreas: 46.6%; Colon: 13.6%; Liver: 11.7%	N+: 84.5%	70	NR	(NR) (NR)	Resection status
Vladov *et al*[38], 2015	R0: 75%	Spleen: 76.7%; Pancreas:40%; Colon: 18.3%; Liver 15%	NR	NR	NR	(NR) (NR)	NR

Tran *et al*[31], 2015	R1: 15.5	Spleen: 48%; Pancreas:27% Liver 14% Colon: 13%	N0: 34.5%	64	NR	(11.5%) (13.8%)	MVR with pancreatectomy, was significantly associated with decreased survival, along with T-stage, N stage, perineural invasion, and
Pacelli *et al*[34], 2013	R0: 38.4%	Pancreas 46; Colon 43	N+: 89.3%	NR	NR	(7%) (NR)	Lymph-node involvement and incomplete resection

MVR: Multivisceral resection; NR: Not reported; AI: Anastomotic insufficiency.

approach. Table 4 sums up the most important studies, highlighting the fact that minimally-invasive MVR is associated with a reduced operative time, reduced blood loss and transfusion requirement. The conversion rates were low by a comparable lymph-node harvest. Prior to scheduling patients for minimal-invasive MVR, relative contraindications like excessive small bowel- and urologic tract involvement should receive attention.

Our analysis of the so far published results of MVR for patients with locally advanced gastric cancer shows 5-year survival rates of 24.1%-37.8% for patients with an R0-resection, while the rate of morbidity was 11.8% to 59.8% and the rate of mortality 0-15%. The authors of these studies therefore consider MVR for locally advanced gastric cancer to be a potentially beneficial procedure, especially if there is a possibility of curative resection.

Comparable results can also be found for MVR of other abdominal tumor entities such as neuroendocrine tumors or gastrointestinal stroma tumors[51]. Similar approaches were also investigated for locally advanced pancreatic adenocarcinoma and colorectal cancer. With the acceptance of higher rates of morbidity and longer operating times MVR for locally advanced pancreatic adenocarcinoma may lead to a long -term survival comparable to that for standard resections of the pancreas[52].

In conclusion, the main limitation of this review is the mainly retrospective studies included and the heterogeneity in reporting short- and long-term outcomes. Nevertheless, MVR for primary cancers are of significant importance in oncologic surgery providing acceptable morbidity- and mortality rates with good long-term survival for selected patients. Negative selection criteria are incomplete surgical resection, recurrent rectal cancer, and lymph-node and lymphovascular involvement. Stage-IV disease should be regarded as a relative contraindication for MVR.

Table 6 Morbidity, mortality and survival rates after multivisceral resection for gastric cancer

Study	*n*	Follow-up (mo)	Morbidity (%)	Mortality (%)	Survival	Stage IV (%)	True pT4b (%)
Carboni *et al*[39], 2005	65	13	27.7	12.3	OS: 21.8 mo	46	80
Colen *et al*[37], 2004	21	NR	39	10	OS: 30 mo	NR	38
D'Amato *et al*[38], 2004	52	NR	34.6	1.9	OS: 31 mo	NR	NR
Jeong *et al*[43], 2009	71	17.6	26.8	NR	3-yr OS: 36.4%	76	63
Kim *et al*[35], 2009	34	NR	11.8	0	OS: 37.8 mo	38	NR
Martin *et al*[36], 2002	268	NR	39.2	NR	OS: 63 mo	NR	21
Oñate-Ocaña *et al*[32], 2008	74	NR	26.9	NR	OS: 30.5 mo	NR	14-38
Ozer *et al*[44], 2009	56	10.8	37.5	12.5	3-yr OS: 53.3%	62	66
Persiani *et al*[46], 2008	51	NR	16.2	2.3	NR	79	19.6
Shchepotin *et al*[33], 1998	353	NR	31.2	13.6	5-yr OS: 25%	NR	89.0
Isozaki *et al*[45], 2000	86	NR	NR	NR	5-yr OS: 35%	NR	53
Molina *et al*[40], 2019	35	31	46	3	5-yr OS. 34%	NR	40
Mita *et al*[42], 2017	103	23.0	37.9	1.0	3-yr OS: 42.1%	0	57
Vladov *et al*[38], 2015	60	NR	28.3	6.7	5-yr OS: 24.1%	NR	70
Tran *et al*[31], 2015	159	NR	59.8	4.3	5-yr OS: MVR with pancreatectomy: 20%; MVR without: 36%	0	67
Pacelli *et al*[34], 2013	112	18.7	33.9	3,6	5-yr OS: 27.2%	NR	88

OS: Overall survival; NR: Not reported; MVR: Multivisceral resection.

ARTICLE HIGHLIGHTS

Research background

Multivisceral resections (MVR) still constitute a challenge for the interdisciplinary team. The indications to perform MVR are not clearly defined.

Research motivation

Motivation was generated by the fact that there are no recommendations regarding MVR.

Research objectives

In order to define indications and factors associated with beneficial oncologic outcomes and reduced perioperative morbidity and mortality this systematic review was conducted.

Research methods

We performed a PubMed-search from 2000 to 2018 including articles reporting on MVR in patients with colon-, rectal- and gastric cancer.

Research results

Available data shows that MVR from locally advanced colorectal and gastric cancer is a feasible option which is associated with acceptable morbidity- and mortality-rates. Oncologic outcome is favorable when clear resection margins can be obtained.

Research conclusions

Patients who are clinically fit and preoperative imaging does not reveal obvious contraindication for radical surgery, the option of MVR should not be abandoned. Clear resection margins are the main goal of aggressive surgical approach.

Research perspectives

Perspectives are to evaluate more patient- and treatmenspecific parameters in order to define more clearly patients who are likely to benefit from this approach.

REFERENCES

1 **Winter DC**, Walsh R, Lee G, Kiely D, O'Riordain MG, O'Sullivan GC. Local involvement of the urinary bladder in primary colorectal cancer: outcome with en-bloc resection. *Ann Surg Oncol* 2007; **14**: 69-73 [PMID: 17063308 DOI: 10.1245/s10434-006-9031-y]

2 **Leijssen LGJ**, Dinaux AM, Amri R, Kunitake H, Bordeianou LG, Berger DL. The Impact of a Multivisceral Resection and Adjuvant Therapy in Locally Advanced Colon Cancer. *J Gastrointest Surg* 2019; **23**: 357-366 [PMID: 30284199 DOI: 10.1007/s11605-018-3962-z]

3 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

4 **Borowski DW**, Bradburn DM, Mills SJ, Bharathan B, Wilson RG, Ratcliffe AA, Kelly SB; Northern Region Colorectal Cancer Audit Group (NORCCAG). Volume-outcome analysis of colorectal cancer-related outcomes. *Br J Surg* 2010; **97**: 1416-1430 [PMID: 20632311 DOI: 10.1002/bjs.7111]

5 **Hunter JA**, Ryan JA, Schultz P. En bloc resection of colon cancer adherent to other organs. *Am J Surg* 1987; **154**: 67-71 [PMID: 2440334 DOI: 10.1016/0002-9610(87)90292-3]

6 **Chen YG**, Liu YL, Jiang SX, Wang XS. Adhesion pattern and prognosis studies of T4N0M0 colorectal cancer following en bloc multivisceral resection: evaluation of T4 subclassification. *Cell Biochem Biophys* 2011; **59**: 1-6 [PMID: 20740326 DOI: 10.1007/s12013-010-9106-z]

7 **Rosander E**, Nordenvall C, Sjövall A, Hjern F, Holm T. Management and Outcome After Multivisceral Resections in Patients with Locally Advanced Primary Colon Cancer. *Dis Colon Rectum* 2018; **61**: 454-460 [PMID: 29521827 DOI: 10.1097/DCR.0000000000001046]

8 **Lehnert T**, Methner M, Pollok A, Schaible A, Hinz U, Herfarth C. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. *Ann Surg* 2002; **235**: 217-225 [PMID: 11807361 DOI: 10.1097/00000658-200202000-00009]

9 **Nielsen MB**, Rasmussen PC, Lindegaard JC, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. *Colorectal Dis* 2012; **14**: 1076-1083 [PMID: 22107085 DOI: 10.1111/j.1463-1318.2011.02893.x]

10 **Rottoli M**, Vallicelli C, Boschi L, Poggioli G. Outcomes of pelvic exenteration for recurrent and primary locally advanced rectal cancer. *Int J Surg* 2017; **48**: 69-73 [PMID: 28987560 DOI: 10.1016/j.ijsu.2017.09.069]

11 **Vermaas M**, Ferenschild FT, Verhoef C, Nuyttens JJ, Marinelli AW, Wiggers T, Kirkels WJ, Eggermont AM, de Wilt JH. Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. *Eur J Surg Oncol* 2007; **33**: 452-458 [PMID: 17071043 DOI: 10.1016/j.ejso.2006.09.021]

12 **Takahashi R**, Hasegawa S, Hirai K, Hisamori S, Hida K, Kawada K, Sakai Y. Safety and feasibility of laparoscopic multivisceral resection for surgical T4b colon cancers: Retrospective analyses. *Asian J Endosc Surg* 2017; **10**: 154-161 [PMID: 28124830 DOI: 10.1111/ases.12355]

13 **Mañas MJ**, Espín E, López-Cano M, Vallribera F, Armengol-Carrasco M. Multivisceral Resection for Locally Advanced Rectal Cancer: Prognostic Factors Influencing Outcome. *Scand J Surg* 2015; **104**: 154-160 [PMID: 25260784 DOI: 10.1177/1457496914552341]

14 **Pellino G**, Biondo S, Codina Cazador A, Enríquez-Navascues JM, Espín-Basany E, Roig-Vila JV, García-Granero E; Rectal Cancer Project. Pelvic exenterations for primary rectal cancer: Analysis from a 10-year national prospective database. *World J Gastroenterol* 2018; **24**: 5144-5153 [PMID: 30568391 DOI: 10.3748/wjg.v24.i45.5144]

15 **Kumamoto T**, Toda S, Matoba S, Moriyama J, Hanaoka Y, Tomizawa K, Sawada T, Kuroyanagi H. Short- and Long-Term Outcomes of Laparoscopic Multivisceral Resection for Clinically Suspected T4 Colon Cancer. *World J Surg* 2017; **41**: 2153-2159 [PMID: 28280917 DOI: 10.1007/s00268-017-3976-9]

16 **Li JC**, Chong CC, Ng SS, Yiu RY, Lee JF, Leung KL. En bloc urinary bladder resection for locally advanced colorectal cancer: a 17-year experience. *Int J Colorectal Dis* 2011; **26**: 1169-1176 [PMID: 21526373 DOI: 10.1007/s00384-011-1210-z]

17 **Kim KY**, Hwang DW, Park YK, Lee HS. A single surgeon's experience with 54 consecutive cases of multivisceral resection for locally advanced primary colorectal cancer: can the laparoscopic approach be performed safely? *Surg Endosc* 2012; **26**: 493-500 [PMID: 22011939 DOI: 10.1007/s00464-011-1907-7]

18 **Gezen C**, Kement M, Altuntas YE, Okkabaz N, Seker M, Vural S, Gumus M, Oncel M. Results after multivisceral resections of locally advanced colorectal cancers: an analysis on clinical and pathological t4 tumors. *World J Surg Oncol* 2012; **10**: 39 [PMID: 22336589 DOI: 10.1186/1477-7819-10-39]

19 **Harris DA**, Davies M, Lucas MG, Drew P, Carr ND, Beynon J; Swansea Pelvic Oncology Group. Multivisceral resection for primary locally advanced rectal carcinoma. *Br J Surg* 2011; **98**: 582-588 [PMID: 21656723 DOI: 10.1002/bjs.7373]

20 **Hallet J**, Zih FS, Lemke M, Milot L, Smith AJ, Wong CS. Neo-adjuvant chemoradiotherapy and multivisceral resection to optimize R0 resection of locally recurrent adherent colon cancer. *Eur J Surg Oncol* 2014; **40**: 706-712 [PMID: 24534363 DOI: 10.1016/j.ejso.2014.01.009]

21 **Hoffmann M**, Phillips C, Oevermann E, Killaitis C, Roblick UJ, Hildebrand P, Buerk CG, Wolken H, Kujath P, Schloericke E, Bruch HP. Multivisceral and standard resections in colorectal cancer. *Langenbecks Arch Surg* 2012; **397**: 75-84 [PMID: 21968828 DOI: 10.1007/s00423-011-0854-z]

22 **Shin US**, Nancy You Y, Nguyen AT, Bednarski BK, Messick C, Maru DM, Dean EM, Nguyen ST, Hu CY, Chang GJ. Oncologic Outcomes of Extended Robotic Resection for Rectal Cancer. *Ann Surg Oncol* 2016; **23**: 2249-2257 [PMID: 26856720 DOI: 10.1245/s10434-016-5117-3]

23 **Tei M**, Otsuka M, Suzuki Y, Kishi K, Tanemura M, Akamatsu H. Safety and feasibility of single-port laparoscopic multivisceral resection for locally advanced left colon cancer. *Oncol Lett* 2018; **15**: 10091-10097 [PMID: 29928379 DOI: 10.3892/ol.2018.8582]

24 **Cukier M**, Smith AJ, Milot L, Chu W, Chung H, Fenech D, Herschorn S, Ko Y, Rowsell C, Soliman H, Ung YC, Wong CS. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally

advanced adherent colon cancer: a single institution experience. *Eur J Surg Oncol* 2012; **38**: 677-682 [PMID: 22632848 DOI: 10.1016/j.ejso.2012.05.001]

25 **Crawshaw BP**, Augestad KM, Keller DS, Nobel T, Swendseid B, Champagne BJ, Stein SL, Delaney CP, Reynolds HL. Multivisceral resection for advanced rectal cancer: outcomes and experience at a single institution. *Am J Surg* 2015; **209**: 526-531 [PMID: 25577290 DOI: 10.1016/j.amjsurg.2014.10.014]

26 **Sanfilippo NJ**, Crane CH, Skibber J, Feig B, Abbruzzese JL, Curley S, Vauthey JN, Ellis LM, Hoff P, Wolff RA, Brown TD, Cleary K, Wong A, Phan T, Janjan NA. T4 rectal cancer treated with preoperative chemoradiation to the posterior pelvis followed by multivisceral resection: patterns of failure and limitations of treatment. *Int J Radiat Oncol Biol Phys* 2001; **51**: 176-183 [PMID: 11516868 DOI: 10.1016/S0360-3016(01)01610-8]

27 **Vladov N**, Lukanova TS, Trichkov Ts, Takorov I, Mihaylov V, Vasilevski I, Odiseeva E. MULTIVISCERAL RESECTIONS FOR GASTRIC CANCER. *Khirurgiia (Sofiia)* 2015; **81**: 116-122 [PMID: 26887058]

28 **Gannon CJ**, Zager JS, Chang GJ, Feig BW, Wood CG, Skibber JM, Rodriguez-Bigas MA. Pelvic exenteration affords safe and durable treatment for locally advanced rectal carcinoma. *Ann Surg Oncol* 2007; **14**: 1870-1877 [PMID: 17406945 DOI: 10.1245/s10434-007-9385-9]

29 **Fujisawa M**, Nakamura T, Ohno M, Miyazaki J, Arakawa S, Haraguchi T, Yamanaka N, Yao A, Matsumoto O, Kuroda Y, Kamidono S. Surgical management of the urinary tract in patients with locally advanced colorectal cancer. *Urology* 2002; **60**: 983-987 [PMID: 12475654 DOI: 10.1016/S0090-4295(02)01987-8]

30 **Dosokey EMG**, Brady JT, Neupane R, Jabir MA, Stein SL, Reynolds HL, Delaney CP, Steele SR. Do patients requiring a multivisceral resection for rectal cancer have worse oncologic outcomes than patients undergoing only abdominoperineal resection? *Am J Surg* 2017; **214**: 416-420 [PMID: 28622838 DOI: 10.1016/j.amjsurg.2017.05.012]

31 **Tran TB**, Worhunsky DJ, Norton JA, Squires MH, Jin LX, Spolverato G, Votanopoulos KI, Schmidt C, Weber S, Bloomston M, Cho CS, Levine EA, Fields RC, Pawlik TM, Maithel SK, Poultsides GA. Multivisceral Resection for Gastric Cancer: Results from the US Gastric Cancer Collaborative. *Ann Surg Oncol* 2015; **22** Suppl 3: S840-S847 [PMID: 26148757 DOI: 10.1245/s10434-015-4694-x]

32 **Oñate-Ocaña LF**, Becker M, Carrillo JF, Aiello-Crocifoglio V, Gallardo-Rincón D, Brom-Valladares R, Herrera-Goepfert R, Ochoa-Carrillo F, Beltrán-Ortega A. Selection of best candidates for multiorgan resection among patients with T4 gastric carcinoma. *J Surg Oncol* 2008; **98**: 336-342 [PMID: 18646043 DOI: 10.1002/jso.21118]

33 **Shchepotin IB**, Chorny VA, Nauta RJ, Shabahang M, Buras RR, Evans SR. Extended surgical resection in T4 gastric cancer. *Am J Surg* 1998; **175**: 123-126 [PMID: 9515528 DOI: 10.1016/S0002-9610(97)00268-7]

34 **Pacelli F**, Cusumano G, Rosa F, Marrelli D, Dicosmo M, Cipollari C, Marchet A, Scaringi S, Rausei S, di Leo A, Roviello F, de Manzoni G, Nitti D, Tonelli F, Doglietto GB; Italian Research Group for Gastric Cancer. Multivisceral resection for locally advanced gastric cancer: an Italian multicenter observational study. *JAMA Surg* 2013; **148**: 353-360 [PMID: 23715879 DOI: 10.1001/2013.jamasurg.309]

35 **Kim JH**, Jang YJ, Park SS, Park SH, Kim SJ, Mok YJ, Kim CS. Surgical outcomes and prognostic factors for T4 gastric cancers. *Asian J Surg* 2009; **32**: 198-204 [PMID: 19892622 DOI: 10.1016/S1015-9584(09)60395-X]

36 **RC 2nd**, Jaques DP, Brennan MF, Karpeh M. Extended local resection for advanced gastric cancer: increased survival versus increased morbidity. *Ann Surg* 2002; **236**: 159-165 [PMID: 12170020 DOI: 10.1097/00000658-200208000-00003]

37 **Colen KL**, Marcus SG, Newman E, Berman RS, Yee H, Hiotis SP. Multiorgan resection for gastric cancer: intraoperative and computed tomography assessment of locally advanced disease is inaccurate. *J Gastrointest Surg* 2004; **8**: 899-902 [PMID: 15531245 DOI: 10.1016/j.gassur.2004.08.005]

38 **D'Amato A**, Santella S, Cristaldi M, Gentili V, Pronio A, Montesani C. The role of extended total gastrectomy in advanced gastric cancer. *Hepatogastroenterology* 2004; **51**: 609-612 [PMID: 15086216]

39 **Carboni F**, Lepiane P, Santoro R, Lorusso R, Mancini P, Sperduti I, Carlini M, Santoro E. Extended multiorgan resection for T4 gastric carcinoma: 25-year experience. *J Surg Oncol* 2005; **90**: 95-100 [PMID: 15844189 DOI: 10.1002/jso.20244]

40 **Molina JC**, Al-Hinai A, Gosseling-Tardif A, Bouchard P, Spicer J, Mulder D, Mueller CL, Ferri LE. Multivisceral Resection for Locally Advanced Gastric and Gastroesophageal Junction Cancers-11-Year Experience at a High-Volume North American Center. *J Gastrointest Surg* 2019; **23**: 43-50 [PMID: 29663302 DOI: 10.1007/s11605-018-3746-5]

41 **Fujiwara T**, Hizuta A, Iwagaki H, Matsuno T, Hamada M, Tanaka N, Orita K. Appendiceal mucocele with concomitant colonic cancer. Report of two cases. *Dis Colon Rectum* 1996; **39**: 232-236 [PMID: 8620794 DOI: 10.1007/BF02068082]

42 **Mita K**, Ito H, Katsube T, Tsuboi A, Yamazaki N, Asakawa H, Hayashi T, Fujino K. Prognostic Factors Affecting Survival After Multivisceral Resection in Patients with Clinical T4b Gastric Cancer. *J Gastrointest Surg* 2017; **21**: 1993-1999 [PMID: 28940122 DOI: 10.1007/s11605-017-3559-y]

43 **Jeong O**, Choi WY, Park YK. Appropriate selection of patients for combined organ resection in cases of gastric carcinoma invading adjacent organs. *J Surg Oncol* 2009; **100**: 115-120 [PMID: 19475581 DOI: 10.1002/jso.21306]

44 **Ozer I**, Bostanci EB, Orug T, Ozogul YB, Ulas M, Ercan M, Kece C, Atalay F, Akoglu M. Surgical outcomes and survival after multiorgan resection for locally advanced gastric cancer. *Am J Surg* 2009; **198**: 25-30 [PMID: 18823618 DOI: 10.1016/j.amjsurg.2008.06.031]

45 **Isozaki H**, Tanaka N, Tanigawa N, Okajima K. Prognostic factors in patients with advanced gastric cancer with macroscopic invasion to adjacent organs treated with radical surgery. *Gastric Cancer* 2000; **3**: 202-210 [PMID: 11984737 DOI: 10.1007/PL00011718]

46 **Persiani R**, Antonacci V, Biondi A, Rausei S, La Greca A, Zoccali M, Ciccoritti L, D'Ugo D. Determinants of surgical morbidity in gastric cancer treatment. *J Am Coll Surg* 2008; **207**: 13-19 [PMID: 18589356 DOI: 10.1016/j.jamcollsurg.2007.12.050]

47 **Smith JD**, Nash GM, Weiser MR, Temple LK, Guillem JG, Paty PB. Multivisceral resections for rectal cancer. *Br J Surg* 2012; **99**: 1137-1143 [PMID: 22696063 DOI: 10.1002/bjs.8820]

48 **Derici H**, Unalp HR, Kamer E, Bozdag AD, Tansug T, Nazli O, Kara C. Multivisceral resections for locally advanced rectal cancer. *Colorectal Dis* 2008; **10**: 453-459 [PMID: 18070183 DOI: 10.1111/j.1463-1318.2007.01427.x]

49 **López-Cano M**, Mañas MJ, Hermosilla E, Espín E. Multivisceral resection for colon cancer: analysis of

prognostic factors. *Dig Surg* 2010; **27**: 238-245 [PMID: 20571272 DOI: 10.1159/000276974]
50 **Dinaux AM**, Leijssen LGJ, Bordeianou LG, Kunitake H, Berger DL. Effects of local multivisceral resection for clinically locally advanced rectal cancer on long-term outcomes. *J Surg Oncol* 2018; **117**: 1323-1329 [PMID: 29205364 DOI: 10.1002/jso.24947]
51 **Hasselgren K**, Sandström P, Gasslander T, Björnsson B. Multivisceral Resection in Patients with Advanced Abdominal Tumors. *Scand J Surg* 2016; **105**: 147-152 [PMID: 26929293 DOI: 10.1177/1457496915622128]
52 **Hartwig W**, Hackert T, Hinz U, Hassenpflug M, Strobel O, Büchler MW, Werner J. Multivisceral resection for pancreatic malignancies: risk-analysis and long-term outcome. *Ann Surg* 2009; **250**: 81-87 [PMID: 19561478 DOI: 10.1097/SLA.0b013e3181ad657b]
53 **Park S**, Lee YS. Analysis of the prognostic effectiveness of a multivisceral resection for locally advanced colorectal cancer. *J Korean Soc Coloproctol* 2011; **27**: 21-26 [PMID: 21431093 DOI: 10.3393/jksc.2011.27.1.21]
54 **Ishiguro S**, Akasu T, Fujita S, Yamamoto S, Kusters M, Moriya Y. Pelvic exenteration for clinical T4 rectal cancer: oncologic outcome in 93 patients at a single institution over a 30-year period. *Surgery* 2009; **145**: 189-195 [PMID: 19167974 DOI: 10.1016/j.surg.2008.09.014]
55 **Bannura GC**, Barrera AE, Cumsille MA, Contreras JP, Melo CL, Soto DC, Mansilla JE. Posterior pelvic exenteration for primary rectal cancer. *Colorectal Dis* 2006; **8**: 309-313 [PMID: 16630235 DOI: 10.1111/j.1463-1318.2005.00938.x]
56 **Laurence G**, Ahuja V, Bell T, Grim R, Ahuja N. Locally advanced primary recto-sigmoid cancers: Improved survival with multivisceral resection. *Am J Surg* 2017; **214**: 432-436 [PMID: 28082009 DOI: 10.1016/j.amjsurg.2016.12.018]
57 **Rizzuto A**, Palaia I, Vescio G, Serra R, Malanga D, Sacco R. Multivisceral resection for occlusive colorectal cancer: Is it justified? *Int J Surg* 2016; **33** Suppl 1: S142-S147 [PMID: 27398688 DOI: 10.1016/j.ijsu.2016.06.021]
58 **Eveno C**, Lefevre JH, Svrcek M, Bennis M, Chafai N, Tiret E, Parc Y. Oncologic results after multivisceral resection of clinical T4 tumors. *Surgery* 2014; **156**: 669-675 [PMID: 24953279 DOI: 10.1016/j.surg.2014.03.040]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 290-296

DOI: 10.13105/wjma.v7.i6.290

ISSN 2308-3840 (online)

SYSTEMATIC REVIEW

Relationship between perioperative anaemia and outcomes in older people with hip fractures: A systematic review and meta-analysis protocol

Kareeann SF Khow, Michelle WK Kee, Pazhvoor N Shibu, Solomon CY Yu, Mellick J Chehade, Renuka Visvanathan

ORCID number: Kareeann SF Khow (0000-0003-3960-1025); Michelle WK Kee (0000-0002-4426-4521); Pazhvoor N Shibu (0000-0001-7451-4643); Solomon CY Yu (0000-0001-7082-1232); Mellick J Chehade (0000-0001-6931-2393); Renuka Visvanathan (0000-0002-1303-9479).

Author contributions: Khow KSF, Kee MWK, Shibu PN, Yu SCY, Chehade MJ and Visvanathan R contributed equally to the work; Khow KSF conceptualized and designed the review together with Kee MWK; Khow KSF drafted the initial paper; all authors reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement: Dr Shibu has received educational grants and honoraria from Novartis Pty Australia and Amgen Pty Ltd. Associate Professor Chehade has received institutional research grant from Stryker and Amgen Pty Ltd. Professor Visvanathan has participated in international initiatives funded by educational grants from Nestle and has presented at symposiums funded by Nestle. She is on the Malnutrition in the Elderly Board with Nestle Australia. Dr Khow, Dr Kee and Associate Professor Yu do not have any conflict of interests.

PRISMA 2009 Checklist statement: The manuscript is designed as per PRISMA 2009 guideline, and checklist is provided as

Kareeann SF Khow, Michelle WK Kee, Pazhvoor N Shibu, Solomon CY Yu, Renuka Visvanathan, Aged and Extended Care Services, the Queen Elizabeth Hospital, Woodville South, SA 5011, Australia

Kareeann SF Khow, Pazhvoor N Shibu, Solomon CY Yu, Renuka Visvanathan, Centre of Research Excellence, Frailty Trans-disciplinary Research to Achieve Healthy Ageing, University of Adelaide, Adelaide, SA 5005, Australia

Mellick J Chehade, Discipline of Orthopaedics and Trauma, Faculty of Medical and Health Sciences, University of Adelaide, Adelaide, SA 5005, Australia

Corresponding author: Kareeann SF Khow, FRACP, MBChB, Research Fellow, Senior Lecturer, Staff Physician, Aged and Extended Care Services, the Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, SA 5011, Australia. kareeann.khow@adelaide.edu.au
Telephone: +61-8-83132144
Fax: +61-8-83132155

Abstract

BACKGROUND

Hip fractures are common with increasing age and is associated with decline in mobility. Both the fracture and the surgery can lead to blood loss, resulting in anaemia. However, it is uncertain at which time point haemoglobin is most strongly associated with different clinical outcomes after hip fracture. Our hypothesis is perioperative anaemia (admission, postoperative and discharge) during hip fracture surgery is associated with poor clinical outcomes.

AIM

To determine the effects of perioperative anaemia during hip fracture surgery on mortality, functional status and other clinical outcomes.

METHODS

Electronic databases will be searched to identify studies evaluating perioperative anaemia and outcomes of hip fracture surgery. Reference lists of included studies will also be searched to identify additional published studies. Eligibility criteria are as follows: Population: People who underwent hip fracture surgery; Exposure: Perioperative anaemia; Comparison: No anaemia before or after hip fracture surgery; Outcome: Mortality, hospital length of stay, postoperative complications, hospital readmission, change of discharge destination, quality of

life and functional status. Risk of bias assessment will be assessed using the Cochrane Collaboration's tool for randomized controlled trials and the modified version of the Epidemiological Appraisal Instrument for observational studies. Data will be pooled for meta-analysis if deemed appropriate.

CONCLUSION

This review seeks to clarify outcomes associated with perioperative anaemia at various time-points around hip fracture surgery. These findings will potentially inform evidence-based clinical practice on interventions in those with anaemia.

Key words: Anaemia; Haemoglobin; Hip fracture; Length of stay; Mortality; Outcomes; Perioperative; Readmission

Core tip: Hip fracture is a growing public health problem because of population aging. Recovery from hip fracture can be slow and complicated by morbidities and decline in functional abilities. Perioperative anaemia is common with hip fractures. However, it is uncertain at which time point haemoglobin level is most strongly associated with different clinical outcomes after hip fracture surgery. Better understanding of the relationship between perioperative haemoglobin and mortality, length of hospital stay, functional status, postoperative complications, hospital readmission and admission to residential care after discharge, is required.

Citation: Khow KS, Kee MW, Shibu PN, Yu SC, Chehade MJ, Visvanathan R. Relationship between perioperative anaemia and outcomes in older people with hip fractures: A systematic review and meta-analysis protocol. *World J Meta-Anal* 2019; 7(6): 290-296
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/290.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.290

INTRODUCTION

Mobility is vital to older people, especially for maintaining functional independence and good quality of life. Older people have identified that living in their own home as long as possible is a priority for them. However, sustaining a hip fracture is a serious life-changing event for many older people, which disrupts their ability to walk.

Hip fractures in the older population are associated with adverse outcomes which may include prolonged hospitalisation, decline in functional status, long-term institutionalisation and excessive mortality[1-3]. For example, less than 50% of patients regain their prior level of mobility at one year after hip fracture, and nearly 20% become immobile[4]. The loss of independence after hip fractures result in older people needing long-term residential care. In a meta-analysis of seventy-five studies involving more than 64000 subjects from multiple countries, the overall mortality at one year was 24.5% and this increased to 34.5% at 2 years[5]. Therefore, the healthcare burden of hip fractures is significant and strategies are needed to mitigate these adverse outcomes.

One potential way to improve outcomes after hip fractures is to better manage anaemia in patients with hip fractures. Hip fractures are associated with significant blood loss, either from the fracture itself or from the surgery to repair it[6]. In the general population, anaemia is present in 10% of women and 11% of men over the age of 65 years[7]. This prevalence of anaemia is higher in older people who had hip fractures. It is present in approximately 50% at the time of hospital admission[8], increasing to more than 90% following hip fracture surgery[8]. Anaemia, independent of other health conditions, places older people at risk of adverse health outcomes. The increased risk of mortality among those with anaemia is well documented[9,10]. However, there is conflicting data about whether anaemia is an independent risk factor for poor postoperative outcome or a marker of severity of comorbid diseases in patients with hip fractures[9,11].

Preoperative anaemia is recognised as a risk factor for mortality, longer length of stay and poorer functional status after hip fracture surgery[12]. It is also recognised as one of the most important risk factor for blood transfusions[12,13]. In a systematic

Manuscript source: Unsolicited Manuscript

Received: April 28, 2019
Peer-review started: April 28, 2019
First decision: May 9, 2019
Revised: June 1, 2019
Accepted: June 17, 2019
Article in press: June 17, 2019
Published online: June 30, 2019

P-Reviewer: Petretta M
S-Editor: Cui LJ
L-Editor: A
E-Editor: Wang J

review published in 2015, preoperative anaemia was associated with a 64% increase in risk of mortality after hip fractures[14]. One of the limitations of this systematic review is that several studies published after 2015 were not included.

In a few studies, the effects of postoperative haemoglobin on clinical outcomes have shown mixed results[15,16]. In addition, little is known about the effects of anaemia prior to hospital discharge on outcomes. To date, only a small number of studies have examined the association between anaemia on discharge with outcomes[8,17,18]. Therefore, a more robust review is required to evaluate the relationship between perioperative anaemia and clinical outcomes in hip fracture surgery.

The primary aim of this systematic review is to determine the relationship between perioperative (preoperative, postoperative and discharge) anaemia and mortality after hip fracture surgery. Secondary aims are to evaluate the relationship between perioperative anaemia and other clinical outcomes such as hospital length of stay, postoperative complications, hospital readmission, rate of permanent transfer to residential care after discharge, and functional status in terms of mobility or disability.

MATERIALS AND METHODS

This systematic review and meta-analysis will be performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement[19].

Definitions

Anaemia refers to a reduced number of circulating red blood cells and is usually based on haemoglobin measurements. Anaemia can occur at various time point of the fracture, either preoperatively (prior to surgery) or postoperatively (up to 7 dafter surgery). There is also interest in haemoglobin just before discharge following the index surgery. These measurements are collectively referred to as perioperative haemoglobin.

Search strategy

We will search for relevant articles in the English language using MEDLINE/PubMed, CINAHL, SCOPUS, EMBASE databases and Cochrane Library from inception until August 2018. The search strategy is provided in Table 1. We will perform a manual search of additional references of articles.

Eligibility criteria

Population: The population of interest is people with hip fractures undergoing surgery. Examples of surgery for hip fractures include sliding hip screw, intramedullary nail and arthroplasty.

Exposure: Studies evaluating the effects of perioperative anaemia which are defined as (1) at the time of admission or before surgery; (2) after surgery (within 7 d); and (3) prior to hospital discharge (as defined by the authors) will be included. Anaemia may be defined according to the World Health Organization criteria as haemoglobin concentration less than 120 g/L for women and less than 130 g/L for men[20]. For the purpose of this review, moderate and severe anaemia were defined as haemoglobin of 80-100 g/L and less than 80 g/L, respectively, for both sexes.

Comparator/control: Participants who had hip fracture surgery without anaemia, at different time points.

Outcomes: This review will consider studies that include any of the following outcomes (1) mortality up to 12 mo post-surgery; (2) hospital length of stay; (3) postoperative complications; (4) hospital readmission; (5) rate of permanent transfer to residential care after discharge; (6) quality of life; (7) mobility or disability.

Study design: All peer-reviewed full-text studies or doctoral dissertations are eligible for initial review. Observational studies designed as longitudinal cohorts, case-control or cross-sectional studies and experimental studies designed as randomized controlled or non-randomized trials will be eligible for inclusion in this review.

Exclusion: This study will exclude case series, case reports and studies published in a language other than English. Studies reporting outcomes of cohorts with (1) acetabulum and fractures of the femoral shaft distal to the subtrochanteric region, (b) high-energy traumatic fracture; (2) pathological fracture and (3) non-surgical management of hip fracture will also be excluded.

Study selection process

Initially, two reviewers (KSK, MWK) will screen the titles and abstracts of all search records independently. After screening, full texts of all potentially eligible studies will be retrieved and examined according to the abovementioned eligibility criteria.

Table 1 Search syntaxes

Database	Search syntax
PubMed	("anaemia" [All Fields] OR "anaemia" [MeSH Terms] OR "haemoglobin" [All Fields]) OR ("haemoglobin" [MeSH Terms] AND ("hip fractures" [MeSH Terms] OR ("hip" [All Fields] AND "fractures" [All Fields])
CINAHL	"hip fracture" AND (anaemia or haemoglobin)
Embase	"hip fracture" and (anaemia or haemoglobin)
Scopus	Hip fracture AND (anaemia or haemoglobin)

Disagreements at both screening levels (title/abstract and full text) will be adjudicated by a third reviewer (SY). A PRISMA-P flow chart will outline the study selection process and reasons for exclusion.

Data extraction

Data will be extracted by two independent reviewers (KSK, MWK) using a standard data abstraction form (Supplementary material). After determination of the study eligibility, information will be extracted from each study regarding study identification (first author, year of publication, number and location where recruitment took place), study design characteristics (sample size, follow-up duration, inclusion and exclusion criteria, quality assessments), patient population (age, gender, medical comorbidities) and haemoglobin levels (before, after surgery or prior to discharge). Data on the following outcomes will be recorded: mortality up to 12 mo, hospital length of stay, postoperative complications, hospital readmission up to 12 mo, rate of permanent transfer to residential care after discharge, quality of life, mobility or disability.

Quality assessment

The quality assessment for all studies will be assessed independently by two reviewers (KSK, MWK). The Cochrane Collaboration's tool will be used for assessing risk of bias among RCT studies[21]. This tool addresses six domains of bias: (1) Sequence generation; (2) Allocation concealment; (3) Blinding of personnel and participants; (4) Completeness of data; (5) Selective reporting; and (6) Other source of bias not covered in the other domains. Based on empirical and theoretical considerations, RCTs with inadequate random sequence generation, allocation concealment, incomplete outcome data, selective reporting, or with other sources of bias will be considered as high risk of bias[21]. When sufficient information was not provided on these three domains of bias to allow a definite judgement, we will consider the risk of bias as unclear. When a study is potentially free of these biases, we will consider the risk as low.

The quality of observational studies will be assessed using the Epidemiological Appraisal Instrument (EAI)[22], a validated and reliable tool. This instrument addresses five domains of bias risk: Reporting, subject selection, measurement quality, data analysis, and generalisation of results. Each of the 43 questions in the EAI was scored as yes (= 2), partial (= 1), no or unable to determine (= 0) with the highest possible score being 86. Each total score will be stratified by quartiles. Quartile 1 (Q1) will be 70-86 (the highest quality), quartile 2 (Q2) will be 46-69, quartile 3 (Q3) will be 24-45 and quartile 4 (Q4) will be 0-23 (the lowest quality). Any disagreement regarding the quality of a study will be resolved by a third reviewer (SY).

Data synthesis

Detailed description of all included studies will be tabulated. Study identification (first author, year of publication, number and location where recruitment occurred), study design and characteristics (observational or experimental, sample size, duration of follow-up), patient population (age, gender), haemoglobin at different time points and clinical outcomes (mortality at different time points, hospital length of stay, hospital readmission at different time points, postoperative complications, rate of admission to residential care after discharge, quality of life, mobility or ability to perform activities of daily living) will be qualitatively described.

Statistical analysis

We will use RevMan 5.3 to conduct the meta-analyses. Meta-analyses of pooled data will not be performed for secondary outcomes or when the number of studies were small or highly heterogenous. The summary effect measures may include hazard ratios (HR), relative risk (RR) or odds ratios (OR). When data are available to be

pooled together, we will use a random-effects model to estimate of effect size. Where possible, we will aggregate each included study's outcome data as HR, RR, or OR with the associated 95%CI as these are assumed to measure the same underlying effect[23]. When the effect size estimate was not reported in the paper, the RR or OR and associated 95%CI will be calculated using the raw data available. In the first instance, the unadjusted effect sizes for each outcome (permitting age and sex adjustment) will be pooled together. In the second instance, the unadjusted and most adjusted effect sizes for each outcome will be pooled together.

RESULTS

Heterogeneity and publication bias

Heterogeneity among included studies will be evaluated using the I^2 statistic, which will describe the proportion of variability in effect size estimates that is due to the difference between studies rather than by chance[21]. According to the Cochrane Handbook for Systematic Reviews[24], I^2 of 0% to 60% can be considered as not important to moderate, while I^2 >60% indicates substantial heterogeneity.

Funnel plots will be used to assess for any publication bias (eyeball test). Egger's test will be used to identify any funnel plot asymmetry arising from publication bias if present[24].

DISCUSSION

This systematic review aims to add to the existing literature by aggregating data on specific outcomes after hip fracture surgery in relation to perioperative anaemia. Our review is broader in scope and considers many more clinical outcomes compared with previous systematic reviews that have predominantly focused on postoperative mortality. Understanding the relationship between perioperative anaemia in hip fracture surgery and clinical outcomes is important from a clinical perspective because clinicians find it challenging to know when to transfuse with RBC. Therefore, this review will inform the evidence-based recommendations for this area of clinical practice.

It is common when undertaking such reviews and meta-analysis that gaps in methodology will be identified and as part of quality improvement, strategies to address these design gaps will be identified. Additionally, areas where knowledge gaps remain may be identified to guide future research directions for the benefit of the clinical care of people with hip fractures.

It can be hypothesized that this review will encounter several limitations. This review may not be able to generalize the findings because studies may potentially define anaemia by different haemoglobin cut-offs leading to variation in interpretation. Therefore, the proposed review may be limited by the pooling together of perioperative anaemia studies with varying levels of validity and heterogeneity. Another limitation concerns the length of stay and functional status endpoints, and it is possible that different studies may have utilized different methods to determine these outcomes, each with varying levels of validity.

In conclusion, given that the links between anaemia and clinical outcomes at different time-points before or after hip fracture surgery are complex and the lack of a comprehensive systematic review in this area, the proposed review will help to provide a summary of the available evidence. These findings will assist the development of future clinical practice and policy in this field.

ACKNOWLEDGEMENTS

Dr Khow is a recipient of the National Health and Medical Research Council Postgraduate Scholarship (2017-2018).

ARTICLE HIGHLIGHTS

Research background

Perioperative anaemia in hip fracture is a common problem that can influence clinical outcomes. However, it is uncertain which outcomes will be affected and if anaemia before or after surgery will have different effects.

Research motivation
A better understanding of how perioperative anaemia influences clinical outcomes after hip fracture surgery will help to develop more timely interventions.

Research objectives
To determine the effects of perioperative anaemia during hip fracture surgery on mortality, hospital length of stay, postoperative complications, hospital readmission, change of discharge destination, quality of life and functional status.

Research methods
Electronic databases will be searched for studies evaluating perioperative anaemia and outcomes of hip fracture surgery. Data on study characteristics, patient demographics, timing of anaemia and clinical outcomes will be extracted. Comparison will be made between participants with anaemia and those without. Data will be pooled for meta-analysis for the primary outcome.

Research conclusions
This systematic review seeks to clarify the outcomes associated with perioperative anaemia at various time-points among patients who had hip fracture surgery. An evaluation of the outcomes associated with perioperative anaemia in hip fracture surgery will potentially inform evidence-based clinical practice on the effectiveness and timing of interventions in those with reduced haemoglobin.

Research perspectives
In presence of small studies evaluating perioperative anaemia among older people having hip fracture surgery, a systematic review and meta-analysis will provide important directions for future research and clinical practice in this field. This protocol will provide an important methodological foundation for the systematic review.

REFERENCES

1 **Abrahamsen B**, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009; **20**: 1633-1650 [PMID: 19421703 DOI: 10.1007/s00198-009-0920-3]
2 **Bentler SE**, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Wallace RB, Ohsfeldt RL, Jones MP, Rosenthal GE, Wolinsky FD. The aftermath of hip fracture: discharge placement, functional status change, and mortality. *Am J Epidemiol* 2009; **170**: 1290-1299 [PMID: 19808632 DOI: 10.1093/aje/kwp266]
3 **Brauer CA**, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA* 2009; **302**: 1573-1579 [PMID: 19826027 DOI: 10.1001/jama.2009.1462]
4 **Vochteloo AJ**, Moerman S, Tuinebreijer WE, Maier AB, de Vries MR, Bloem RM, Nelissen RG, Pilot P. More than half of hip fracture patients do not regain mobility in the first postoperative year. *Geriatr Gerontol Int* 2013; **13**: 334-341 [PMID: 22726959 DOI: 10.1111/j.1447-0594.2012.00904.x]
5 **Hu F**, Jiang C, Shen J, Tang P, Wang Y. Preoperative predictors for mortality following hip fracture surgery: a systematic review and meta-analysis. *Injury* 2012; **43**: 676-685 [PMID: 21683355 DOI: 10.1016/j.injury.2011.05.017]
6 **Smith GH**, Tsang J, Molyneux SG, White TO. The hidden blood loss after hip fracture. *Injury* 2011; **42**: 133-135 [PMID: 20236640 DOI: 10.1016/j.injury.2010.02.015]
7 **Guralnik JM**, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004; **104**: 2263-2268 [PMID: 15238427 DOI: 10.1182/blood-2004-05-1812]
8 **Halm EA**, Wang JJ, Boockvar K, Penrod J, Silberzweig SB, Magaziner J, Koval KJ, Siu AL. The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. *J Orthop Trauma* 2004; **18**: 369-374 [PMID: 15213502 DOI: 10.1097/00005131-200407000-00007]
9 **Penninx BW**, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 474-479 [PMID: 16720744 DOI: 10.1093/gerona/61.5.474]
10 **Dong X**, Mendes de Leon C, Artz A, Tang Y, Shah R, Evans D. A population-based study of hemoglobin, race, and mortality in elderly persons. *J Gerontol A Biol Sci Med Sci* 2008; **63**: 873-878 [PMID: 18772477 DOI: 10.1093/gerona/63.8.873]
11 **Denny SD**, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med* 2006; **119**: 327-334 [PMID: 16564775 DOI: 10.1016/j.amjmed.2005.08.027]
12 **Fowler AJ**, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015; **102**: 1314-1324 [PMID: 26349842 DOI: 10.1002/bjs.9861]
13 **Beattie WS**, Karkouti K, Wijeysundera DN, Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology* 2009; **110**: 574-581 [PMID: 19212255 DOI: 10.1097/ALN.0b013e31819878d3]
14 **Potter LJ**, Doleman B, Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. *Anaesthesia* 2015; **70**: 483-500 [PMID: 25764405 DOI: 10.1111/anae.12978]
15 **Lawrence VA**, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL. Higher Hb level is associated with better early functional recovery after hip fracture repair. *Transfusion* 2003; **43**: 1717-1722 [PMID: 14641869 DOI: 10.1046/j.0041-1132.2003.00581.x]
16 **Willems JM**, de Craen AJ, Nelissen RG, van Luijt PA, Westendorp RG, Blauw GJ. Haemoglobin predicts length of hospital stay after hip fracture surgery in older patients. *Maturitas* 2012; **72**: 225-228 [PMID:

22525146 DOI: 10.1016/j.maturitas.2012.03.016]
17 **Su H**, Aharonoff GB, Zuckerman JD, Egol KA, Koval KJ. The relation between discharge hemoglobin and outcome after hip fracture. *Am J Orthop (Belle Mead NJ)* 2004; **33**: 576-580 [PMID: 15603520]
18 **Adunsky A**, Arad M, Blumstein T, Weitzman A, Mizrahi EH. Discharge hemoglobin and functional outcome of elderly hip fractured patients undergoing rehabilitation. *Eur J Phys Rehabil Med* 2008; **44**: 417-422 [PMID: 19002091]
19 **Moher D**, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1 [PMID: 25554246 DOI: 10.1186/2046-4053-4-1]
20 **Nutritional Anaemias**. Report of a WHO scientific group. World Health Organization Technical Report Series. 1968; 5-37
21 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]
22 **Genaidy AM**, Lemasters GK, Lockey J, Succop P, Deddens J, Sobeih T, Dunning K. An epidemiological appraisal instrument - a tool for evaluation of epidemiological studies. *Ergonomics* 2007; **50**: 920-960 [PMID: 17457750 DOI: 10.1080/00140130701237667]
23 **Loef M**, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. *Prev Med* 2012; **55**: 163-170 [PMID: 22735042 DOI: 10.1016/j.ypmed.2012.06.017]
24 **Higgins JP**, Green S. Cochrane handbook for systematic reviews of interventions, vol. 5: Wiley Online Library; 2008; [DOI: 10.1002/9780470712184]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 297-308

DOI: 10.13105/wjma.v7.i6.297

ISSN 2308-3840 (online)

SYSTEMATIC REVIEW

Treatment options for rumination syndrome: A systematic review

Andrew Ming-Liang Ong, Shu-Wen Tay, Yu-Tien Wang

ORCID number: Andrew Ming-Liang Ong (0000-0002-9199-2038); Shu-Wen Tay (0000-0001-6390-4101); Yu-Tien Wang (0000-0002-7224-2514).

Author contributions: Ong AML wrote the manuscript and performed the research. Wang YT and Tay SW performed the research and contributed to the editing of the manuscript. All authors have approved the final version of the manuscript. The manuscript is original work of author. All data, tables, figures, etc. used in the manuscript are prepared originally by authors, otherwise the sources are cited and reprint permission should be attached.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Manuscript source: Invited

Andrew Ming-Liang Ong, Shu-Wen Tay, Yu-Tien Wang, Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore 169856, Singapore

Andrew Ming-Liang Ong, Yu-Tien Wang, Duke-NUS Graduate Medical School, Singapore 169856, Singapore

Corresponding author: Andrew Ming-Liang Ong, MBChB, MRCP, Assistant Professor, Doctor, Department of Gastroenterology and Hepatology, Singapore General Hospital, 20 College Road, Level 3, Academia Building, Singapore 169856, Singapore.
andrew.ong.m.l@singhealth.com.sg
Telephone: +65-6321-4684
Fax: +65-6227-3623

Abstract

BACKGROUND

Rumination syndrome (RS) is characterized by recurrent effortless postprandial regurgitation of recently ingested food from the stomach to the oral cavity and has been associated with quality of life impairment and malnutrition. There is a general lack of consensus on the most appropriate treatment options for RS.

AIM

To summarize the literature on treatment options for RS.

METHODS

We conducted a systematic review according to PRISMA guidelines. We searched Medline (1946 to February 2019), EMBASE (1947 to February 2019), PsycINFO (1806 to February 2019) and Cochrane central register of controlled trials for articles discussing treatment options for adult patients (> 18 years) with RS. All relevant articles were accessed in full text. We extracted data on study designs, patient profiles, duration of symptoms, follow up periods, date, diagnostic criteria, interventions and outcomes. Risk of bias assessment was carried out independently by 3 reviewers *via* Cochrane Risk of Bias tool and Newcastle Ottawa Scale for randomized controlled trials and Cohort studies respectively.

RESULTS

Twelve articles were identified. A total of 254 patients were included in the analysis, with a mean age of 36.1 (range 18-89). 185 patients (72.8%) were females. 5 studies looked into behavioral therapies, primarily diaphragmatic breathing (DB) 2 studies looked at baclofen, 1 fundoplication and 1 supportive lifestyle changes. 3 studies looked at a combination of therapies involving pharmacological, behavioral and psychotherapies.

CONCLUSION

manuscript

Received: April 22, 2019
Peer-review started: April 23, 2019
First decision: May 24, 2019
Revised: May 31, 2019
Accepted: June 10, 2019
Article in press: June 10, 2019
Published online: June 30, 2019

P-Reviewer: Iliescu L, Wang YP, Koulaouzidis A, Tarnawski AS, Kato J, Cerwenka H
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu JH

Although evidence for treatment options is still limited, the strongest evidence point towards the use of DB and Baclofen, and both should be considered depending on their availabilities.

Key words: Rumination; Rumination syndrome; Diaphragmatic breathing; Treatment; Systematic review

Core tip: Rumination syndrome (RS) is a relatively common but underdiagnosed gastroenterological condition. Due to recent advances in research, we have decided to perform the first systematic review on treatment options for RS. Our results show that diaphragmatic breathing has the strongest data for efficacy in this condition.

Citation: Ong AML, Tay SW, Wang YT. Treatment options for rumination syndrome: A systematic review. *World J Meta-Anal* 2019; 7(6): 297-308
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/297.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.297

INTRODUCTION

Rumination syndrome (RS) is characterized by recurrent effortless postprandial regurgitation of recently ingested food from the stomach to the oral cavity[1,2]. Although rumination was historically described mainly in children or adults with impaired mental development, it is now recognized in adults regardless of mental state[2,3]. Although not considered to be life-threatening, RS has been associated with quality of life impairment and even malnutrition[2].

Currently, the diagnosis of RS in adults is based on careful history and subsequently applying the Rome IV criteria[4], often also supported by postprandial High Resolution Impedance Manometry (HRIM) findings of reflux episodes associated with a preceding abdominal pressure increase of > 30 mmHg[5]. These findings also allow RS to be discriminated from gastroesophageal reflux disease (GERD), a common competing diagnosis in these patients, often resulting in several years of delay before the diagnosis of RS is made.

There is a general lack of consensus on the most appropriate treatment options for RS. Therefore, the aim of this systematic review is to summarize the literature on studies that looked into treatment options for adult RS patients, and ascertain what is most evidence-based approach in treating them.

MATERIALS AND METHODS

Literature search

We followed PRISMA guidelines and the medical literature was searched using OVID within the databases Medline (1946 to February 2019), EMBASE (1947 to February 2019), PsycINFO (1806 to February 2019) and Cochrane central register of controlled trials. Searches were based on controlled vocabulary including medical subject heading terms (MeSH) where possible (*e.g.*, "rumination syndrome" and "eructation"). In addition, a combination of keywords, free text terms and database-specific subject headings for rumination, RS, eructation, postprandial regurgitation, feeding disorder, treatment, therapy, behavioral therapy, non-pharmacological treatment were included. In case of multiple reports of one trial were found, we selected the most updated one.

Abstracts of the papers identified by the initial search were evaluated by the lead reviewer (AO) for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. In order to identify potentially eligible studies published only in abstract form, conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, Federation of Neurogastroenterology and Motility) between 2001 and 2019 were also hand-searched.

The bibliographies of studies included in the final analysis as well as relevant

reviews were also screened for additional relevant articles. The website ClinicalTrials.gov was also searched to look for trials not included in the mentioned databases.

Data extraction and analysis

We included studies evaluating management of adults over 18 with a diagnosis of RS. Articles involving pediatrics or patients with eating disorders, and those with no mention of treatment strategies or without identifiable outcomes were excluded. Editorials, case reports of single cases, letters, qualitative studies, clinical guidelines and narrative reviews were also excluded. Articles were restricted to English language. Titles and abstracts were then screened by 3 independent reviewers (Ong AML, Wang YT, Tay SW) onto a Microsoft (Richmond, VA) Excel spreadsheet. Using a standardized form, the 3 reviewers independently extracted data and assessed study risk of bias and quality using the Cochrane Risk of Bias tool[6] for randomized controlled trials (RCTs) and Newcastle Ottawa Scale (NOS)[7] for cohort studies. A trial was judged with low risk of bias when all six domains of the Cochrane risk of bias tool were classified as low risk of bias for RCTs. Studies that achieved at least six stars for the NOS were considered studies of high quality[7]. No attempts at assessing study quality was made for studies with case series. Any disagreements were resolved by consensus. No studies in the search were discarded because of assessed quality.

Data on study design, location, patient profile, duration of symptoms, follow up periods, date, diagnostic criteria, intervention, outcome, and follow-up were extracted. Due to significant heterogeneity among studies such as study design, treatment and outcome measurements, no head to head comparisons or meta-analysis was performed.

RESULTS

We retrieved 298 articles based on our search criteria (Figure 1). After excluding duplicates (n = 85), pediatric studies (n = 111), studies involving eating disorders (n = 27), singular case reports (n = 22) and studies without mention of treatment strategies (n = 41), we arrived at 12 studies for analysis (Figure 1). These studies consist of 2 RCTs, 1 prospective cohort, 5 prospective observational, 2 mixed retro-spective/pro-spective observational and 2 retrospective observational studies.

A total of 254 patients were included in the analysis, with a mean age of 36.1 (range 18-89). 185 patients (72.8%) were females. 5 studies looked into behavioral therapies, primarily diaphragmatic breathing (DB), where 2 studies were done with electromyography (EMG) guidance[8,9], 1 study was done with HRiM guidance[10] and the other 2 without any visual guidance[11,12]. 2 studies looked at the utility of baclofen[13,14], 1 looked at utility of fundoplication[15] and 1 looked at supportive lifestyle changes[16]. 3 studies looked at a combination of therapies involving pharmaco-logical, behavioral and psychotherapies[2,17,18]. Characteristics of the studies can be found in Table 1.

Assessment of bias for studies

Using the Cochrane risk of bias tool[6], the RCT by Barbal[8] had low risk of bias for the following domains: Allocation, missing outcome data, outcome measures, selection of reported results. However, there were some concerns of bias *via* deviations from intended interventions as study patients may be aware, they were given placebo. Also, the interaction with a health care professional may improve symptoms and adherence to treatment. There was also no mention of compliance rates in treatment as well as some concerns of bias in outcome measurement due to lack of blinding of outcome assessors. For the RCT by Pauwels[14], there was low risk of bias for the following domains: Allocation, deviation from intended intervention, missing outcome data, outcome measurement and selection of reported results. The cohort study by Barba[9] scored 6 on the NOS with a star given for the following domains: representativeness, selection, ascertainment of exposure, demonstration of outcome not present as start, adequate follow up duration and adequacy of follow up.

DISCUSSION

We performed a systematic review looking at adult patients diagnosed with RS, and identified 12 articles evaluating the efficacy of various treatment modalities for RS and ranked them in order of level of evidence (Table 2).

The studies with the strongest evidence were the 2 RCTs looking at EMG-guided biofeedback and Baclofen. In the former[8], 12 patients who underwent 3 biofeedback

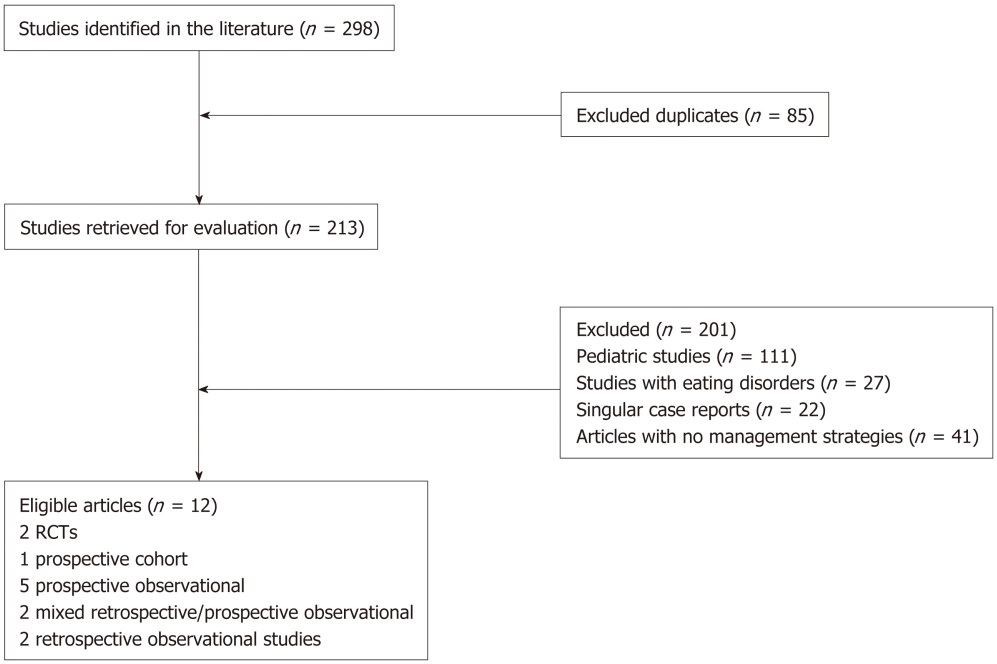

Figure 1 Flow diagram of assessment of studies identified.

sessions had 74% reduction in rumination symptoms compared to 1% reduction in the placebo group with oral simethicone. The improvements with biofeedback appeared sustainable in the long-term with improvement of symptoms at each subsequent follow up. The study when assessed for quality based on the Cochrane Risk of Bias tool[6] had generally low risk of bias, although there were some concerns about the lack of blinding of outcome assessors as well as the placebo group being aware they were in the placebo arm. The other RCT[14] showed that Baclofen at 5-10 mg three times daily reduced the number of symptoms of regurgitation *via* event markers on HRIM and overall treatment evaluation via questionnaire where 63% of patients improved on Baclofen compared to 26% of patients on placebo treatment ($P < 0.0001$). The study quality was assessed to also have low risk of bias apart from having a heterogonous population of RS and supragastric belching, although this more accurately mimics real-world situations where there is significant overlap in presentation for these 2 conditions.

The exercises that were part of the biofeedback protocols[8,9] were essentially abdominal breathing exercises otherwise known as DB[19]. DB was further supported by other non-RCT studies included in this analysis. There were variations on how these were performed, from using EMG guidance[8], HRiM guidance[10] or just delivered without visual aids[11,12]. Some of the studies showed that even a single session of DB training can improve symptoms, but as these symptoms tend to recur over time, compliance to home exercises is likely important to maintain sustainability of response.

Many of the studies analyzed performed physiological tests prior to the treatment and post-treatment, thus allowing an insight into possible mechanisms of the origin of symptoms in these patients. Although the exact pathogenesis of RS is still unknown, the primary initiating mechanism is commonly a post-prandial gastric pressurization[10,11] that possibly results from anterior abdominal muscle contractions[9]. However, a low esophageal sphincter (LES) pressure is also required to facilitate the upward movement of gastric contents as Halland[10] showed that high intragastric pressure waves led to rumination episodes only when accompanied by reduction in esophagogastric junction (EGJ) pressure. Furthermore, post-prandially patients demonstrated contraction of intercostals muscles to facilitate a negative intra-thoracic pressure[9]. It is likely this combination of increased intra-abdominal pressure coupled with negative intra-thoracic pressure and a permissive EGJ that allows rumination to take place. The significance of a low LES pressure has also been highlighted in some of the studies. Patients with low LES baseline pressures were shown to have a poorer outcome to treatment for RS[17]. Reasons for this low LES pressure can be a learned prolonged postprandial voluntary relaxation of the diaphragmatic crura or increased TLESRs[20]. Other suggested possibilities include increased abdominal pressure displacing the EGJ proximally away from the crura thus losing the crural contribution

Table 1 Characteristics of studies included in analysis

Study	Site	Type of study	*n*	Fem (%)	Age (yr) (range)	Diagnostic criteria	Physiological tests done	Treatment	Description of treatment	Primary outcome	Main Results	Proposed mechanism of action	Follow up period (mo)
Barba *et al*[8]	Spain	RCT, Placebo controlled	12	7 (58)	Median 42 (19-69)	Rome 3 rumination syndrome	EMG$^+$ activity of abdomino-thoracic muscles, done PRE and POST	EMG$^+$ guided biofeedback	Pre-meals, patients were trained to control the activity of the abdomino-thoracic muscles under visual control of EMG$^+$ recordings displayed on a monitor. Specifically, they were instructed to voluntarily reduce the activity of intercostal and anterior abdominal muscles and to increase the activity of the diaphragm. After each biofeedback session, patients were instructed to perform the same exercises daily at home for 5 min before and after breakfast, lunch, and dinner. At the end of the treatment period, patients were encouraged to continue practicing these same exercises over time. 3 such sessions performed over 10 d	Reduction in rumination episodes measured over 10 d, patient reported	Regurgitation episodes decreased by 74 ± 6% in the biofeedback group (n = 12) but only by 1 ± 14% in the placebo group (n = 11; P < 0.001). Biofeedback significantly reduced the activity of the abdominothoracic muscles, whereas the placebo had no effect; Number of daily rumination episodes decreased to 7.7 ± 1.9 immediately after biofeedback, 3.0 ± 1.1 by 1 mo, 1.2 ± 0.5 by 3 mo, and 0.7 ± 0.4 by 6 mo (P < 0.001)	Modified basal postprandial muscular tone; Possibly increase awareness in patients to suppress rumination	6 mo
Pauwels *et al*[14]	Belgium	RCT, Placebo controlled	10	6 (60)	Mean 42 (18-61)	Rome 4 rumination syndrome and/or supra-gastric belching	Oesophageal HRiM$^+$ done PRE and POST	Baclofen	5 mg tds first week then increased to 10 mg tds second week, followed by 1 wk washout period, before 2 wk crossover to alternative treatment	Number of symptoms of regurgitation via event marker on HRiM$^+$ and overall treatment evaluation (OTE)	Median number of times that the "regurgitation" marker was pushed significantly lower in baclofen group compared to placebo [4 (0–14) *vs* 6 (0–19), P =0.04] Patients reported significantly better OTE ratings after baclofen compared to placebo [mean score 1 (0–2) *vs* 0 (−1–1), P =0.03]. On baclofen treatment, 63% of patients improved on Baclofen compared to 26% on placebo (P < 0.0001)	Increased LES$^+$ pressure: Postprandial LES$^+$ pressure significantly higher in the baclofen arm compared to placebo [17.79 (12.72–22.68) *vs* 13.06 (7.16–16.91) mm Hg (P = 0.0002)]. Borderline negative correlation between postprandial LES pressure and the number of rumination episodes in the baclofen condition (P = 0.056, r = −0.54). Reduced TLESR$^+$: Postprandial TLESRs was significantly lower after baclofen compared to placebo [4 (1–8) *vs* 7 (3–12), P = 0.017].	No long term follows up

Barba *et al*[9]	Spain	Prospective cohort with controls	24	17 (71)	14-76	Rome 3 rumination syndrome	EMG$^+$ activity, done PRE and POST treatment	EMG$^+$ guided biofeedback	Pre-meals, patients were trained to control the activity of the abdomino-thoracic muscles under visual control of EMG$^+$ recordings displayed on a monitor. Specifically, they were instructed to voluntarily reduce the activity of intercostal and anterior abdominal muscles and to increase the activity of the diaphragm. After each biofeedback session, patients were instructed to perform the same exercises daily at home for 5 min before and after breakfast, lunch, and dinner. At the end of the treatment period, patients were encouraged to continue practicing these same exercises over time. 3 such sessions performed over 10 d	Not defined	Post-biofeedback session, patients experienced a decrease in the number of regurgitation events (8 recorded *vs* 18 in the basal challenge test; $P <$ 0.001). The improvement observed during the first biofeedback session was strengthened by the following biofeedback sessions. Regurgitation events had decreased by 70% ($P <$ 0.001). By the end of the 3 biofeedback sessions, postprandial abdominal symptoms were reduced (1.6 score; $P <$ 0.001 *vs* basal). Further reductions in the number of rumination events during the 6-mo observation period while controls had no changes	Modified basal postprandial muscular tone; Possibly increase awareness in patients to suppress rumination	6 mo
Halland *et al*[10]	United States	Prospective observa-tional	16	9 (56)	Mean 37	Rome 3 rumination	Oesopha-geal HRiM$^+$ done PRE, during and POST treatment	HRM$^+$ guided biofeedback therapy	Behavioral therapy delivered by a single subspecialist gastroenterologist where he placed his hand on the patient's abdomen and instructed patients in diaphragmatic breathing, which entails abdominal rather than chest motion. Patients were also instructed to observe the HRM$^+$ monitor to observe the impact of DB on reduction in gastric pressurizations and regurgitation.	Not defined	Rumination episodes reduced from a median of 5 (2–10) to 1 (0–2) ($P <$ 0.001) during, and 3 (1–5) after ($P <$ 0.001 *vs* during) diaphragmatic breathing.	Diaphragmatic breathing increased EGJ pressure ($P <$ 0.001) and restored a negative gastroesophageal pressure gradient [20 mmHg (80-7)] by reducing postprandial intragastric pressure. DB may also alter vagal acticity and reduce TLESR whilst increasing LES tone	Nil

O'Brien *et al*[2]	United States	Retrospective and Prospective observational	36	29 (81)	Mean 27	Not elaborated	All had oesophageal manometry, 20 had pH studies. Tests done PRE treatment	Various	6 prokinetics 7 antacids 3 behavioural therapy (e.g. biofeedback); 2 psychotherapy; 2 combined behavioural and psychotherapy	Not defined	12/16 patients reported subjected improvement, but not broken down to individual treatment options. No therapy deemed effective enough compared to another	N/A	Mean 25 (7-74)
Soykan *et al*[18]	United States	Retrospective and Prospective observational	10	6 (60)	Mean 28.5 (16-63)	Rome 2 for rumination syndrome	All had oesophageal manometry, electrogastrography, gastric emptying study. All done PRE treatment	Various	5 biofeedback; 2 prokinetics;1 prokinetic and acid blockade; 1 leuprolide acetate and antacid; 1 no treatment	Not defined	all 5 undergoing biofeedback improved, 1 taking prokinetic improved	N/A	Mean 31.2 (6-72)
Vijayvargiya *et al*[12]	United States	Retrospective observational	57	54 (95)	Mean 30.3 (14-62)	Rome 3 for rumination syndrome and rectal evacuation disorder	11 oesophageal manometry, 45 gastric emptying, 3 pH studies, 6 barium oesophagogram, 12 SPECT[+]. All done PRE treatment	Diaphragmatic breathing	*Via* behavioural psychologist with instructions onf diaphragmatic breathing to abort or control regurgitation	Not defined	Not reported	N/A	N/A
Tucker *et al*[11]	United Kingdom	Prospective observational	46	34 (74)	18-68	HRM[+] criteria (Rommel)	All had oesophageal HRM[+] PRE treatment	Diaphragmatic breathing	All patients received a 20 min behavioural intervention immediately after HRM[+] investigation. This included a description of the abnormal findings, cause of symptoms and explanation of the rationale for behavioural therapy. Behavioural instruction was focused on deep muscle relaxation and diaphragmatic breathing	Not defined	Complete improvement in rumination in 20/46 (43%). Partial improvement in 13 (28%)	N/A	Median 5 (3-11)

Lee *et al*[17]	South Korea	Prospective observational	21	8 (38.1%)	Mean 41.9	Modified Rome 2 for rumination ayndrome	All had oesophageal HRM$^+$, pH study and gastric emptying tests PRE treatment	Various	All given levosulpride 25 mg TDS$^+$; supportive psychotherapy, education and reassurance given monthly, with 15 min sessions over a minimum of 6 mo via therapists experienced in eating disorders	Not defined	8 (38.1%) showed improvement, 47.6% unchanged while 3 (14.3%) worsened. Those who improved were statistically more likely to have undergone treatment for > 6 mo and less likely to have low mean LES$^+$ pressure	N/A	Mean 19 (15-24)
Oelschlager *et al*[15]	United States	Prospective observational	5	4 (80%)	Mean 40.6 (18-61)	Rome 2 for rumination syndrome	All had oesophageal manometry and pH studies PRE treatment	Fundoplication	1 laparoscopic, 4 open Nissen fundoplication	Not defined	all had resolution of symptoms;3/5 had pathological acid exposure, 4/5 had hypotensive LES$^+$, 3/5 had hiatal hernias	Restoration of LES$^+$ dysfunction	Median 6 mo, 2 wk - 1 yr
Blondeau *et al*[13]	Belgium	Prospective observational	12	8 (67)	45 (18-89)	Clinical diagnosis	All had oesophageal HRiM$^+$ PRE and POST treatment	Baclofen	10 mg TDS$^+$ for a week	Not defined	Patients on baclofen recorded significantly fewer symptoms during the study [6 (2–22); *P* 0.01). The number of symptom markers for regurgitation was significantly reduced from 9 (0–11) to 1 (0–13) (*P* 0.01); The total number of flow events was significantly reduced from 473 to 282 (39.2%) during baclofen treatment (*P* 0.02)	Increase in LES$^+$ function and reduction in TLESR$^+$; Possible central mechanism of action to reduce sensitivity of stomach during distension and reduction of compulsive behaviour of straining; The number of TLESR$^+$s during the postprandial period was significantly reduced from 15 (9-19) in baseline conditions to 7 (6-15) during baclofen treatment (*P* 0.03). The number of strains was reduced from 32 (17-48) in baseline conditions to 17 (2-70) during baclofen treatment (*P* 0.1).	No long term follows up
Johnson *et al*[16]	United States	Retrospective observational	5	3 (60)	Mean 26.8 (18-43)	Clinical diagnosis	1 barium oesophagogram; 1 gastric emptying test; all done PRE	Lifestyle changes	All advised to eat slowly, chew completely, avoid food triggers, regular exercises, weight reduction, stress management strategies	Not defined	All 5 had complete cessation of symptoms	reduction in behavioural and cognitive processes that may develop and maintain symptoms; improvement in coping mechanisms for symptoms	Mean 34.4 (22-43)

EMG: Electromyography; HRiM: High resolution impedance manometry; LES: Lower esophageal sphincter; TLESR: Transient lower esophageal sphincter relaxation; TDS: Three times daily; HRM: High resolution manometry; SPECT: Single photon emission computed tomography.

Table 2 Summary of treatment options for rumination syndrome

Treatment	Strength of evidence	Treatment outcome
Diaphragmatic Breathing	RCT[8]	Regurgitation episodes decreased by 74% in the biofeedback group compared to 1% in placebo ($P < 0.001$)
	Prospective cohort with controls[9]	Regurgitation events decreased by 70% ($P < 0.001$).
	Prospective observational[10]	Median rumination episodes reduced from 5 (2–10) to 1 (0–2) ($P < 0.001$)
	Retrospective observational[12]	Not reported
	Prospective observational[11]	Complete improvement in rumination in 43%. Partial improvement in 28%
Baclofen	RCT[14]	Median regurgitation events lower with baclofen compared to placebo [4 (0–14) *vs* 6 (0–19), $P = 0.04$]
	Prospective observational[13]	Median regurgitation events significantly reduced from 9 (0-11) to 1 (0-13) (P 0.01)
Surgery	Prospective observational[15]	100% (5/5) resolution of symptoms
Psychotherapy	Prospective observational[17]	38.1% showed improvement. 47.6% unchanged.
	Retrospective observational[16]	100% (5/5) resolution of symptoms

to the EGJ. An unrecognized central mechanism may also be involved since healthy adults are not able to induce rumination[21].

The physiology tests also allow us to understand the rationale for these treatment options, especially in DB, where the evidence appears strongest in terms of quantity and quality. In the study by Halland[10], they demonstrated that DB may improve crural function *via* several mechanisms. DB can directly augment the tone of the LES by voluntary contraction of the crural diaphragm. DB can also prevent the increased intra-gastric pressure from displacing the EGJ proximally, thus not allowing a permissive EGJ during such episodes. Also, DB may alter vagal activity and prevent TLESRs from happening and thus maintain a more prolonged high pressure LES tone. DB also likely competes with the need for the learned behavior of gastric straining, and this abolishes the trigger to ruminate when performed post meals[22]. Barba[8] showed that EMG guided-biofeedback, of which DB was part of the intervention, significantly reduced the activity of the abdominothoracic muscles, whereas the placebo had no effect, and this correlated with reduction of rumination symptoms. Based on their EMG findings pre and post, they postulate that patients with RS have an abnormal level of abdominothoracic muscular tone. They then showed it was possible to specifically target the relevant muscles and unlearn this coordinated abdominothoracic maneuver which generates rumination (*e.g.*, reducing activity of intercostals and anterior abdominal muscle while increasing activity of diaphragm reduces rumination symptoms).

Other studies not involving DB also shed light on mechanisms of RS and its treatment. 2 studies[13,14] showed that baclofen reduced the number of rumination episodes possibly by reduction in TLESRs and increasing postprandial LES pressure which were both significantly different in the intervention group compared to placebo. These mechanisms are similar in those postulated to take place post-DB. Baclofen may have other mechanisms of action as well, as shown by[13] where baclofen reduced voluntary gastric straining events and the authors postulate that this could be either related to central mechanisms of reducing compulsive behaviours of straining or by reducing the mechanosensitivity of the stomach as studies[23] have shown that patients with RS often have increased gastric sensitivity to distension.

There are likely psychosocial and cognitive processes in play that initiate and perpetuate symptoms in RS as evident by patients reporting onset of symptoms following acute illness[24], surgeries[18], psychological stress[18] and major life events[11,18,24]. Comorbid psychiatric disturbances such as depression, anxiety and somatoform disorders[12,18] were frequently found in RS patients, and it is not entirely clear whether these are causes or consequences of RS. Pediatric studies[25] have shown that successfully treating psychiatric disorders, when present, is helpful for RS. It is not unreasonable to think that the same applies to adult patients as patients with psychiatric disorders may have a lack of motivation which interferes with compliance to behavioral treatments[12], and therefore needs to be addressed. Behavioral treatments targeting stress reduction and improving coping mechanisms to symptoms have also been shown to be helpful in reducing symptoms in RS[16]. A single open label study looked at 21 adults with RS[17] and looked the effect of supportive

psychotherapy together with a prokinetic leveosulpiride. Only 38% of patients showed improvement, so perhaps psychotherapy itself is not efficacious but possibly, a more targeted form of psychotherapy in association with behavioral treatments may be effective. As such, investigators are currently actively recruiting patients and looking into using a form of Cognitive Behavioral Therapy to treat this condition (https://clinicaltrials.gov/ct2/show/NCT03113682).

Interestingly, it has been suggested that refractory cases of rumination be treated with surgery such as fundoplication[15]. In this study, all 5 patients had complete cessation of symptoms post-surgery, although 4 out of 5 patients had a hypotensive LES while 3 out of 5 had hiatal hernias and pathological acid exposure, thus improvement in their symptoms could have been due to improvement in their GERD. It is therefore not recommended to treat RS patients with surgery without concomitant GERD or structural abnormalities at this point without further evidence. However, this study showed the likely contribution of an incompetent LES in the overall picture manifestation of RS.

There were some limitations to our analysis. We only included studies in English, and we also excluded pediatric studies since our focus was on adult patients. However, some of the results from pediatric studies could still be relevant in understanding the efficacy of RS treatment. Even though most of the studies included some form of physiological testing, the studies were heterogenous and tests such as gastric emptying studies or 24-h pH impedance studies were often not performed. Thus, the diagnosis of GERD and gastroparesis may be missed in some of these patients labeled as RS, and therefore caution needs to be exercised in interpreting some of the study results. It was difficult to make strong conclusions based on the strength of the data as only 3 studies were controlled and only 2 were randomized interventions. In view of the limited literature available in this field, we retained observational studies despite knowing that they were prone to bias, and thus our recommendations are not based on strong evidence, but rather a summary of what is available in the literature (Tables 2 and 3).

In conclusion, RS may present similarly to other conditions such as GERD and gastroparesis and is likely under-recognized, therefore clinicians need to be aware of this syndrome in their differential diagnosis. Although evidence for treatment options is still limited, the strongest evidence points towards the use of DB and Baclofen, and both should be considered depending on their availabilities. Most of the studies analyze are limited by the small sample sizes and variability in delivery of biofeedback. Therefore, further studies are needed to tackle these knowledge gaps.

Table 3 Suggested approach in treatment of rumination syndrome

Condition	Treatment
Initial treatment	Extensive explanation of condition and underlying mechanism together with reassurance of benign nature of condition[2,20]
	Diaphragmatic breathing by trained personnel (with EMG guidance or HRiM if available)
	If no response to diaphragmatic breathing after ensuring compliance, Baclofen 5-10 mg three times daily
For refractory cases	Consider alternative diagnosis (GERD, gastroparesis, functional dyspepsia, supragastric belching) and treat appropriately
	Since both DB and baclofen appear to be effective and work via different mechanisms, we postulate that a switching to the other therapy or a combination of these therapies could be useful in cases refractory to either treatments
	Address psychological illness, if present. Consider adjunctive psychological therapies to correct cognitive processes that may perpetuate symptoms

EMG: Electromyography; GERD: Gastroesophageal reflux disease; DB: Diaphragmatic breathing.

ARTICLE HIGHLIGHTS

Research background
Rumination syndrome (RS) is a relatively common yet underdiagnosed condition.

Research motivation
There is no consensus on how to treat patients diagnosed with runination syndrome.

Research objectives
Our objectives are to systematically review the literature on the efficacy of treatment options for adults with RS.

Research methods
We conducted a systematic review according to PRISMA guidelines. We searched Medline (1946 to February 2019), EMBASE (1947 to February 2019), PsycINFO (1806 to February 2019) and Cochrane central register of controlled trials for articles discussing treatment options for adult patients (> 18 years) with RS. All relevant articles were accessed in full text. We extracted data on study designs, patient profiles, duration of symptoms, follow up periods, date, diagnostic criteria, interventions and outcomes. Risk of bias assessment was carried out independently by 3 reviewers *via* Cochrane Risk of Bias tool and Newcastle Ottawa Scale for RCTs and Cohort studies respectively.

Research results
12 articles were identified. The strongest evidence pointed towards diaphragmatic breathing (DB), and less so for baclofen. A total of 254 patients were included in the analysis.

Research conclusions
DB has the strongest evidence for efficacy in adults with RS.

Research perspectives
The quality of the evidence is still weak. More research needs to be done in this field.

REFERENCES

1 **Malcolm A**, Thumshirn MB, Camilleri M, Williams DE. Rumination Syndrome. *Mayo Clin Proc* 1997; **72**: 646-652 [DOI: 10.1016/S0025-6196(11)63571-4]
2 **O'Brien MD**, Bruce BK, Camilleri M. The rumination syndrome: Clinical features rather than manometric diagnosis. *Gastroenterology* 1995; **108**: 1024-1029 [DOI: 10.1016/0016-5085(95)90199-X]
3 **Chial HJ**, Camilleri M, Williams DE, Litzinger K, Perrault J. Rumination syndrome in children and adolescents: diagnosis, treatment, and prognosis. *Pediatrics* 2003; **111**: 158-162 [PMID: 12509570 DOI: 10.1542/peds.111.1.158]
4 **Stanghellini V**, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, Talley NJ. Gastroduodenal Disorders. *Gastroenterology* 2016; **150**: 1380-1392 [PMID: 27147122 DOI: 10.1053/j.gastro.2016.02.011]
5 **Kessing BF**, Bredenoord AJ, Smout AJ. Objective manometric criteria for the rumination syndrome. *Am J Gastroenterol* 2014; **109**: 52-59 [PMID: 24366235 DOI: 10.1038/ajg.2013.428]
6 **Higgins JPT**, Savović J, Page MJ, Sterne JAC. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). 2018; 52
7 **Wells GA**, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale

(NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
8 **Barba E**, Accarino A, Soldevilla A, Malagelada JR, Azpiroz F. Randomized, Placebo-Controlled Trial of Biofeedback for the Treatment of Rumination. *Am J Gastroenterol* 2016; **111**: 1007-1013 [PMID: 27185077 DOI: 10.1038/ajg.2016.197]
9 **Barba E**, Burri E, Accarino A, Malagelada C, Rodriguez-Urrutia A, Soldevilla A, Malagelada JR, Azpiroz F. Biofeedback-guided control of abdominothoracic muscular activity reduces regurgitation episodes in patients with rumination. *Clin Gastroenterol Hepatol* 2015; **13**: 100-6.e1 [PMID: 24768808 DOI: 10.1016/j.cgh.2014.04.018]
10 **Halland M**, Parthasarathy G, Bharucha AE, Katzka DA. Diaphragmatic breathing for rumination syndrome: efficacy and mechanisms of action. *Neurogastroenterol Motil* 2016; **28**: 384-391 [PMID: 26661735 DOI: 10.1111/nmo.12737]
11 **Tucker E**, Knowles K, Wright J, Fox MR. Rumination variations: aetiology and classification of abnormal behavioural responses to digestive symptoms based on high-resolution manometry studies. *Aliment Pharmacol Ther* 2013; **37**: 263-274 [PMID: 23173868 DOI: 10.1111/apt.12148]
12 **Vijayvargiya P**, Iturrino J, Camilleri M, Shin A, Vazquez-Roque M, Katzka DA, Snuggerud JR, Seime RJ. Novel Association of Rectal Evacuation Disorder and Rumination Syndrome: Diagnosis, Co-morbidities and Treatment. *United European Gastroenterol J* 2014; **2**: 38-46 [PMID: 24724013 DOI: 10.1177/2050640613518774]
13 **Blondeau K**, Boecxstaens V, Rommel N, Farré R, Depeyper S, Holvoet L, Boeckxstaens G, Tack JF. Baclofen improves symptoms and reduces postprandial flow events in patients with rumination and supragastric belching. *Clin Gastroenterol Hepatol* 2012; **10**: 379-384 [PMID: 22079512 DOI: 10.1016/j.cgh.2011.10.042]
14 **Pauwels A**, Broers C, Van Houtte B, Rommel N, Vanuytsel T, Tack J. A Randomized Double-Blind, Placebo-Controlled, Cross-Over Study Using Baclofen in the Treatment of Rumination Syndrome. *Am J Gastroenterol* 2018; **113**: 97-104 [PMID: 29206813 DOI: 10.1038/ajg.2017.441]
15 **Oelschlager BK**, Chan MM, Eubanks TR, Pope CE, Pellegrini CA. Effective treatment of rumination with Nissen fundoplication. *J Gastrointest Surg* 2002; **6**: 638-644 [DOI: 10.1016/S1091-255X(01)00068-3]
16 **Johnson WG**, Corrigan SA, Crusco AH, Jarrell MP. Behavioral assessment and treatment of postprandial regurgitation. *J Clin Gastroenterol* 1987; **9**: 679-684 [PMID: 3443732 DOI: 10.1097/00004836-198712000-00013]
17 **Lee H**, Rhee PL, Park EH, Kim JH, Son HJ, Kim JJ, Rhee JC. Clinical outcome of rumination syndrome in adults without psychiatric illness: a prospective study. *J Gastroenterol Hepatol* 2007; **22**: 1741-1747 [PMID: 17914944 DOI: 10.1111/j.1440-1746.2006.04617.x]
18 **Soykan I**, Chen J, Kendall BJ, McCallum RW. The rumination syndrome: clinical and manometric profile, therapy, and long-term outcome. *Dig Dis Sci* 1997; **42**: 1866-1872 [PMID: 9331149 DOI: 10.1023/A:1018854925196]
19 **Chitkara DK**, Van Tilburg M, Whitehead WE, Talley NJ. Teaching diaphragmatic breathing for rumination syndrome. *Am J Gastroenterol* 2006; **101**: 2449-2452 [PMID: 17090274 DOI: 10.1111/j.1572-0241.2006.00801.x]
20 **Tack J**, Blondeau K, Boecxstaens V, Rommel N. Review article: the pathophysiology, differential diagnosis and management of rumination syndrome. *Aliment Pharmacol Ther* 2011; **33**: 782-788 [PMID: 21303399 DOI: 10.1111/j.1365-2036.2011.04584.x]
21 **Halland M**, Pandolfino J, Barba E. Diagnosis and Treatment of Rumination Syndrome. *Clin Gastroenterol Hepatol* 2018; **16**: 1549-1555 [PMID: 29902642 DOI: 10.1016/j.cgh.2018.05.049]
22 **Hejazi RA**, McCallum RW. Rumination syndrome: a review of current concepts and treatments. *Am J Med Sci* 2014; **348**: 324-329 [PMID: 24642653 DOI: 10.1097/MAJ.0000000000000229]
23 **Thumshirn M**, Camilleri M, Hanson RB, Williams DE, Schei AJ, Kammer PP. Gastric mechanosensory and lower esophageal sphincter function in rumination syndrome. *Am J Physiol* 1998; **275**: G314-G321 [PMID: 9688659 DOI: 10.1152/ajpgi.1998.275.2.G314]
24 **Amarnath RP**, Abell TL, Malagelada JR. The rumination syndrome in adults. A characteristic manometric pattern. *Ann Intern Med* 1986; **105**: 513-518 [PMID: 3752757 DOI: 10.7326/0003-4819-105-4-513]
25 **Green AD**, Alioto A, Mousa H, Di Lorenzo C. Severe pediatric rumination syndrome: successful interdisciplinary inpatient management. *J Pediatr Gastroenterol Nutr* 2011; **52**: 414-418 [PMID: 21407115 DOI: 10.1097/MPG.0b013e3181fa06f3]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 309-322

DOI: 10.13105/wjma.v7.i6.309

ISSN 2308-3840 (online)

SYSTEMATIC REVIEW

Surgery with adjuvant or neoadjuvant treatment *vs* surgery alone for resectable pancreatic cancer: A network meta-analysis

Pu Shen, Kai-Jun Huang, Chuan-Zhao Zhang, Li Xiao, Tao Zhang

ORCID number: Pu Shen (0000-0001-7740-6672); Kai-Jun Huang (0000-0002-5172-3212); Chuan-Zhao Zhang (0000-0003-1267-2245); Li Xiao (0000-0003-4025-2555); Tao Zhang (0000-0001-9189-0667).

Author contributions: Shen P and Zhang T designed and organized the study protocol; Huang KJ and Xiao L reviewed and selected the papers; Shen P and Zhang CZ extracted and analyzed the data and wrote the paper; all authors had access to the data and statistical analyses, approved the final article, and attested to the validity of the results.

Supported by the Medical Scientific Research Foundation of Guangdong Province, No. A2017229.

Conflict-of-interest statement: The authors disclose no potential conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Pu Shen, Li Xiao, Tao Zhang, Department of Anesthesia, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Kai-Jun Huang, Chuan-Zhao Zhang, Department of General Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong Province, China

Corresponding author: Tao Zhang, MD, Doctor, Professor, Department of Anesthesia, the First Affiliated Hospital, Sun Yat-sen University, No. 58, Zhongshan II Road, Guangzhou 510080, Guangdong Province, China. zhangt45@mail2.sysu.edu.cn
Telephone: +86-20-37583761
Fax: +86-20-37583761

Abstract

BACKGROUND

Pancreatic cancer is one of the most common and lethal malignancies worldwide. The common treatment options for resectable pancreatic cancer include surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, the optimal treatment is still controversial.

AIM

To identify the most effective approach for pancreatic cancer using network meta-analysis.

METHODS

Eligible studies were searched from PubMed, MEDLINE, EMBASE, Cochrane database, and Google scholar. We searched and included randomized controlled trials reporting on neoadjuvant and adjuvant therapies. For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. For indirect comparisons, Bayesian network meta-analysis was used to combine direct and indirect evidence. We used relative hazard ratios (HRs) to estimate death difference of different treatments, and relative odds ratios (ORs) for toxic effects. Treatment effects were ranked based on their efficacy for improving survival or reducing toxicity using rankogram. The quality of evidence of estimates from direct comparison and network meta-analysis was evaluated following the GRADE approach.

RESULTS

We included 13 high quality trials with 1591 participants in this network meta-analysis. Compared with surgery alone [pooled HR = 0.7, 95% confidence

Manuscript source: Unsolicited manuscript

Received: April 13, 2019
Peer-review started: April 15, 2019
First decision: May 16, 2019
Revised: June 4, 2019
Accepted: June 10, 2019
Article in press: June 10, 2019
Published online: June 30, 2019

P-Reviewer: Hara K, Ahmed M, Fabozzi M, Bramhall S
S-Editor: Dou Y
L-Editor: Wang TQ
E-Editor: Ma YJ

interval (CI): 0.62-0.79] and surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72), surgery with adjuvant CT had a higher rate of overall survival. In contrast, standard pairwise meta-analysis showed a statistically significant survival advantage of surgery with adjuvant CT compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; $P < 0.001$). Rankogram showed that surgery with adjuvant CT was most likely to rank the best in terms of overall survival (probability: 94.2%), followed by surgery alone (probability: 5.8%). No significant differences in overall toxicity or haematological toxicity were found between all the therapies. High quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

CONCLUSION
Surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT, suggesting surgery with adjuvant CT is the optimal treatment for resectable pancreatic cancer.

Key words: Pancreatic cancer; Surgery; Network meta-analysis; Adjuvant therapy; Neoadjuvant therapy

Core tip: No consensus is available in previous studies about the most beneficial treatment option for resectable pancreatic cancer. This is the first network meta-analysis comparing the efficiency of surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. We investigated these treatment options in terms of overall survival and toxicity. We found that surgery with adjuvant CT prolonged overall survival compared with surgery alone and surgery with adjuvant CRT. Surgery with adjuvant CT is the optimal treatment for resectable pancreatic cancer.

Citation: Shen P, Huang KJ, Zhang CZ, Xiao L, Zhang T. Surgery with adjuvant or neoadjuvant treatment *vs* surgery alone for resectable pancreatic cancer: A network meta-analysis. *World J Meta-Anal* 2019; 7(6): 309-322
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/309.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.309

INTRODUCTION

Pancreatic cancer is one of the most common and lethal malignancies[1]. Surgical resection is the only potential curative treatment for pancreatic cancer. However, even after radical removal of the tumor (R0), the prognosis remained poor, with the 5-year survival rate being less than 25% and the median survival time being 14-21 mo[2-4]. High incidence of both locoregional and distant recurrences is responsible for the poor prognosis. Thus, a multimodal approach is needed to decrease the high recurrence rate as well as increase overall survival[5,6].

Several neoadjuvant or adjuvant therapies have been shown to be beneficial in selected patients. These therapies are neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, there are debates over which therapy can benefit patients mostly. Regarding neoadjuvant therapy, recent meta-analysis found no significant difference in the overall survival between neoadjuvant CRT and surgery[7]. With regard to adjuvant therapy, the benefit of adjuvant therapy for resectable pancreatic cancer is still controversial, especially the impact of adjuvant CRT. Adjuvant CRT using fluorouracil is considered standard of care in the United States. However, the EORTC trial demonstrated no benefit of adjuvant CRT over observation in patients with resected pancreatic cancer (median survival: 1.3 year *vs* 1.0 year)[8]. Thus, more powerful and comprehensive evidence is needed to evaluate the best treatment strategy for resectable pancreatic cancer.

There have been several traditional meta-analyses comparing the benefit of neoadjuvant therapy or adjuvant therapy. However, all of the previous meta-analyses

only addressed neoadjuvant therapy[7,9-11] or adjuvant therapy alone[12-14]. Thus, it is interesting and meaningful for us to perform this network meta-analysis, that is, to compare both neoadjuvant and adjuvant therapies with surgery alone. The advantage of network meta-analysis is that it can compare different treatments without direct clinical trials. That is, if we have only clinical trials comparing A to B and B to C, we can estimate A to C using network met-analysis. Besides, treatment options can be ranked based on their efficacy for improving survival or reducing toxicity in network meta-analysis.

The aim of this network meta-analysis was to identify the most effective treatment for resectable pancreatic cancer by comparing overall survival and toxic effects after neoadjuvant or adjuvant CT and CRT.

MATERIALS AND METHODS

The protocol of this network meta-analysis was registered with the prospective register of systematic reviews, PROSPERO (CRD42017057053). This network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[15] and Cochrane guidelines[16].

Search strategy

Eligible studies were searched from PubMed, Medline, EMBASE, Cochrane database, and Google scholar, using a combination of following terms "pancreatic cancer", "pancreatic neoplasm", "neoadjuvant therapy", and "adjuvant therapy". A manual search through published articles was performed additionally. No publication year was restricted in the search. The search was carried out independently by two authors.

Inclusion and exclusion criteria

The following inclusion criteria were used: (a) Randomized controlled trials; (b) Studies investigating surgery alone, neoadjuvant therapies, or adjuvant therapies for resectable pancreatic cancer; and (c) Studies that had at least one of the following outcomes: Survival and toxicity. Single-arm studies, nonrandomized cohort studies, and studies comparing different ways of adjuvant or neoadjuvant treatment were not included in this network meta-analysis.

Data extraction and quality assessment

The information on study design, methods, patient characteristics, treatment protocols, and outcome (overall survival and toxicity) was extracted independently by two authors. We extracted reported adjusted hazard ratios (HRs) to measure overall survival. When HRs were not reported, we estimated them from summary statistics (Kaplan-Meier curves) in accordance with practical methods for incorporating summary time-to-event data into meta-analysis[17]. If there was no enough information to estimate HRs, median survival durations would be used in this network meta-analysis[18]. Only grade 3 or 4 toxicities (overall toxicities and haematological toxicities) were extracted and analyzed in this network meta-analysis. The quality of randomized control study was assessed by the Cochrane Collaboration's tool[19]. Data collection and study quality assessment were performed following the Quality of Reporting of Meta-Analyses statement.

Data synthesis and analysis

The study outcomes were overall survival and toxicity after neoadjuvant or adjuvant therapies. For network meta-analysis of overall survival, the preferred outcome measure was reported HRs, followed by estimated HRs and median survival durations. Relative treatment effects (HRs) in multi-arm trials were converted to arm-specific outcomes[18]. For network meta-analysis of toxicity (overall toxicity and haematological toxicities), we used odds ratios (ORs) as outcome measures. ORs were calculated from the summary number of reported toxicity events and summary number of exposure patients in each trial. Since the definition and reporting type of toxicity were diverse in the included studies, we only summarize seven toxicity events [nausea/vomiting, infection/fever, asthenia/fatigue, diarrhea, hematological toxicity (leukopenia, thrombopenia, and anemia)] as overall toxicity.

For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. Heterogeneity was quantified using *I*-squared statistic. Publication bias was evaluated using the funnel plot. Traditional pairwise meta-analysis was performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, United Kingdom).

For indirect comparisons, we conducted random-effects Bayesian network meta-

analysis using Markov chain Monte Carlo methods in The R Programming Language 3.3.2 [R Core Team (2016), R Foundation for Statistical Computing, Vienna, Austria]. Network meta-analysis assumes "consistency" of treatment effects across all included randomized trials, that is, the direct and indirect estimates are the same effects. Network consistency was evaluated by comparing the direct estimates to the indirect estimates using the node splitting model. We used non-informative uniform and normal prior distributions in network meta-analysis. And we used a thinning interval of 500 for each chain and yielded 5000 iterations to obtain the posterior distributions of model parameters. Convergence of iterations was assessed using Gelman-Rubin-Brooks statistic. Trace plot and density plot were used to assess the convergence of the model. The summary effect of each comparison will be presented as point estimate (HR) and the corresponding 95% confidence interval (CI). The probability of each arm achieving the best rank among all the options was calculated and is presented as rankogram. The efficacy of different treatments was ranked using rankogram.

Quality of evidence

We evaluated the quality of evidence of estimates from direct comparison and network meta-analysis following the GRADE approach. The quality of evidence has four levels orderly: High, moderate, low, and very low quality. In this approach, the quality of direct evidence from RCTs is high initially and can be rated down based on risk of bias, indirectness, imprecision, inconsistency, or publication bias. The quality of indirect evidence starts at the lowest level of direct evidence that contributes as the preferred loops to the indirect evidence, and can be rated down based on imprecision or intransitivity. Network meta-analysis combines both direct and indirect evidence to reach a more comprehensive result, thus, the quality of evidence from network meta-analysis is assigned with the higher level of the direct and indirect evidence.

RESULTS

Characteristic of included studies

We identified 350 potentially relevant articles without duplicates from database searches and manual searches. After initial screening of these records, we excluded 252 articles because they investigated neither neoadjuvant nor adjuvant therapy of pancreatic cancer. We detailedly assessed the remaining 98 articles by abstracts and excluded 68 not reporting randomized control studies. After assessing full texts of the potential eligible 30 articles, we included 14 articles[8,20-32] (13 trials) in the network meta-analysis (Figure 1). If a single trial was reported in different publications, we combined the data of the different publications. And if a single outcome in a same trial was reported in different publications, the result of the latest publication would be used. The ESPAC-1 trial[29] included three subgroups, as the subgroup with two-by-two factorial design was updated in the following report[28]; this subgroup comparison was recognized as ESPAC-plus trial[28] and the last two subgroups as ESPAC-1 trial[29] in this meta-analysis. Also, we included data from ESPAC-3-v1[25] which was not included in the ESPAC-1 trial to avoid duplication.

The methodological quality of the included 13 trials was high (Supplemental Table 1). Four trials did not report sequence and six trials did not report allocation concealment. Although blinding was not reported in any trial, the primary outcome (overall survival) would not be affected by blinding or not, and a low risk of bias was recognized. Finally, we included 13 high quality trials with 1591 participants in this network meta-analysis (Figure 2). A total of 1591 participants were randomized to receive either neoadjuvant CRT with surgery (n = 51), surgery alone (n = 703), surgery with adjuvant CT (n = 665), or surgery with adjuvant CRT (n = 172).

The characteristics of the 13 included trials are summarized in Table 1 and Supplemental Table 2. All of the included trials were two-arm studies except the ESPAC-1 plus trial[28], which was a four-arm trial using a two-by-two factorial design. The recruitment period ranged from 3 to 8 years. Both pancreatic adenocarcinoma and invasive ductal pancreatic cancer were included in this meta-analysis. For trials including periampullary carcinoma, the data about periampullary cancer were excluded[8]. The median age ranged from 57 to 71.5 years old. Most (> 90%) of included participants had primary tumor stage T1-T3, and most of them had nodal status N0-N1. The schedule of CT or CRT can be recognized briefly in Table 1.

Direct comparison meta-analysis of overall survival

Standard pairwise meta-analysis of direct comparisons was feasible for the following comparisons: neoadjuvant CRT with surgery *vs* surgery alone (2 trials, n = 104), surgery with adjuvant CT *vs* surgery alone (7 trials, n = 1080), and surgery with

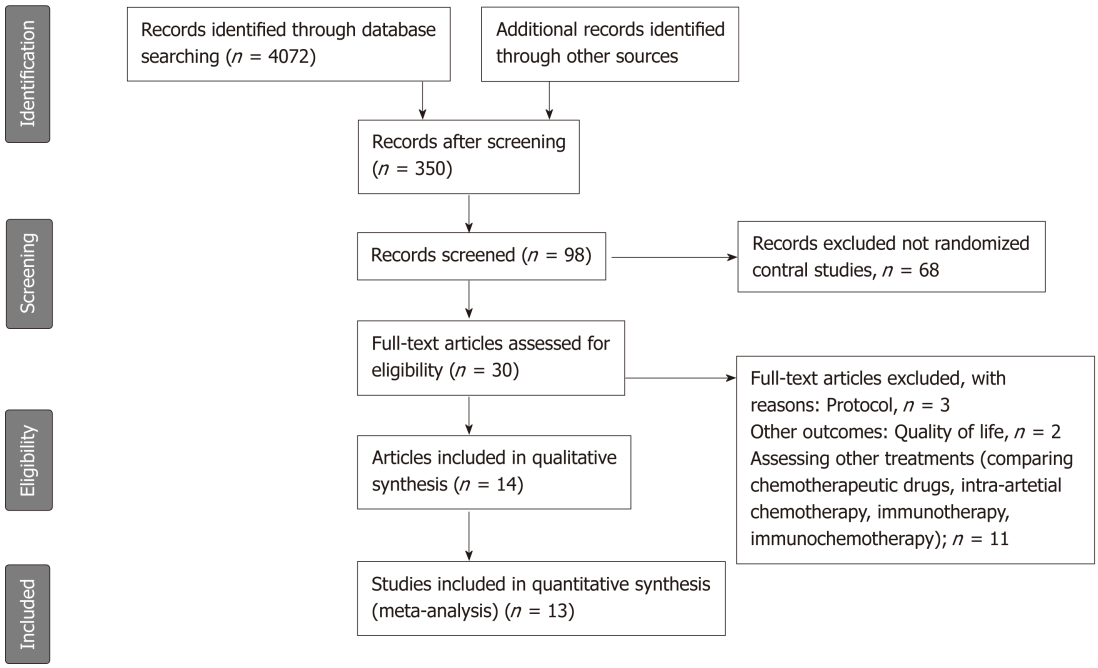

Figure 1 PRISMA flow chart of literature search showing the identification, screening, eligibility, and inclusion phases of the search.

adjuvant CRT *vs* surgery alone (3 trials, n = 254), and surgery with adjuvant CRT *vs* surgery with adjuvant CT (1 trial, n = 90). Only surgery with adjuvant CT showed a statistically significant survival advantage compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; P < 0.001) (Figure 3). No statistical difference was found in other direct comparisons. Heterogeneity was found only in the comparison of surgery with adjuvant CRT *vs* surgery alone (I^2 = 72%). No publication bias was found using the funnel plot.

Network meta-analysis of overall survival

All 12 trials reported information on survival and were included for Bayesian network meta-analysis. Density plot, trace plot, and Brooks-Gelman-Rubin diagnosis plot in Bayesian network meta-analysis of overall survival showed satisfied convergence of network plot model (Supplemental Figure 1). We summarize the result of network meta-analysis of overall survival in Figure 4. Surgery with adjuvant CT showed statistically better overall survival compared with surgery alone (pooled HR = 0.7, 95%CI: 0.62-0.79), which is similar to the results in direct comparison. Surgery with adjuvant CT also statistically improved survival compared with surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72). No significant results were found between other comparisons (neoadjuvant CRT with surgery *vs* surgery alone, surgery with adjuvant CRT *vs* surgery alone, surgery with adjuvant CT *vs* neoadjuvant CRT with surgery, and surgery with adjuvant CRT *vs* surgery with adjuvant CT) (Figure 4).

Network meta-analysis results are consistent with the results from traditional pairwise meta-analysis, suggesting no inconsistency between direct and indirect evidence. We also compared the results of direct and corresponding indirect comparison using node-splitting model. No inconsistency was found (surgery with adjuvant CT *vs* surgery alone, P = 0.789; surgery with adjuvant CRT *vs* surgery alone, P = 0.562; and surgery with adjuvant CT *vs* surgery with adjuvant CRT P = 0.205). Heterogeneity between studies was found using the random-effects model (I^2_{pair} = 59.9; I^2_{cons} = 67.6).

Rankogram (Figure 5) summarizes the ranking probability of the four treatment strategies in terms of overall survival. Surgery with adjuvant CT had the highest probability (94.2%) to rank the best in terms of improving overall survival, followed by surgery alone (5.8%), neoadjuvant CRT with surgery (0%), and surgery with adjuvant CRT (0%).

The results of grading the quality of evidence for overall survival are summarized in Table 2. Based on network meta-analysis, high quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

Table 1 Study characteristics of included studies

Study	Arms	Number	Period	Country	Schedule
Casadei *et al*[20], 2015	NCRT + S	18	2007-2014	Italy	2 cycles of gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 d, then 45 Gy radiation with gemcitabine 50 mg/m^2 twice weekly for 6 wk
	Surgery	20			
Golcher *et al*[21], 2015	NCRT + S	33	2003-2009	Germany, Switzerland	8 Gy to 55.8 Gy (tumor) or 50.4 Gy (regional lymph nodes) radiation with gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2 on days 1, 8, 22, and 29
	Surgery	33			
Oettle *et al*[22,26], 2007, 2013	S + ACT	179	1998-2004	Germany, Austria	3 cycles of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 wk
	Surgery	175			
Kosuge *et al*[27], 2006	S + ACT	45	1992-2000	Japan	2 courses of cisplatin 80 mg/m^2 on the first day; 5-fluorouracil 500 mg/m^2 daily for the first 5 d
	Surgery	44			
Ueno *et al*[24], 2009	S + ACT	58	2002-2005	Japan	3 cycles of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 wk
	Surgery	60			
Bakkevold *et al*[31], 1993	S + ACT	30	1984-1987	Norway	6 cycles of 5-fluorouracil 500 mg/m^2, doxorubicin 40 mg/m^2, and mitomycin C 6 mg/m^2 once every 3 wk
	Surgery	31			
Smeenk *et al*[8], 2007 Klinkenbijl *et al*[30], 1999	S + ACDT	110	1987-1995	Europe	2 courses of 20 Gy radiotherapy (2 Gy/d, 5 d/wk at weeks 1-2 and 5-6) and 25 mg/kg 5-fluorouracil daily for 5 d
	Surgery	108			
Kalser *et al*[32], 1985	S + ACDT	21	1974-1982	USA	2 courses of 20 Gy (5 d a week) radiotherapy and 500 mg/m^2 fluorouracil daily for 3 d
	Surgery	22			
Van Laethem *et al*[23], 2010	S + ACDT	45	2004-2007	France	2 cycles of gemcitabine 1000 mg/m^2 weekly for 3 wk; followed by 50.4 Gy radiotherapy and 300 mg/m^2 gemcitabine weekly for two weeks
	S + ACT	45			4 cycles of gemcitabine 1000 mg/m^2 weekly for 3 wk
Neoptolemos *et al*[25,28,29], 2001, 2004, 2009 (ESPAC-1)	S + ACDT	73	1994-2000	Europe	2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1-3
	S + ACT	75			6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d

	S + ACT + ACDT	72			2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1-3; then 6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	69			
ESPAC-1 plus	S + ACDT	33	1994-2000	Europe	2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1–3
	Surgery	36			
	S + ACT	97			6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	95			
ESPAC-3 (V1)	S + ACT	61	1994-2000	Europe	6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	61			

NCRT + S: Neoadjuvant chemoradiotherapy with surgery; S + ACT: Surgery with adjuvant chemotherapy; S + ACRT: Surgery with adjuvant chemoradiotherapy.

Network meta-analysis of toxicity

Data on toxicity were available in seven trials. We summarize all the reported toxicity events [nausea/vomiting, infection/Fever, asthenia/Fatigue, diarrhea, and hematological toxicity (leukopenia, thrombopenia, and anemia)] in Supplemental Table 3. Neoadjuvant or adjuvant CT and CRT were well tolerated, and grade 3 or 4 toxicities occurred infrequently. We summarize the result of network meta-analysis on overall toxicity and haematological toxicity in Figure 4. Density plot, trace plot, and Brooks-Gelman-Rubin diagnosis plot showed satisfied convergence of network plot model (Supplemental Figure 2). No significant differences in overall toxicity or haematological toxicity were found between all the comparisons (neoadjuvant CRT with surgery, surgery with adjuvant CRT, and surgery with adjuvant CT) (Figure 4).

DISCUSSION

This study is the first analysis to compare efficacy of neoadjuvant therapies, adjuvant therapies, and surgery alone for resectable pancreatic cancer together in a single analysis. In our network meta-analysis, we included 13 high quality trials with 1591 participants. We demonstrated three principal findings in our analysis: surgery with adjuvant CT has better survival compared with surgery alone and surgery with adjuvant CRT; neoadjuvant CRT with surgery shows no significant difference in survival compared with surgery alone and adjuvant therapies; and toxicities after CT or CRT are well tolerated and show no significant difference among the treatment strategies included in this meta-analysis.

In our network meta-analysis, high quality evidence confirmed the survival advantage of adjuvant CT over surgery alone. Although overall survival associated with adjuvant CT had been evaluated in several head-to-head comparisons[22,24,25,27,31], the absence of statistical significance led to equivocal conclusions[24,31]. Previous meta-analysis also demonstrated a survival difference when comparing surgery alone and surgery with adjuvant CT[12-14]. However, the most recent meta-analysis[13] was performed in 2007 and only included five randomized control studies. Moreover, it used only median survival time and 5-year survival rate instead of HRs to estimate survival difference, which was less precise. In our study, we estimated the survival difference by combining direct and indirect comparisons of different treatments. Moreover, we used both reported HRs and estimated HRs from all the included studies to minimize the selection bias. Thus, we provided the most powerful and reliable evidence that adjuvant CT is better than surgery alone in increasing overall survival for resectable pancreatic cancer.

The survival difference between adjuvant CT and adjuvant CRT for resectable pancreatic cancer remains controversial. Only a few studies demonstrated the

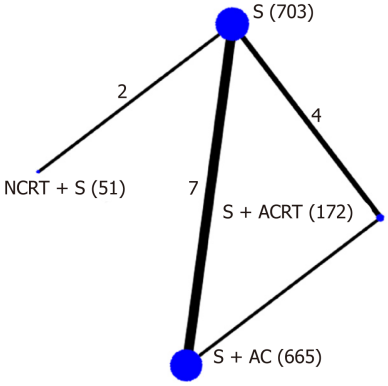

Figure 2 Network plot. Network plot showing the following different treatment strategies for resectable pancreatic cancer: neoadjuvant chemoradiotherapy with surgery (NCRT + S) (*n* = 51), surgery alone (S) (*n* = 703), surgery with adjuvant chemotherapy (S + ACT) (*n* = 665), or surgery with adjuvant chemoradiotherapy (S + ACRT) (*n* = 172).

survival difference between adjuvant CT and adjuvant CRT[23,29]. A phase II randomized controlled study involving 90 participants compared the toxicity and survival between adjuvant gemcitabine alone and gemcitabine-based CRT, and no significant difference was found in survival due to small sample size[23]. The ESPAC-1 trial compared the survival using a two-by-two factorial design (observation, CRT alone, CT alone, or both)[29]. However, the trial was not powered to compare these four groups directly, and only found a potential benefit of adjuvant CT but not adjuvant CRT. In our study, moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival. We confirmed the survival benefit of adjuvant CT over surgery with adjuvant CRT for the first time. Pancreatic cancer is a systemic disease and micrometastasis after surgery may be responsible for high recurrence and low survival. Thus, adjuvant CT but not CRT can benefit the survival of pancreatic cancer patients after surgery. However, CRT in the included studies was performed mainly using external beam, and more highly targeted radiotherapy is now available. The survival benefit between highly targeted radiotherapy and adjuvant CT should be reevaluated in the future study.

CT agents for adjuvant CT are diverse. It is still controversial regarding the best CT agents for adjuvant CT. The ESPAC-3 trial demonstrated that fluorouracil plus folinic acid resulted in similar overall survival to gemcitabine in patients after complete resection of pancreatic cancer[33]. A recent network meta-analysis showed that adjuvant CT with fluorouracil or gemcitabine provided better overall survival than observation[34]. S-1 is another new CT agent for pancreatic cancer. Recent randomized control trials showed that S-1 was superior to gemcitabine, suggesting that S-1 is a new standard care for resected pancreatic cancer[35-37]. In our study, CT agents for adjuvant therapy included gemcitabine[22,24], cisplatin[27], 5-fluorouracil plus doxorubicin plus mitomycin C[31], and fluorouracil plus folinic acid[31]. We combined all of the adjuvant CT with different CT agents in a single arm in this network meta-analysis, because we assumed that the effect of different CT agents for adjuvant CT was consistent. Besides, we tried to compare the effect difference of adjuvant CT with adjuvant CRT and neoadjuvant CRT, and the effect difference was not affected by different CT agents.

The necessity and survival benefit of neoadjuvant therapy for pancreatic cancer is controversial. Borderline pancreatic cancer recently emerged as a category clinically distinct from resectable or locally advanced disease. Neoadjuvant therapy is currently recommended for borderline resectable disease in the National Comprehensive Cancer Network guidelines[38,39]. However, only two reported RCTs access neoadjuvant CRT for resectable pancreatic cancer so far, and both two RCTs found no survival benefit of neoadjuvant CRT. One of the included RCTs involving 38 participants chose R0 resection as the primary endpoint[20], and another RCT involving 66 patients was terminated early due to slow recruiting[21]. Neoadjuvant therapy is also assessed in our network meta-analysis. Only neoadjuvant CRT with surgery was assessed, as no RCTs about neoadjuvant CT can be found. We found no significant result when comparing neoadjuvant CRT with surgery alone, adjuvant CT, and adjuvant CRT. Now, several randomized controlled trials are ongoing to investigate the survival benefit of neoadjuvant CRT for the treatment of borderline and resectable pancreatic cancer[40-43]. Our result showed no survival benefit of neoadjuvant CRT. Thus, we should be cautious with using neoadjuvant CRT for resectable pancreatic cancer until other powerful evidence exists.

Table 2 Pooled hazard ratio of overall survival from direct and network meta-analysis

Intervention	Direct meta-analysis		Network meta-analysis	
	HR	Evidence	HR	Evidence
Compared to surgery alone				
Neoadjuvant CRT + S	0.96 (0.68, 1.37)	Low[1,2]	1.10 (0.64, 1.90)	Low
S + adjuvant CT	0.75 (0.63, 0.89)	High	0.70 (0.62, 0.79)	High
S + adjuvant CRT	0.88 (0.51, 1.54)	Moderate[3]	1.10 (0.97, 1.30)	Moderate
Compared to neoadjuvant CRT + S				
S + adjuvant CT	-	-	0.63 (0.36, 1.10)	Low
S + adjuvant CRT	-	-	1.00 (0.57, 1.80)	Low
Compared to S + adjuvant CT				
S + adjuvant CRT	0.98(0.59, 1.64)	Low[4]	1.6 (1.40, 1.80)	Moderate

[1]Risk of bias: one of included trial did not report allocation concealment and random sequence generation.
[2]Imprecision: small sample size.
[3]Inconsistency: heterogeneity was found in this comparison (I^2 = 72%).
[4]Imprecision: wide confidence interval. HR: Hazard ratio; CRT: Chemoradiotherapy; S: Surgery; CT: Chemotherapy.

Our network meta-analysis has several strengths. It is the first comprehensive analysis of all the major treatment strategies for resectable pancreatic cancer including neoadjuvant therapy, surgery, and adjuvant therapy. We combined both direct and indirect evidence to reach more precise conclusions, which also allowed us to compare therapies indirectly and rank different therapies clearly. Furthermore, we assessed both overall survival and toxicity of all the therapies. Our meta-analysis provides comprehensive and clear evidence for the treatment of resectable pancreatic cancer, which is great important and meaningful in clinical care.

The limitations of this meta-analysis also need to be acknowledged. First of all, the RCTs included in this analysis were conducted over four decades, and changes in CRT schedule, CT agents, schedules, and surgery techniques may affect the results. However, transitivity assumption was met and there was no evidence of statistically significant inconsistency in this network. This may have less effect on the result. Second, we included both neoadjuvant and adjuvant therapies to offer a comprehensive overview. However, we included only a limited number of trials (n = 13), and only two trials evaluated neoadjuvant therapies. Thus, although no sig-nificant result about overall survival was found when comparing neoadjuvant therapies with other treatments, this conclusion about neoadjuvant therapies should be interpreted with some caution. Finally, since the definition and reporting type of toxicity were diverse in the included studies, we only summarized seven typical toxicity events as overall toxicity. Although some toxicity events may be neglected in this analysis, the results should still provide effective estimates.

In conclusion, our network meta-analysis show that surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT. Therefore, we recommend surgery with adjuvant CT as the optimal care for resectable pancreatic cancer. Later research should be focused on the best agents for adjuvant CT.

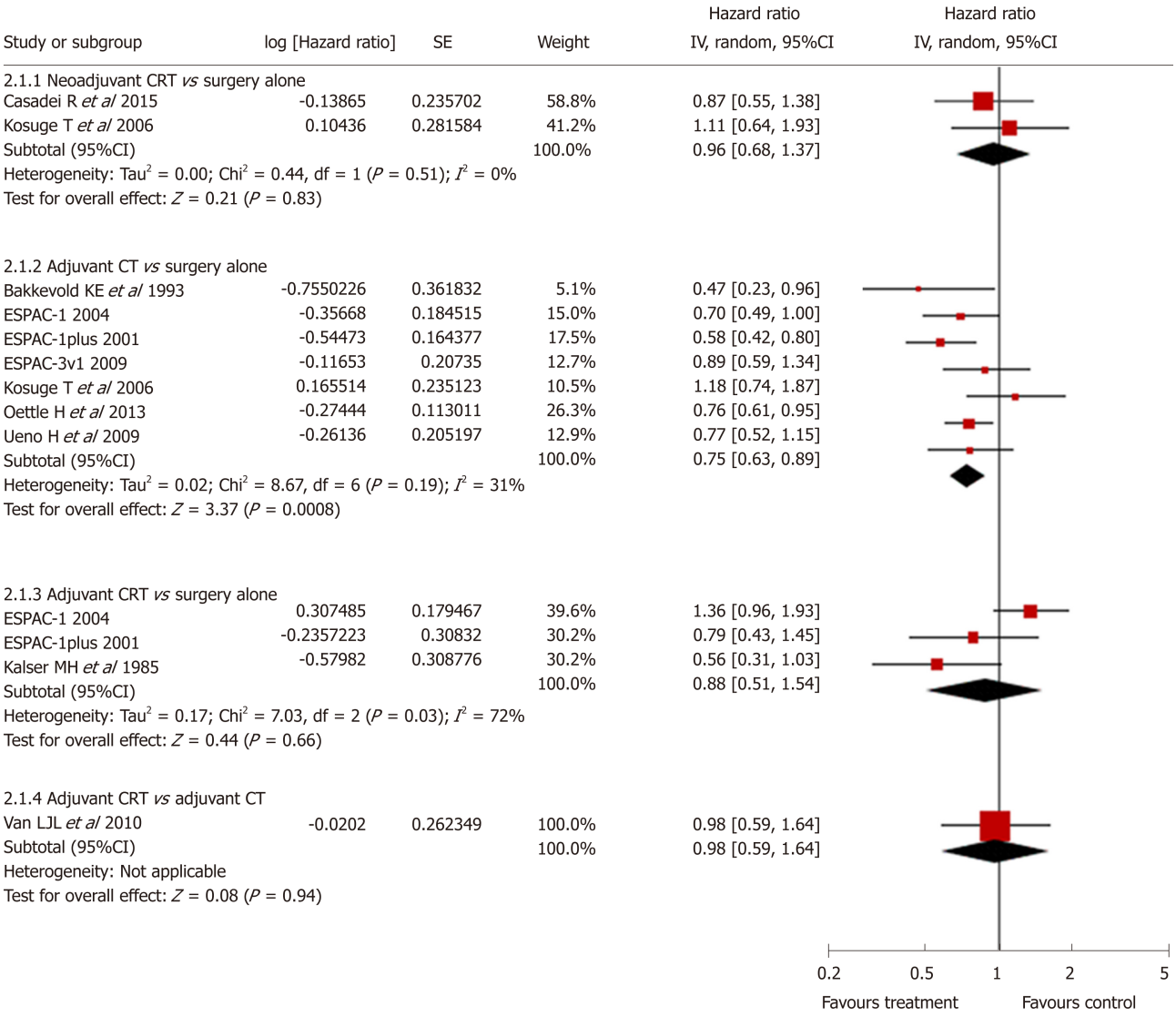

Figure 3 Forest plot of direct comparison meta-analysis of overall survival. Squares and horizontal lines correspond to the study-specific HRs and 95% CIs, respectively. The area of the squares correlates with the weight of each enrolled study, and the diamonds represent the summary HRs and 95% CIs. HRs: Hazard ratios; CI: Confidence interval.

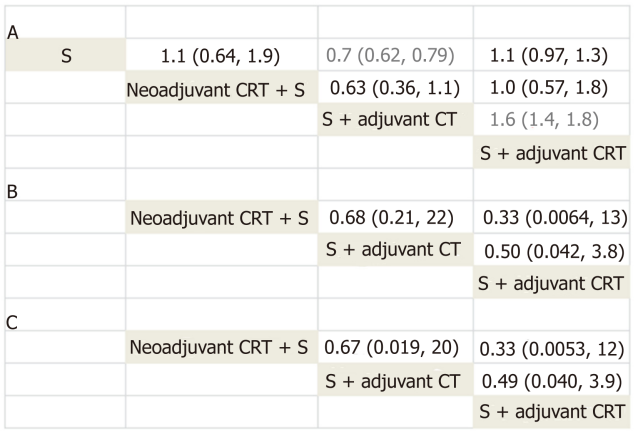

Figure 4 Network meta-analysis of overall survival (A), overall toxicity (B), and haematological toxicity (C). The column treatment is compared with the row treatment. Overall survival was estimated using pooled hazard ratios and 95% confidence intervals. Toxicity was estimated using pooled odds ratios and 95% confidence intervals.

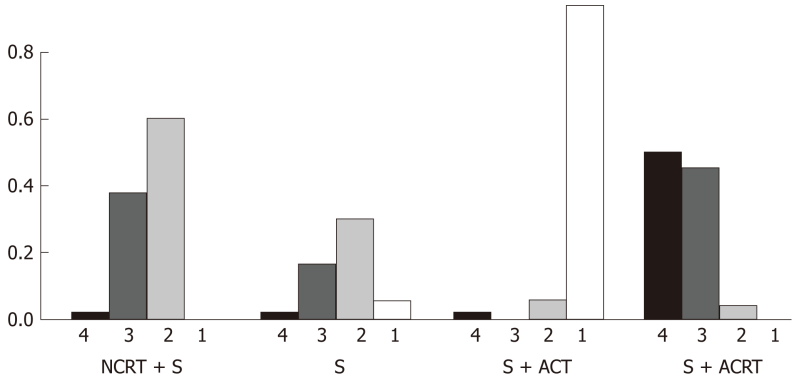

Figure 5 Rankogram of overall survival. The height of column represents the probability of ranking the first (1) second (2), third (3), and fourth (4). NCRT + S: Neoadjuvant chemoradiotherapy with surgery; S: Surgery alone; S + ACT: Surgery with adjuvant chemotherapy; S + ACRT: Surgery with adjuvant chemoradiotherapy.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is one of the most common and lethal malignancies worldwide. The common treatment options for resectable pancreatic cancer include surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, the optimal treatment is still controversial.

Research motivation

The optimal treatment for resectable pancreatic cancer is still controversial.

Research objectives

This study aimed to identify the most effective approach for resectable pancreatic cancer using network meta-analysis.

Research methods

Eligible studies were searched from PubMed, Medline, EMBASE, Cochrane database, and Google scholar. We searched and included randomized controlled trials reporting on neoadjuvant and adjuvant therapies. For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. For indirect comparisons, Bayesian network meta-analysis was used to combine direct and indirect evidence. We used relative hazard ratios (HRs) to estimate survival difference between different treatments, and relative odds ratios (ORs) for toxic effects. Treatment effects were ranked based on their efficacy for improving survival or reducing toxicity using rankogram. The quality of evidence of estimates from direct comparison and network meta-analysis were evaluated following the GRADE approach.

Research results

We included 13 high quality trials with 1591 participants in this network meta-analysis. Compared with surgery alone (pooled HR = 0.7, 95%CI: 0.62-0.79) and surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72), surgery with adjuvant CT had a higher rate of overall survival. In contrast, standard pairwise meta-analysis only showed a statistically significant survival advantage of surgery with adjuvant CT compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; $P < 0.001$). Rankogram showed that surgery with adjuvant CT was most likely to rank the best in terms of overall survival (probability: 94.2%), followed by surgery alone (probability: 5.8%). No significant differences in overall toxicity or haematological toxicity were found between all the therapies. High quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

Research conclusions

Our network meta-analysis show that surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT.

Research perspectives

We recommend surgery with adjuvant CT as the optimal care for resectable pancreatic cancer. Later research should be focused on the best agents for adjuvant CT.

REFERENCES

1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F.

Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]
2 **Carpelan-Holmström M**, Nordling S, Pukkala E, Sankila R, Lüttges J, Klöppel G, Haglund C. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. *Gut* 2005; **54**: 385-387 [PMID: 15710987 DOI: 10.1136/gut.2004.047191]
3 **Gooiker GA**, van Gijn W, Wouters MW, Post PN, van de Velde CJ, Tollenaar RA; Signalling Committee Cancer of the Dutch Cancer Society. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. *Br J Surg* 2011; **98**: 485-494 [PMID: 21500187 DOI: 10.1002/bjs.7413]
4 **Richter A**, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. *World J Surg* 2003; **27**: 324-329 [PMID: 12607060 DOI: 10.1007/s00268-002-6659-z]
5 **Silvestris N**, Brunetti O, Vasile E, Cellini F, Cataldo I, Pusceddu V, Cattaneo M, Partelli S, Scartozzi M, Aprile G, Casadei Gardini A, Morganti AG, Valentini V, Scarpa A, Falconi M, Calabrese A, Lorusso V, Reni M, Cascinu S. Multimodal treatment of resectable pancreatic ductal adenocarcinoma. *Crit Rev Oncol Hematol* 2017; **111**: 152-165 [PMID: 28259290 DOI: 10.1016/j.critrevonc.2017.01.015]
6 **Kim SM**, Eads JR. Adjuvant and Neoadjuvant Therapy for Resectable Pancreatic and Periampullary Cancer. *Surg Clin North Am* 2016; **96**: 1287-1300 [PMID: 27865278 DOI: 10.1016/j.suc.2016.07.004]
7 **Liu W**, Fu XL, Yang JY, Liu DJ, Li J, Zhang JF, Huo YM, Yang MW, Hua R, Sun YW. Efficacy of Neo-Adjuvant Chemoradiotherapy for Resectable Pancreatic Adenocarcinoma: A PRISMA-Compliant Meta-Analysis and Systematic Review. *Medicine (Baltimore)* 2016; **95**: e3009 [PMID: 27082545 DOI: 10.1097/MD.0000000000003009]
8 **Smeenk HG**, van Eijck CH, Hop WC, Erdmann J, Tran KC, Debois M, van Cutsem E, van Dekken H, Klinkenbijl JH, Jeekel J. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg* 2007; **246**: 734-740 [PMID: 17968163 DOI: 10.1097/SLA.0b013e318156eef3]
9 **Tang K**, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *Pancreatology* 2016; **16**: 28-37 [PMID: 26687001 DOI: 10.1016/j.pan.2015.11.007]
10 **Petrelli F**, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Aitini E, Barni S; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. *Pancreas* 2015; **44**: 515-521 [PMID: 25872127 DOI: 10.1097/MPA.0000000000000314]
11 **Festa V**, Andriulli A, Valvano MR, Uomo G, Perri F, Andriulli N, Corrao S, Koch M. Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. *JOP* 2013; **14**: 618-625 [PMID: 24216547 DOI: 10.6092/1590-8577/1724]
12 **Yu Z**, Zhong W, Tan ZM, Wang LY, Yuan YH. Gemcitabine Adjuvant Therapy for Resected Pancreatic Cancer: A Meta-analysis. *Am J Clin Oncol* 2015; **38**: 322-325 [PMID: 23934134 DOI: 10.1097/COC.0b013e3182a46782]
13 **Boeck S**, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. *Oncology* 2007; **72**: 314-321 [PMID: 18187951 DOI: 10.1159/000113054]
14 **Stocken DD**, Büchler MW, Dervenis C, Bassi C, Jeekel H, Klinkenbijl JH, Bakkevold KE, Takada T, Amano H, Neoptolemos JP; Pancreatic Cancer Meta-analysis Group. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005; **92**: 1372-1381 [PMID: 15812554 DOI: 10.1038/sj.bjc.6602513]
15 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
16 **Higgins JPT**, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from: URL: http://handbook-5-1.cochrane.org/
17 **Tierney JF**, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**: 16 [PMID: 17555582 DOI: 10.1186/1745-6215-8-16]
18 **Woods BS**, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. *BMC Med Res Methodol* 2010; **10**: 54 [PMID: 20537177 DOI: 10.1186/1471-2288-10-54]
19 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]
20 **Casadei R**, Di Marco M, Ricci C, Santini D, Serra C, Calculli L, D'Ambra M, Guido A, Morselli-Labate AM, Minni F. Neoadjuvant Chemoradiotherapy and Surgery Versus Surgery Alone in Resectable Pancreatic Cancer: A Single-Center Prospective, Randomized, Controlled Trial Which Failed to Achieve Accrual Targets. *J Gastrointest Surg* 2015; **19**: 1802-1812 [PMID: 26224039 DOI: 10.1007/s11605-015-2890-4]
21 **Golcher H**, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, Jungnickel H, Schreiber S, Grabenbauer GG, Meyer T, Merkel S, Fietkau R, Hohenberger W. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol* 2015; **191**: 7-16 [PMID: 25252602 DOI: 10.1007/s00066-014-0737-7]
22 **Oettle H**, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310**: 1473-1481 [PMID: 24104372 DOI: 10.1001/jama.2013.279201]
23 **Van Laethem JL**, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010; **28**: 4450-4456 [PMID: 20837948 DOI: 10.1200/JCO.2010.30.3446]
24 **Ueno H**, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, Doi R, Monden M, Hatori T, Tanaka

M, Shimada M, Kanemitsu K. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer* 2009; **101**: 908-915 [PMID: 19690548 DOI: 10.1038/sj.bjc.6605256]

25 **Neoptolemos JP**, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Büchler MW. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 2009; **100**: 246-250 [PMID: 19127260 DOI: 10.1038/sj.bjc.6604838]

26 **Oettle H**, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297**: 267-277 [PMID: 17227978 DOI: 10.1001/jama.297.3.267]

27 **Kosuge T**, Kiuchi T, Mukai K, Kakizoe T; Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. *Jpn J Clin Oncol* 2006; **36**: 159-165 [PMID: 16490736 DOI: 10.1093/jjco/hyi234]

28 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]

29 **Neoptolemos JP**, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; **358**: 1576-1585 [PMID: 11716884 DOI: 10.1016/S0140-6736(01)06651-X]

30 **Klinkenbijl JH**, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, Arnaud JP, Gonzalez DG, de Wit LT, Hennipman A, Wils J. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999; **230**: 776-82; discussion 782-4 [PMID: 10615932 DOI: 10.1097/00000658-199912000-00006]

31 **Bakkevold KE**, Arnesjø B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. *Eur J Cancer* 1993; **29A**: 698-703 [PMID: 8471327 DOI: 10.1016/S0959-8049(05)80349-1]

32 **Kalser MH**, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985; **120**: 899-903 [PMID: 4015380 DOI: 10.1001/archsurg.1985.01390320023003]

33 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]

34 **Liao WC**, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, Tu YK. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013; **14**: 1095-1103 [PMID: 24035532 DOI: 10.1016/S1470-2045(13)70388-7]

35 **Uesaka K**, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y; JASPAC 01 Study Group. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016; **388**: 248-257 [PMID: 27265347 DOI: 10.1016/S0140-6736(16)30583-9]

36 **Shimoda M**, Kubota K, Shimizu T, Katoh M. Randomized clinical trial of adjuvant chemotherapy with S-1 versus gemcitabine after pancreatic cancer resection. *Br J Surg* 2015; **102**: 746-754 [PMID: 25833230 DOI: 10.1002/bjs.9775]

37 **Hagiwara Y**, Ohashi Y, Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T; JASPAC 01 Study Group. Health-related quality of life of adjuvant chemotherapy with S-1 versus gemcitabine for resected pancreatic cancer: Results from a randomised phase III trial (JASPAC 01). *Eur J Cancer* 2018; **93**: 79-88 [PMID: 29477795 DOI: 10.1016/j.ejca.2018.01.081]

38 **Belli C**, Cereda S, Anand S, Reni M. Neoadjuvant therapy in resectable pancreatic cancer: a critical review. *Cancer Treat Rev* 2013; **39**: 518-524 [PMID: 23122322 DOI: 10.1016/j.ctrv.2012.09.008]

39 **Kelly KJ**, Winslow E, Kooby D, Lad NL, Parikh AA, Scoggins CR, Ahmad S, Martin RC, Maithel SK, Kim HJ, Merchant NB, Cho CS, Weber SM. Vein involvement during pancreaticoduodenectomy: is there a need for redefinition of "borderline resectable disease"? *J Gastrointest Surg* 2013; **17**: 1209-17; discussion 1217 [PMID: 23620151 DOI: 10.1007/s11605-013-2178-5]

40 **Takahashi S**, Ohno I, Ikeda M, Kobayashi T, Akimoto T, Kojima M, Konishi M, Uesaka K. Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: study protocol for an open-label, multicentre, prospective phase II trial (JASPAC05). *BMJ Open* 2017; **7**: e018445 [PMID: 29061632 DOI: 10.1136/bmjopen-2017-018445]

41 **Labori KJ**, Lassen K, Hoem D, Grønbech JE, Søreide JA, Mortensen K, Smaaland R, Sorbye H, Verbeke C, Dueland S. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. *BMC Surg* 2017; **17**: 94 [PMID: 28841916 DOI: 10.1186/s12893-017-0291-1]

42 **Okada KI**, Shimokawa T, Hirono S, Kawai M, Sho M, Satoi S, Matsumoto I, Eguchi H, Murakami Y, Yamada S, Doi M, Yamaue H; NAC-GA investigators. Effect of Neoadjuvant Nab-Paclitaxel plus Gemcitabine Therapy on Overall Survival in Patients with Borderline Resectable Pancreatic Cancer: A Prospective Multicenter Phase II Trial (NAC-GA Trial). *Oncology* 2017; **93**: 343-346 [PMID: 28719890 DOI: 10.1159/000478660]

43 **Versteijne E**, van Eijck CH, Punt CJ, Suker M, Zwinderman AH, Dohmen MA, Groothuis KB, Busch

OR, Besselink MG, de Hingh IH, Ten Tije AJ, Patijn GA, Bonsing BA, de Vos-Geelen J, Klaase JM, Festen S, Boerma D, Erdmann JI, Molenaar IQ, van der Harst E, van der Kolk MB, Rasch CR, van Tienhoven G; Dutch Pancreatic Cancer Group (DPCG). Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials* 2016; **17**: 127 [PMID: 26955809 DOI: 10.1186/s13063-016-1262-z]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2019 June 30; 7(6): 323-338

DOI: 10.13105/wjma.v7.i6.323

ISSN 2308-3840 (online)

META-ANALYSIS

Single strain probiotics for dyslipidemia, fatty liver, and obesity: A systematic review and meta-analysis

Krit Pongpirul, Kantima Janchot, Yudi Dai

ORCID number: Krit Pongpirul (0000-0003-3818-9761); Kantima Janchot (0000-0002-6244-3419); Yudi Dai (0000-0002-0400-4557).

Author contributions: Pongpirul K contributed to conception and design of the study; Pongpirul K, Janchot K and Dai Y contributed to acquisition of data, analysis and interpretation of data, drafting the article, final approval.

Supported by The Thailand Research Fund and Panacee Group Co., Ltd, No. RDG6150124; and Ratchadapiseksompotch Fund (Matching fund), Faculty of Medicine, Chulalongkorn University, No. RA-MF-12/62.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Krit Pongpirul, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Krit Pongpirul, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States

Kantima Janchot, Panacee Group Co., Ltd, Bangkok 10110, Thailand

Yudi Dai, Harvard T.H. Chan School of Public Health, Boston, MA 02115, United States

Corresponding author: Krit Pongpirul, MD, MPH, PhD, Assistant Professor, Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Rd., Pathumwan, Bangkok 10330, Thailand. doctorkrit@gmail.com
Telephone: +66-866055088
Fax: +66-24111789

Abstract

BACKGROUND

A number of non-systematic reviews on the effects or mechanisms of probiotics on improving dyslipidemia, fatty liver, and obesity have been available but inconclusive to determine the independent effects of probiotics on each of the three conditions.

AIM

To perform a systematic review and meta-analysis on potential benefits of probiotics among individuals with fatty liver or obesity or hyperlipidemia.

METHODS

A systematic literature search was performed using PubMed and Embase. Adult participants of any gender without major comorbidities who received probiotics were considered following these criteria: (1) Studies on a single genus of probiotics with or without prebiotics; (2) Studies specifying the probiotic dosage into colony-forming units (CFUs); and (3) Studies on food-based probiotics were excluded. The primary outcome measures for fatty liver, obesity, and dyslipidemia were fibrosis score (kPa), body mass index (BMI; kg/m^2), and serum lipid profiles (mg/dL), respectively. The secondary outcome measures for fatty liver and obesity were liver enzymes (U/L) and subcutaneous fat area (cm^2).

RESULTS

A total of 13 articles, published between 1997 and 2018, fulfilled the selection criteria. Three probiotics were included, of which *Lactobacillus* was the most commonly studied (10 studies), followed by *Bifidobacterium* (two studies) and

Manuscript source: Invited manuscript

Received: April 6, 2019
Peer-review started: April 8, 2019
First decision: June 4, 2019
Revised: June 11, 2019
Accepted: June 18, 2019
Article in press: June 18, 2019
Published online: June 30, 2019

P-Reviewer: Arslan N, de Oliveira C, Sherif Z, Tarantino G, Tziomalos K
S-Editor: Gong ZM
L-Editor: A
E-Editor: Wang J

Pediococcus (one study). Probiotics significantly reduced BMI (P = 0.013), total cholesterol (P = 0.011), and low-density lipoprotein (P = 0.006) while increased high-density lipoprotein (P = 0.028); high heterogeneities were observed. Only Lactobacillus could decrease triglyceride level (P = 0.005) with low heterogeneity. No included studies reported fibrosis score, liver functions, subcutaneous fat outcomes.

CONCLUSION
Single probiotics, especially *Lactobacillus*, have a potentially beneficial effect on improving obesity and dyslipidemia. Evidence on the fatty liver is limited.

Key words: Fatty liver; Obesity; Hyperlipidemia; Dyslipidemia; Probiotics; Non-alcoholic fatty liver disease; Overweight

Core tip: No consensus is available about the benefit of single probiotics on improving dyslipidemia, fatty liver, and obesity. This meta-analysis investigated the effect of single, non-food-based probiotics, with specified dosage and duration, on body mass index, serum lipid profiles, fibrosis score, liver functions, and subcutaneous fat.

Citation: Pongpirul K, Janchot K, Dai Y. Single strain probiotics for dyslipidemia, fatty liver, and obesity: A systematic review and meta-analysis. *World J Meta-Anal* 2019; 7(6): 323-338
URL: https://www.wjgnet.com/2308-3840/full/v7/i6/323.htm
DOI: https://dx.doi.org/10.13105/wjma.v7.i6.323

INTRODUCTION

The gut microbiota is a diverse and dynamic collection of micro-organisms that live in the human gastrointestinal tract. They are essential for maintaining the health of the human host in the "symbiosis" state whereas a "dysbiosis" could lead to a number of diseases or worsen health conditions[1]. Probiotics are live bacteria and yeasts that are presented either in "functional food" (*i.e.*, fermented food such as yogurt, cheese, miso, kimchi, and kefir) or as supplements in several forms. Probiotics have been claimed to boost the digestive system, support the immune system and reduce the risks associated with metabolic syndrome[2].

There are three main types of fat metabolism disorders: Dyslipidemia, fatty liver, and obesity. Identified as a major risk factor for cardiovascular disease (CVD), dyslipidemia has been the main point of scientific interest affecting clinical practice especially pharmacological intervention[3]. Metabolic activity of the gut microbiota has been proposed as an influencer of the human serum lipid content[3]; it was estimated that 1% reduction in serum total cholesterol level could yield as high as 3% reduction in CVD risk[4]. Probiotics that exhibit a cholesterol reduction effect is of great interest because they are safer and usually cheaper than chemical drugs. Potential mechanisms for the cholesterol reduction effect of probiotics consumption have been discussed in a recent review[3].

Non-alcoholic fatty liver disease (NAFLD) has been the most common chronic liver disease along with the prevalent obesity worldwide. The alteration of gut microbiota has been shown to promote the development of NAFLD by mediating processes of inflammation, insulin resistance, bile acids, as well as choline metabolisms[5]. Probiotics are one of the common ways to manipulate the gut microbiota as part of NAFLD management.

The number of overweight (body mass index; BMI 25-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) individuals has been rising worldwide[6]. The gut microbiota synthesizes short-chain fatty acids and amino acids, ferment otherwise indigestible carbohydrates, and contribute to the energy supplied to the animal and human host[7,8]. Evidence on the association between bacterial richness/dysbiosis and weight loss[9] suggested that modifying gut microbiota including probiotics administration is a potential target for obesity treatment[10].

Unlike other conventional interventions, the practical uses of probiotics have greatly varied. As mentioned earlier, probiotics could be in functional food or as a

supplement. They could be used as live organisms with the unclear quantified amount; commonly measured in colony-forming units (CFU). Assessment of a single probiotic is scientifically difficult since more than one genus/species/strains are commonly offered simultaneously. Probiotics are usually regarded as supplements, so their therapeutic effects do not require to be supported by robust scientific evidence by the national food and drug authorities. Although conducting a randomized controlled trial (RCT) on this type of complex intervention is relatively more difficult than other interventions, a substantial amount of clinical experiments on probiotics have been prevalent in a variety of healthy and disease-specific study populations.

A number of non-systematic reviews on the effects or mechanisms of probiotics on improving dyslipidemia[3], fatty liver[5], and obesity[10] have been available. However, previous reviews could not determine the independent effects of probiotics on each of the three conditions. Also, many reviews could not differentiate the effects of various amounts of probiotics, especially when mixed and/or food-based probiotics were explored.

This systematic review aimed to identify clinical trials on the use of probiotics alone or in combination with prebiotics for improving fatty liver, obesity, or dyslipidemia. The selected studies must quantify the number of probiotics and explicitly describe the outcome measures. This review did not restrict to any specific kind of probiotics or any country. Probiotics in functional foods or combined in a mixture with substances other than prebiotics were excluded.

MATERIALS AND METHODS

Protocol and registration

This systematic review has been registered in PROSPERO (CRD42019125511) and the protocol ID=CRD42019125511.

Literature search

The conducting and reporting of this systematic review and meta-analysis followed the PRISMA statement guidelines[11] whereas the inclusion criteria reporting followed the PICOS scheme. A systematic literature search was performed by two independent authors (KJ and YD) using PubMed and Embase. The search was limited to human subjects and English language. Adult individuals of any gender who received probiotics were considered as the intervention group whereas those who received placebo were considered as the comparator group. Only controlled trials with and without randomization were included. The search strategy was based on various combinations of words for both database and focused on two main concepts: probiotics and fat metabolism. The last search was conducted on March 1, 2019.

For the PubMed database the following combination was applied: ((Overweight-[Mesh] OR overweight[tiab] OR obese[tiab] OR obesity[tiab] OR "body weight"[tiab] OR "body mass index"[tiab]) OR ("Fatty Liver"[Mesh] OR "fatty liver"[tiab] OR Fibroscan[tiab] OR Ultrasound[tiab] OR "liver function tests"[Mesh] OR "liver function tests"[tiab] OR "Aspartate Aminotransferases"[tiab] OR "Alanine Transaminase"[tiab] OR "Alkaline phosphatase"[tiab] OR "gammaglutamyl transpeptidase"[tiab] OR albumin*[tiab] OR bilirubin[tiab]) OR (Dyslipidemias[Mesh] OR dyslipidemia*[tiab] OR Hyperlipidemia[tiab] OR Hyperlipoprote-inemias[tiab] OR Hypertriglyceridemia[tiab] OR Hypercholesterolemia[tiab] OR Cholesterol[Mesh] OR cholesterol[tiab] OR plasma lipids[tiab] OR Triglycerides[Mesh] OR Triglyceride*[tiab] HDL[tiab] OR LDL[tiab] OR VLDL[tiab])) AND ((Probiotics[Mesh] OR probiotics[tiab] OR probiotic[tiab] OR (Synbiotics[Mesh] OR synbiotics[tiab] OR synbiotic[tiab]) OR (Lactobacillales[Mesh] OR Lactobacillales[tiab] OR Lactobacillus[tiab] OR Pediococcus[tiab] OR Leuconostoc [tiab] OR Oenococcus[tiab] OR Weissella[tiab] OR Lactococcus[tiab] OR Streptococcus[tiab]) OR (Bifidobacteriales[Mesh] OR Bifidobacteriales[tiab] OR Bifidobacterium[tiab] OR Aeriscardovia[tiab] OR Alloscardovia[tiab] OR Bifidobacterium[tiab] OR Bombiscardovia[tiab] OR Galliscardovia[tiab] OR Gardnerella[tiab] OR Neoscardovia[tiab] OR Parascardovia[tiab] OR Pseudoscardovia[tiab] OR Scardovia[tiab]) OR (Saccharomyces[Mesh] OR Saccharomyces[tiab])) AND (Humans[Mesh] AND English[lang]).

For the Embase database the following combination was applied: ('obesity'/exp OR 'adipositas':ti,ab OR 'adiposity':ti,ab OR 'alimentary obesity':ti,ab OR 'body weight, excess':ti,ab OR 'corpulency':ti,ab OR 'fat overload syndrome':ti,ab OR 'nutritional obesity':ti,ab OR 'obesitas':ti,ab OR 'obesity':ti,ab OR 'overweight':ti,ab OR 'body weight'/exp OR 'body weight':ti,ab OR 'total body weight':ti,ab OR 'weight, body':ti,ab OR 'body mass'/exp OR 'bmi (body mass index)':ti,ab OR 'quetelet

index':ti,ab OR 'body mass':ti,ab OR 'body mass index':ti,ab OR 'fatty liver'/exp OR 'fat liver':ti,ab OR 'fatty liver':ti,ab OR 'fatty liver disease':ti,ab OR 'fatty liver infiltration':ti,ab OR 'hepatic steatosis':ti,ab OR 'hepatosteatosis':ti,ab OR 'liver fatty infiltration':ti,ab OR 'liver steatosis':ti,ab OR 'liver, fatty':ti,ab OR 'steatosis, liver':ti,ab OR 'liver function test'/exp OR 'function test, liver':ti,ab OR 'hepatic function test':ti,ab OR 'liver function test':ti,ab OR 'liver function tests':ti,ab OR 'test, liver function':ti,ab OR 'echography'/exp OR 'doptone':ti,ab OR 'duplex echography':ti,ab OR 'echogram':ti,ab OR 'echography':ti,ab OR 'echoscopy':ti,ab OR 'echosound':ti,ab OR 'high resolution echography':ti,ab OR 'scanning, ultrasonic':ti,ab OR 'sonogram':ti,ab OR 'sonography':ti,ab OR 'ultrasonic detection':ti,ab OR 'ultrasonic diagnosis':ti,ab OR 'ultrasonic echo':ti,ab OR 'ultrasonic examination':ti,ab OR 'ultrasonic scanning':ti,ab OR 'ultrasonic scintillation':ti,ab OR 'ultrasonography':ti,ab OR 'ultrasound diagnosis':ti,ab OR 'ultrasound scanning':ti,ab OR 'aspartate aminotransferase'/exp OR '1 aspartate 2 oxoglutarate aminotransferase':ti,ab OR '1 aspartate:2 oxoglutarate aminotransferase':ti,ab OR 'got':ti,ab OR 'aminotransferase, aspartate':ti,ab OR 'aspartate amino transferase':ti,ab OR 'aspartate aminotransferase':ti,ab OR 'aspartate aminotransferases':ti,ab OR 'aspartate transaminase':ti,ab OR 'aspartic aminotransferase':ti,ab OR 'aspartic transminase':ti,ab OR 'e.c. 2.6.1.1':ti,ab OR 'glutamate aspartate transaminase':ti,ab OR 'glutamate oxalacetate transaminase':ti,ab OR 'glutamate oxalacetic transaminase':ti,ab OR 'glutamate oxalate transaminase':ti,ab OR 'glutamate oxalic transaminase':ti,ab OR 'glutamate oxaloacetate aminotransferase':ti,ab OR 'glutamate oxaloacetate transaminase':ti,ab OR 'glutamate oxaloacetic acid transaminase':ti,ab OR 'glutamatoxalacetate transaminase':ti,ab OR 'glutamic aspartic aminotransferase':ti,ab OR 'glutamic aspartic transaminase':ti,ab OR 'glutamic oxal acetatic transaminase':ti,ab OR 'glutamic oxalacetic acid transaminase':ti,ab OR 'glutamic oxalacetic transaminase':ti,ab OR 'glutamic oxalacetic transferase':ti,ab OR 'glutamic oxalic transaminase':ti,ab OR 'glutamic oxaloacetic acid transaminase':ti,ab OR 'glutamic oxaloacetic aminotransferase':ti,ab OR 'glutamic oxaloacetic transaminase':ti,ab OR 'glutamine oxaloacetic transaminase':ti,ab OR 'glutaminic oxalacetic transaminase':ti,ab OR 'l asparate 2 oxoglutarate transaminase':ti,ab OR 'l aspartate 2 oxoglutarate aminotransferase':ti,ab OR 'l aspartate aminotransferase':ti,ab OR 'l aspartate:2 oxoglutarate aminotransferase':ti,ab OR 'l aspartate:2 oxoglutarate transaminase':ti,ab OR 'l aspatate:2 oxoglutarate aminotransferase':ti,ab OR 'levo aspartate aminotransferase':ti,ab OR 'transaminase a':ti,ab OR 'alanine aminotransferase'/exp OR 'gpt':ti,ab OR 'alanin aminotransferase':ti,ab OR 'alanine 2 oxoglutarate aminotransferase':ti,ab OR 'alanine 2 oxoisovalerate aminotransferase':ti,ab OR 'alanine alpha ketoglutarate transaminase':ti,ab OR 'alanine alpha oxoglutarate transaminase':ti,ab OR 'alanine amino transferase':ti,ab OR 'alanine aminotransferase':ti,ab OR 'alanine transaminase':ti,ab OR 'alanine transpeptidase':ti,ab OR 'alanine:2 oxoglutarate aminotransferase':ti,ab OR 'e.c. 2.6.1.2':ti,ab OR 'glutamate alanine transaminase':ti,ab OR 'glutamate pyruvate aminotransferase':ti,ab OR 'glutamate pyruvate transaminase':ti,ab OR 'glutamate pyruvatetransaminase':ti,ab OR 'glutamic alanine aminotransferase':ti,ab OR 'glutamic pyruvate transaminase':ti,ab OR 'glutamic pyruvic aminotransferase':ti,ab OR 'glutamic pyruvic transaminase':ti,ab OR 'glutamopyruvic transaminase':ti,ab OR 'l alanine 2 oxoglutarate aminotransferase':ti,ab OR 'l alanine:2 oxoglutarate aminotransferase':ti,ab OR 'alkaline phosphatase'/exp OR 'alcalic phosphatase':ti,ab OR 'alkali phosphatase':ti,ab OR 'alkalic phosphatase':ti,ab OR 'alkaline monophosphoesterase':ti,ab OR 'alkaline phosphatase':ti,ab OR 'alkaline phosphohydrolase':ti,ab OR 'alkaline phosphomonoesterase':ti,ab OR 'alkalinic phosphatase':ti,ab OR 'basic phosphatase':ti,ab OR 'e.c. 3.1.3.1':ti,ab OR 'heat stable alkaline phosphatase':ti,ab OR 'orthophosphoric monoester phosphohydrolase':ti,ab OR 'phosphatase, alkaline':ti,ab OR 'gamma glutamyltransferase'/exp OR '(5 glutamyl) peptide:amino acid 5 glutamyltransferase':ti,ab OR '4 glutamyl transferase':ti,ab OR 'alpha glutamyltranspeptidase':ti,ab OR 'e.c. 2.3.2.2':ti,ab OR 'gamma glutamyl transferase':ti,ab OR 'gamma glutamyl transpeptidase':ti,ab OR 'gamma glutamyltransferase':ti,ab OR 'gamma glutamyltranspeptidase':ti,ab OR 'gamma gt':ti,ab OR 'gammaglutamyltransferase':ti,ab OR 'gammaglutamyl transpeptidase':ti,ab OR 'glutamate transpeptidase':ti,ab OR 'glutamic transferase':ti,ab OR 'glutamyl transferase':ti,ab OR 'glutamyl transpeptidase':ti,ab OR 'glutamyltransferase':ti,ab OR 'glutamyltranspeptidase':ti,ab OR 'levo glutamyltranspeptidase':ti,ab OR 'transpeptidase':ti,ab OR 'albuminoid'/exp OR 'albumin derivative':ti,ab OR 'albuminoid':ti,ab OR 'albumins':ti,ab OR 'bilirubin'/exp OR '1, 3, 6, 7 tetramethyl 4, 5 dicarboxyethyl 2, 8 divinyl (b 13) dihydrobilenone':ti,ab OR 'bilirubin':ti,ab OR 'bilirubin acid':ti,ab OR 'bilirubin delta':ti,ab OR 'bilirubin ix alpha':ti,ab OR 'bilirubin ixalpha':ti,ab OR 'bilirubin pigment':ti,ab OR 'bilirubin sulfate isomer':ti,ab OR 'bilirubin sulphate isomer':ti,ab OR 'bilirubinate':ti,ab OR

'bilirubine':ti,ab OR 'bilirubinoid':ti,ab OR 'calcium bilirubinate':ti,ab OR 'haematoidin':ti,ab OR 'hematoidin':ti,ab OR 'indirect bilirubin':ti,ab OR 'mesobilirubin':ti,ab OR 'unconjugated bilirubin':ti,ab OR 'dyslipidemia'/exp OR 'dyslipaemia':ti,ab OR 'dyslipemia':ti,ab OR 'dyslipidaemia':ti,ab OR 'dyslipidaemias':ti,ab OR 'dyslipidemia':ti,ab OR 'dyslipidemias':ti,ab OR 'lipidaemia, dys':ti,ab OR 'lipidemia, dys':ti,ab OR 'hyperlipidemia'/exp OR 'hyperlipaemia':ti,ab OR 'hyperlipemia':ti,ab OR 'hyperlipidaemia':ti,ab OR 'hyperlipidaemia type ii':ti,ab OR 'hyperlipidaemia type iii':ti,ab OR 'hyperlipidaemia type v':ti,ab OR 'hyperlipidaemias':ti,ab OR 'hyperlipidemia':ti,ab OR 'hyperlipidemia type ii':ti,ab OR 'hyperlipidemia type iii':ti,ab OR 'hyperlipidemia type v':ti,ab OR 'hyperlipidemias':ti,ab OR 'hyperlipidemic':ti,ab OR 'lipaemia':ti,ab OR 'lipemia':ti,ab OR 'lipidaemia':ti,ab OR 'lipidemia':ti,ab OR 'hyperlipoproteinemia'/exp OR 'essential familial hyperproteinaemia':ti,ab OR 'essential familial hyperproteinemia':ti,ab OR 'familial hyperlipoproteinaemia':ti,ab OR 'familial hyperlipoproteinemia':ti,ab OR 'hereditary hyperlipoproteinaemia':ti,ab OR 'hereditary hyperlipoproteinemia':ti,ab OR 'hyperlipoproteinaemia':ti,ab OR 'hyperlipoproteinaemias':ti,ab OR 'hyperlipoproteinemia':ti,ab OR 'hyperlipoproteinemias':ti,ab OR 'hypertriglyceridemia'/exp OR 'hypertriglyceridaemia':ti,ab OR 'hypertriglyceridemia':ti,ab OR 'idiopathic familiary hypertriglyceridaemia':ti,ab OR 'idiopathic familiary hypertriglyceridemia':ti,ab OR 'mckusick 14575':ti,ab OR 'triglyceride storage disease':ti,ab OR 'triglyceridemia':ti,ab OR 'hypercholesterolemia'/exp OR 'cholesteremia':ti,ab OR 'cholesterinemia':ti,ab OR 'cholesterolemia':ti,ab OR 'hypercholesteremia':ti,ab OR 'hypercholesterinaemia':ti,ab OR 'hypercholesterinemia':ti,ab OR 'hypercholesterolaemia':ti,ab OR 'hyperchole-sterolemia':ti,ab OR 'cholesterol'/exp OR '3 hydroxy 5 cholestene':ti,ab OR '3beta hydroxy 5 cholestene':ti,ab OR '3beta hydroxycholest 5 ene':ti,ab OR '5 cholesten 3beta ol':ti,ab OR 'beta cholesterol':ti,ab OR 'cholest 5 en 3beta ol':ti,ab OR 'cholest 5 ene 3 ol':ti,ab OR 'cholesterin':ti,ab OR 'cholesterine':ti,ab OR 'cholesterol':ti,ab OR 'cholesterol release':ti,ab OR 'dythol':ti,ab OR 'nsc 8798':ti,ab OR 'plasma lipids':ti,ab OR 'triacylglycerol'/exp OR 'acylglycerol, tri':ti,ab OR 'fatty acid triglyceride':ti,ab OR 'triacyl glyceride':ti,ab OR 'triacylglycerol':ti,ab OR 'triglyceride':ti,ab OR 'triglycerides':ti,ab OR 'tryglyceride':ti,ab OR 'high density lipoprotein'/exp OR 'hdl':ti,ab OR 'alpha 7 lipoprotein':ti,ab OR 'alpha lipoprotein':ti,ab OR 'high density lipoprotein':ti,ab OR 'high density lipoprotein phospholipid':ti,ab OR 'lipoprotein, alpha':ti,ab OR 'lipoprotein, high density':ti,ab OR 'lipoproteins, hdl':ti,ab OR 'pre alpha lipoprotein':ti,ab OR 'very high density lipoprotein':ti,ab OR 'low density lipoprotein'/exp OR 'ldl':ti,ab OR 'beta lipoprotein':ti,ab OR 'lipoprotein, beta':ti,ab OR 'lipoprotein, low density':ti,ab OR 'lipoproteins, ldl':ti,ab OR 'low density lipoprotein':ti,ab OR 'very low density lipoprotein'/exp OR 'vldl':ti,ab OR 'lipoproteins, vldl':ti,ab OR 'pre beta lipoprotein':ti,ab OR 'prebeta lipoprotein':ti,ab OR 'prebetalipoprotein':ti,ab OR 'very low density lipoprotein':ti,ab) AND ('probiotic agent'/exp OR 'probiotic':ti,ab OR 'probiotic agent':ti,ab OR 'probiotics':ti,ab OR 'synbiotic agent'/exp OR 'synbiotic':ti,ab OR 'synbiotic agent':ti,ab OR 'synbiotics':ti,ab OR 'lactobacillales'/exp OR 'lactobacillales':ti,ab OR 'lactobacillus'/exp OR 'betabacterium':ti,ab OR 'lactobacileae':ti,ab OR 'lactobacilleae':ti,ab OR 'lactobacillus':ti,ab OR 'lactobacteria':ti,ab OR 'lactobacilli':ti,ab OR 'pediococcus'/exp OR 'pediococcus':ti,ab OR 'leuconostoc'/exp OR 'leuconostoc':ti,ab OR 'oenococcus'/exp OR 'oenococcus':ti,ab OR 'weissella'/exp OR 'weissella':ti,ab OR 'lactococcus'/exp OR 'lactococcus':ti,ab OR 'streptococcus'/exp OR 'strepto-cocceae':ti,ab OR 'streptococcus':ti,ab OR 'streptococcus species':ti,ab OR 'streptococcal component':ti,ab OR 'streptococci':ti,ab OR 'bifidobacteriales'/exp OR 'bifidobacteriales':ti,ab OR 'bifidobacterium'/exp OR 'bifidobacterium':ti,ab OR bombiscardovia:ti,ab OR galliscardovia:ti,ab OR 'gardnerella'/exp OR 'gardnerella':ti,ab OR neoscardovia:ti,ab OR parascardovia:ti,ab OR pseudoscardovia:ti,ab OR 'scardovia wiggsiae'/exp OR 'saccharomyces'/exp OR 'saccharomyces':ti,ab) AND 'randomized controlled trial'/exp.

Study selection

A systematic review management software, Covidence, was used. The titles and abstracts of the primary studies identified in the electronic search were screened by the same two authors. The duplicate studies were excluded. The following inclusion criteria were set for inclusion in this meta-analysis: (1) Controlled clinical experiments with or without randomization on individuals of any gender at least 18 years of age who received probiotics with or without prebiotics for improving fatty liver, obesity, or dyslipidemia; and (2) Studies containing fibrosis score (kPa), body mass index (BMI; kg/m^2), serum lipid profiles: Total cholesterol (TC; mg/dL), high density lipoprotein (HDL; mg/dL), low density lipoprotein (LDL; mg/dL), triglyceride (TG; mg/dL), liver enzymes: Alanine transaminase (ALT; IU/L), aspartate transaminase

(AST; IU/L), alkaline phosphatase (ALP; IU/L), gamma-glutamyl transpeptidase (GGT; IU/L), subcutaneous fat (%), subcutaneous fat area (cm^2). The following exclusion criteria were set: (1) Review articles, letters, comments and case reports; (2) Studies on food-based probiotics (*e.g*., yogurt, fermented/sour milk, soy product); (3) Studies where it was impossible to convert the probiotic dosage into colony-forming units (CFUs); and (4) Studies where it was impossible to calculate the outcomes of interest. The trial authors were requested if incomplete data were reported. If the trial authors did not respond within two weeks, only available data were used. Any disagreement was resolved through discussion and the final determination was made by the first author (KP).

Data extraction

The same two authors extracted the data for the following variables: (1) Authors, year of publication, and study type; (2) Genus, species, and characteristics, including dosage of the probiotics; and (3) Clinical outcomes, including fibrosis score, BMI, serum lipid profile, liver enzymes, subcutaneous fat. All relevant text, tables, and figures were examined for data extraction. Discrepancies between the two reviewers were resolved by the first author (KP).

Risk of bias

Two authors (KJ and YD) independently assessed the risk of bias in the included trials using the Cochrane Risk of Bias tool 2.0 in the following domains: bias arising from the randomization process; bias due to deviations from intended intervention; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported result. The reviewers resolved any disagreement by discussion and consensus.

Additional analysis

The analysis was performed by the following subgroups: Intake duration (< 12 weeks *vs* 12 weeks), dose per day (< $100x10^8$ CFU *vs* ≥ $100x10^8$ CFU), and the presence of prebiotics (with *vs* without).

Statistical analysis

Mean differences (MD) between the intervention and control groups, along with 95% Confidence Interval (95%CI) were reported for continuous variables. Clinical and methodological heterogeneity was assessed by examining participant characteristics, probiotics type, duration of probiotics usage and dose, outcomes, as well as the design of the study. Statistical heterogeneity was assessed using the I^2 and X^2 statistics. The level of heterogeneity as defined in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity. For the X^2 test, statistical heterogeneity of the included trials was assessed with a p-value of less than 0.05 (statistically significant). The random-effects meta-analysis by DerSimonian and Laird method was used as clinical, methodological, and statistical heterogeneity was encountered. The meta-analysis was performed using Stata/MP software version 15 (StataCorp 2017, College Station, TX, United States).

RESULTS

Study selection

The literature search yielded 3736 articles. After 287 duplicates were removed, 3449 titles and abstracts were screened, and 3293 irrelevant articles were removed. Of 156 articles selected for full-text screening, 143 were excluded for the following reasons: 23 were not controlled trials, 23 studies targeted irrelevant patient population, 49 studied focused on food-based probiotics and/or mixed probiotics, 12 did not specify the probiotic doses, 36 did not have quantifiable outcomes of interest. Finally, a total of 13 articles, dated between 1997 to 2018, fulfilled the selection criteria and were included in this meta-analysis[12-24] (Figure 1).

Study characteristics

Included studies were published between 2006 to 2018 in various countries. All of the included studies are Randomized Controlled Trials (RCTs). Participants were randomly allocated to a control group or intervention group which reduce bias. Participants are 18 years of age or older which was related to inclusion criteria. Treatment periods were divided from 63 days to the longest period of 168 days (Table 1).

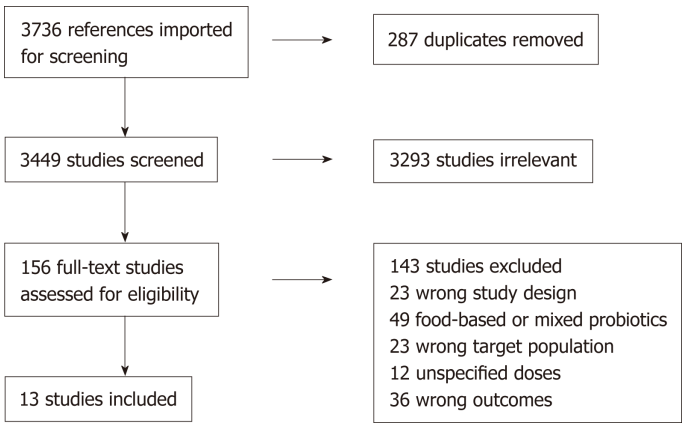

Figure 1 Study selection.

Probiotics

Ten studies used *Lactobacillus*, two studies used *Bifidobacterium*, and one study used *Pediococcus*. Due to the low number of studies accessing the effect of *Bifidobacterium* and *Pediococcus*, meta-regression for each genus was not performed. Especially, the study by Childs *et al*. intervened subjects by *Bifidobacterium* and *Bifidobacterium* plus a prebiotic. Meta-regression based on Childs's study suggested that *Bifidobacterium* had no significant impact on TC (SMD = 0.219; 95%CI: -0.213 to 0.651; P = 0.320) and LDL (SMD = 0.00; 95%CI: -0.49 to 0.49; P = 1.000). However, *Bifidobacterium*' s protective effect on HDL (SMD = 1.49; 95%CI: 0.51-2.47; P = 0.003) and triglycerides (SMD = -0.40; 95%CI: -0.71 to -0.09; P = 0.011) was significant.

BMI

BMI was measured in seven trials before and after the administration of probiotic and placebo products (Figure 2). Overall, meta-analysis showed that probiotics significantly reduced BMI compared to placebo (SMD = -1.47; 95%CI: -2.63 to -0.13; P = 0.013); however, between-study heterogeneity was high (I^2 = 95.5%; P = 0.000). Subgroup analysis based on the type of probiotic genus revealed that *Lactobacillus* induced a great reduction in BMI (SMD = -1.56; 95%CI: -3.01 to -0.12; P = 0.034) (Table 2). However, heterogeneity between studies in *Lactobacillus* was still large (I^2 = 96.1%; P = 0.000).

TC

A total of 10 studies examined the effects of probiotic on TC (Figure 3). The administration of probiotics was associated with significant decrease in TC levels (SMD = -0.72; 95%CI: -1.28 to -0.16; P = 0.011), but with high heterogeneity (I^2 = 92.3%; P = 0.000) between the studies. Subgroup analysis with regards to probiotic genus was performed. *Lactobacillus* significantly reduced TC levels (SMD = -0.72; 95%CI: -1.28 to -0.16; P = 0.011). However, it is worth noting the high heterogeneity between studies (I^2 = 93.4%; P = 0.000).

LDL

The overall estimate of the ten studies showed a huge reduction in LDL in the treatment groups compared with the placebo groups (SMD = -0.85; 95%CI: -1.33 to -0.28; P = 0.006), but the heterogeneity was large (I^2 = 91.3%; P = 0.000) (Figure 4). The effect size was even larger in *Lactobacillus* group (SMD = -0.95; 95%CI: -1.62 to -0.28; P = 0.006).

HDL

An overall significant increase after intervention was reported for HDL levels in ten studies (SMD = 0.84; 95%CI: 0.09-1.59; P = 0.028) (Figure 5). The effect of probiotic on HDL did not change much when it came to subgroup analysis for *Lactobacillus* (SMD = -0.95; 95%CI: -1.62 to -0.28).

TG

The meta-analysis based on indicated a non-significant change in triglycerides post intervention (SMD = -0.06; 95%CI: -0.505 to 0.385; P = 0.792) (Figure 6). However, an analysis for *Lactobacillus* showed a significant decrease in triglycerides (SMD = -0.32; 95%CI: -0.54 to -0.095; P = 0.005) and with a low between-study heterogeneity (I^2 = 7.7%; P = 0.363).

Table 1 Characteristics of the included studies

First author	Year	Study period	Country	Study design	Participant, *n*	Age range (yr)	Treatment period (d)	Ref.
Simons	2006	2004-2005	Australia	Randomized, double blind, placebo-controlled	44	30-75	70	[24]
Ooi	2010	-	Malaysia	Randomized, double blind, placebo-controlled	32	18 years of age or older	84	[21]
Jones	2012	-	Canada	Randomized, double blind, placebo-controlled	127	20-75	63	[19]
Fuentes	2013	-	Spain	Randomized, double blind, placebo-controlled	60	18-65	84	[15]
Sanchez	2014	-	Canada	Randomized, double blind, placebo-controlled	93	18-55	168	[23]
Childs	2014	2008-2009	United Kingdom	Randomized, double blind, placebo-controlled, factorial, cross-over	42	25-65	21	[13]
Rajkumar	2015	-	India	Randomized, single blind, placebo-controlled	45	20-25	45	[22]
Ahn	2015	2012-2014	South Korea	Randomized, double blind, placebo-controlled	92	-	84	[12]
Higashikawa	2016	2013	Japan	Randomized, double blind, placebo-controlled	41	20-70	84	[17]
Fuentes	2016	2010	Spain	Randomized, double blind, placebo-controlled	60	18-25	84	[16]
Kim	2017	-	South Korea	Randomized, double blind, placebo-controlled	66	-	84	[20]
Costabile	2017	2015	United Kingdom	Randomized, double blind, placebo-controlled	46	18-50	84	[14]
Inoue	2018	-	Japan	Randomized, double blind, placebo-controlled	38	66-78	84	[18]

Other outcomes

No included studies reported fibrosis score, liver functions, subcutaneous fat outcomes.

Risk of bias

The analyses of the risk of bias of the included studies were summarized in Figure 7. Generally, all studies were classified as low risk of bias. Five articles clearly explained the methods used for randomization, while eight studies did not describe the process of randomizing. Twelve studies blinded the patients, researchers and outcome assessors whereas Rajkumar's study did not blind the patients and filed staff since the

Table 2 Sensitivity analysis and subgroup analysis

Subgroup/sensitivity analysis		No. of groups	SMD (95%CI)	*P*-value	Heterogeneity (I^2, *P*-value)
BMI					
Intake duration	< 12 wk	6	-0.535 (-0.782, -0.289)	0.000	95.1% (0.000)
	= 12 wk	2	-0.220 (-0.920, 0.479)	0.537	98.1% (0.000)
Dose per day	Low-dosage (< $100*10^8$ CFU)	4	0.024 (-0.351, 0.399)	0.900	94.4% (0.000)
	High-dosage (≥ $100*10^8$ CFU)	4	-0.829 (-1.125, -0.532)	0.00	96.7% (0.000)
Combined with or without prebiotics	Probiotic alone	6	-0.481 (-0.730, -0.233)	0.000	95.4% (0.000)
	Combined with prebiotics	2	-0.638 (-1.304, 0.027)	0.060	97.9% (0.000)
Total cholesterol					
Intake duration	< 12 wk	6	-0.225 (-0.443, -0.006)	0.044	86.9% (0.000)
	= 12 wk	4	-0.665 (-0.906, -0.424)	0.000	94.9% (0.000)
	> 12 wk	1	-0.200 (-0.607,0.208)	0.337	
Dose per day	Low-dosage (< $100*10^8$ CFU)	9	-0.496 (-0.664,0.328)	0.000	93.4% (0.000)
	High-dosage (≥ $100*10^8$ CFU)	2	0.031 (-0.310, 0.371)	0.860	0.00% (0.336)
Combined with or without prebiotics	Probiotic alone	9	-0.466 (-0.630, -0.303)	0.000	92.7% (0.000)
	Combined with prebiotics	2	0.004 (-0.377, 0.386)	0.983	93.6% (0.000)
LDL					
Intake duration	< 12 wk	4	-0.306 (-0.524, -0.088)	0.006	81.2% (0.000)
	= 12 wk	6	-0.871 (-1.113, -0.628)	0.000	94.1% (0.000)
	> 12 wk	1	-0.250 (-0.658, 0.159)	0.213	
Dose per day	Low-dosage (< $100*10^8$ CFU)	9	-0.558 (-0.725, -0.391)	0.000	91.9% (0.000)
	High-dosage (≥ $100*10^8$ CFU)	2	-0.333 (-0.685, 0.020)	0.064	92.7% (0.000)
Combined with or without prebiotics	Probiotic alone	9	-0.609 (-0.774, -0.445)	0.000	92.0% (0.000)
	Combined with prebiotics	2	-0.042 (-0.415, 0.331)	0.826	84.8% (0.010)
HDL					
Intake duration	< 12 wk	4	0.557 (0.329, 0.784)	0.000	94.0% (0.000)
	= 12 wk	6	0.273 (0.027, 0.520)	0.030	96.6% (0.000)
	> 12 wk	1	-0.501 (-0.914, -0.087)	0.018	
Dose per day	Low-dosage (< $100*10^8$ CFU)	9	0.445 (0.272, 0.617)	0.000	95.7% (0.000)
	High-dosage (≥ $100*10^8$ CFU)	2	-0328 (-0.682, 0.025)	0.069	93.7% (0.000)
Combined with or without prebiotics	Probiotic alone	9	0.162 (-0.004, 0.329)	0.056	95.4% (0.000)
	Combined with prebiotics	2	1.158 (0.735, 1.581)	0.000	96.2% (0.000)
Triglycerides					
Intake duration	< 12 wk	4	-0.277 (-0.493, -0.061)	0.000	0% (0.614)
	= 12 wk	4	-0.135 (-0.411, 0.140)	0.336	93.0% (0.000)
Dose per day	Low-dosage (< $100*10^8$ CFU)	6	-0.298 (-0.489, -0.107)	0.770	97.4% (0.000)
	High-dosage (≥ $100*10^8$ CFU)	2	0.055 (-0.314, 0.424)	0.069	0.0% (0.567)
Combined with or without prebiotics	Probiotic alone	6	-0.185 (-0.376, 0.006)	0.058	88.3% (0.000)
	Combined with prebiotics	2	-0.368 (0.740, 0.004)	0.052	39.4% (0.199)

SMD: Standard mead difference; CI: Confidence interval; CFU: Colony forming unit; BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

capsules looked different. All studies explicitly explained the methods used for dealing with incomplete outcome data. Three studies worked well in allocation concealment whereas eight studies failed to make the process of allocation concealment clear. Two studies might have a high bias from the predictable allocation of intervention and placebo. At last, all studies had no problem with selective outcome reporting.

DISCUSSION

This systematic review revealed that probiotics have a potentially beneficial effect on improving obesity and dyslipidemia. Probiotics were found to significantly decrease

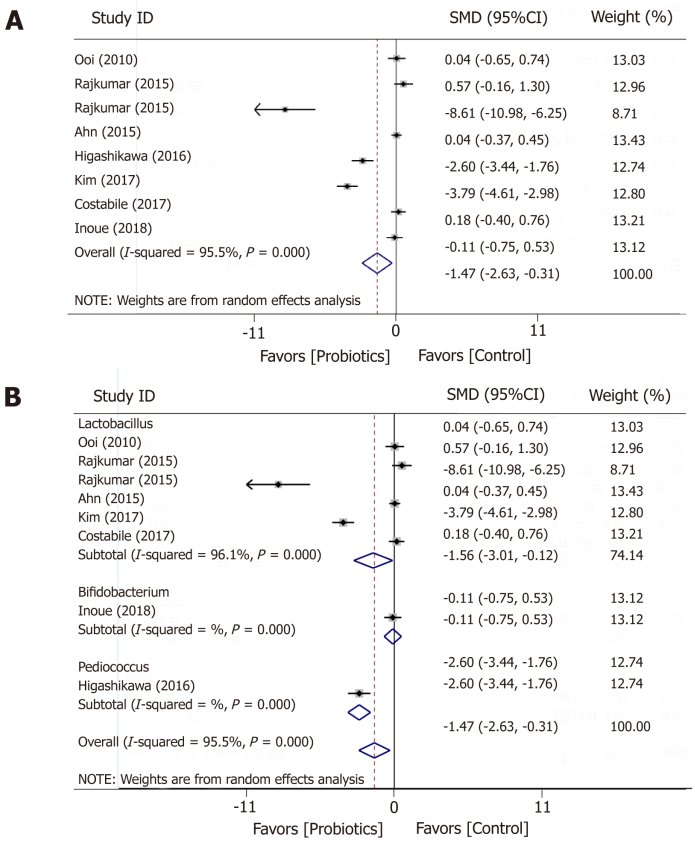

Figure 2 Meta-analysis forest plot concerning body mass index (A) and body mass index by genus (B).

BMI, levels of TC and LDL as well as increase HDL level. However, the effect of probiotics on TG was not statistically significant.

Our study filled the gap that previous studies assessing the effect of probiotics focused more on multiple probiotic strains by including trials using the single strain as treatment. Our results seem to be different from most of the previous studies. Sun's meta-analysis found that compared to multiple probiotic strains, a single strain did not have a significant effect on TC, HDL, and triglyceride[25]. However, due to the limited number of studies which intervened with a single strain included in their meta-analysis, caution is required while coming to the conclusion. In our study, 13 studies that used single strain as treatment are enrolled. The considerable number of trials enrolled guarantee more reliable results.

While existing studies showed that probiotics administered in different forms such as fermented milk, bread, tablet, powder or capsule had different effects on lipid profiles and BMI; in this meta-analysis, only studies not using food-based probiotic as interventions are included. Therefore, compared to previous studies, this meta-analysis could isolate the effects of probiotics from other supplements better. Multiple genera of probiotics could have different additive or synergistic effects in comparison with the single genus of probiotics. Hence, caution is needed to extrapolate multiple genera of probiotics' significant effects on lipid profiles and BMI to a single genus of probiotics. This meta-analysis fills the gap in this area. Thirteen studies are included in this meta-analysis. Compared to previous studies, a sufficient number of studies lead to more reliable conclusions.

Another impacted finding of this study is the daily consumption of probiotics more than $100*10^8$ CFU had a greater benefit on BMI reduction than daily dosage lower than $100*10^8$ CFU. Currently, there are no uniform standard regards to the among of daily intake of probiotics. This study suggests that to ensure an effect on reducing BMI, the number of probiotics may be more than $100*10^8$ CFU.

Another awaiting-to-answer question is the range of intake duration. Among 13 included studies, six trials treated subjects for less than 12 weeks, while the other six trials chose the exact 12 wk for intervention. Only one study intervened subjects for more than 12 wk. Considering studies' concentration around 12 weeks, we grouped studies into ≤ 12 wk and > 12 wk. Omitting the study that was longer than 12 wk, sensitivity analysis showed that ≤ 2 wk' intake of probiotic has a significant effect on

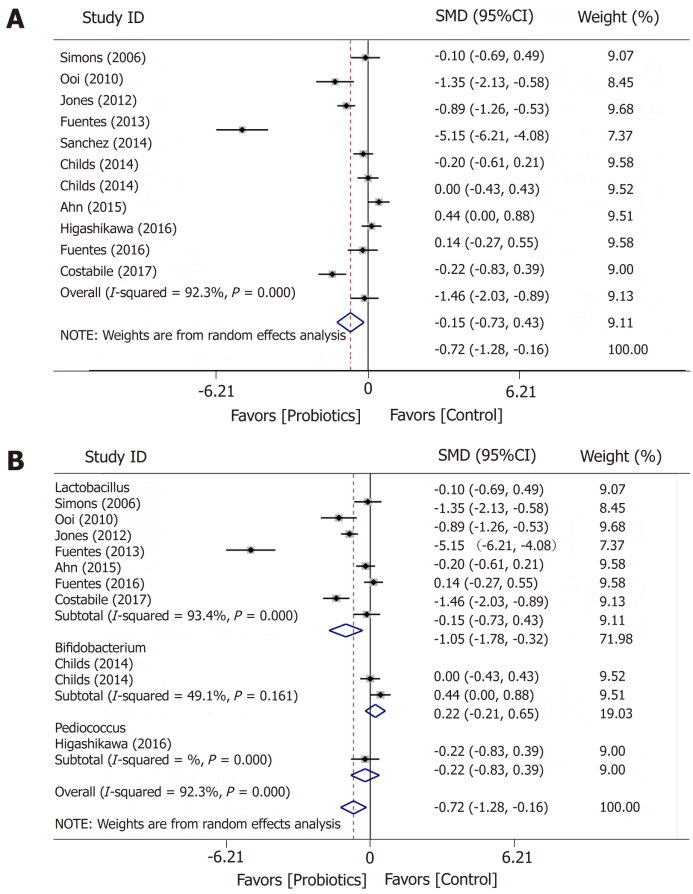

Figure 3 Meta-analysis forest plot concerning total cholesterol (A) and total cholesterol by genus (B).

TC, LDL, and HDL. Hence, although comparison among various lengths of administration terms should be done to further confirm the effect of administration term, we could come to a preliminary conclusion that intake duration of no more than 12 wk could ensure a significant effect of probiotics on TC, LDL, and HDL.

The meta-analysis revealed that probiotics did not significantly reduce the level of triglycerides. Subgroup analysis showed that when restricting studies to those whose duration of intake is less than 12 wk, the effect of probiotics on triglycerides became significant. This result was in agreement with other studies[25,26].

A number of limitations of this study should be acknowledged. First, the findings were limited to fat metabolism but not metabolic syndrome as a whole. Second, the included studies did not report adverse effects, which indicates the safety and tolerance of probiotic capsules. Hence, when making a clinical recommendation of probiotic agents, adverse effects need to be taken into account and be carefully investigated. Third, limited studies reported effects of probiotics combined with other prebiotics. Two of the included studies reported synbiotics' effects on lipid profiles. Child's study found that compared with using Bifidobacterium alone, the combination with xylo-oligosaccharides resulted in a significant but modest change in HDL. In addition, Rajkumar's study showed a superior influence of synbiotics on lipid profiles in comparison to using probiotics alone. A further meta-analysis of more studies is required to confirm the augmentation of the impacts of probiotics alone on serum lipid profiles. Last but not least, crossover studies and parallel studies were included. Crossover studies have more methodological advantages and are easier to control individual-varying confounders compared to parallel RCTs. However, crossover studies could introduce additional bias when studies have insufficient washout periods. One of our included studies used crossover design with a washout period of 28 d. Whether the washout period is long enough to avoid additional bias needs further study.

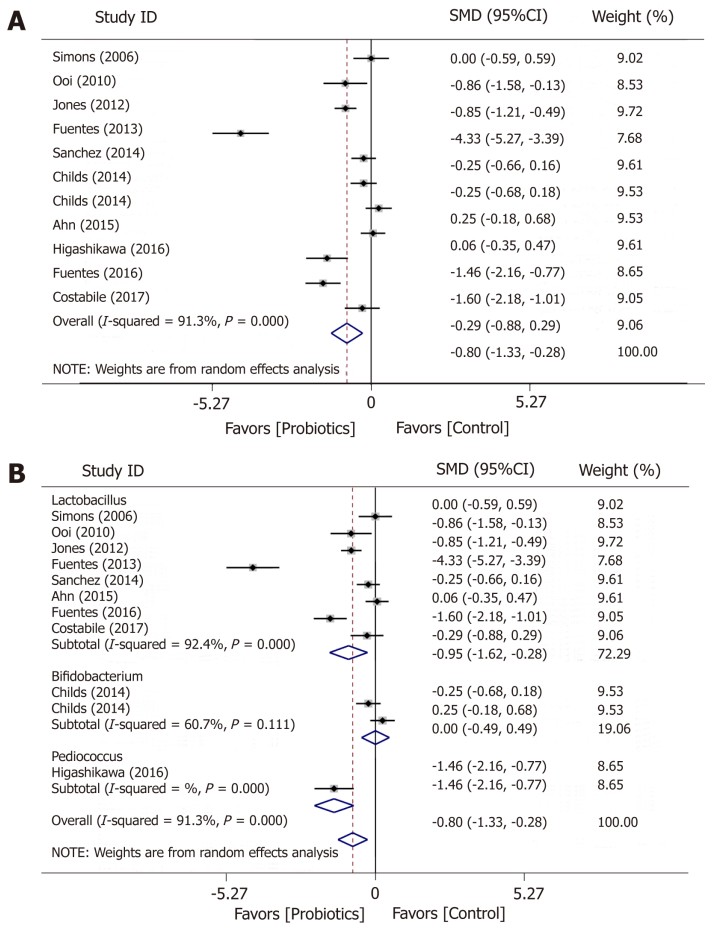

Figure 4 Meta-analysis forest plot concerning low density lipoprotein (A) and low density lipoprotein by genus (B).

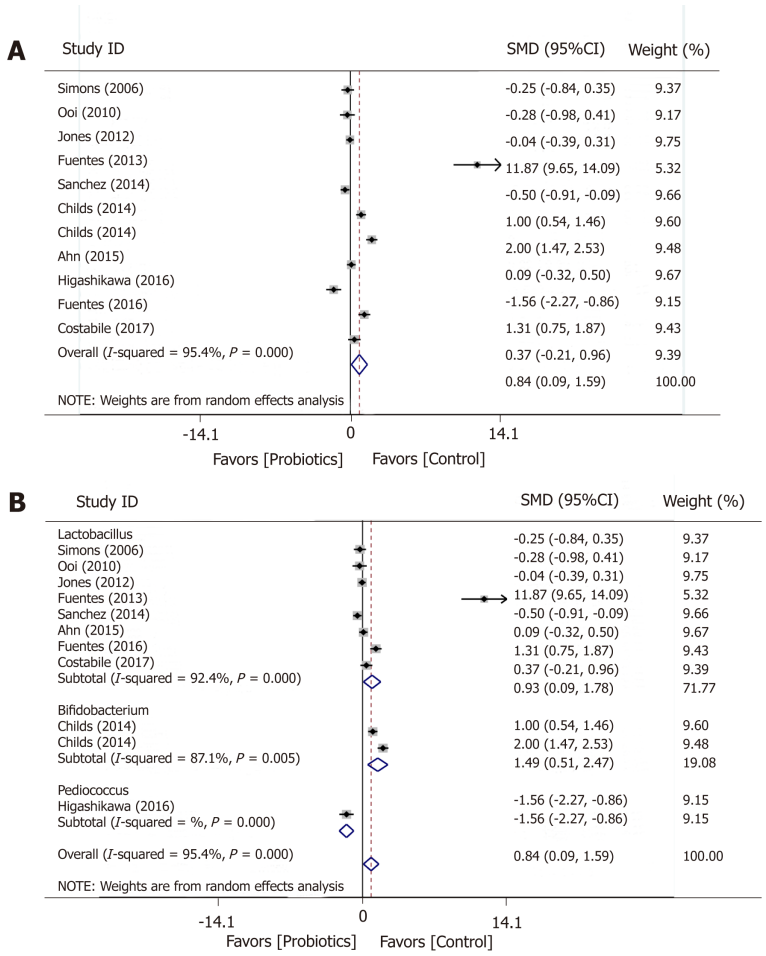

Figure 5 Meta-analysis forest plot concerning high density lipoprotein (A) and high density lipoprotein by genus (B).

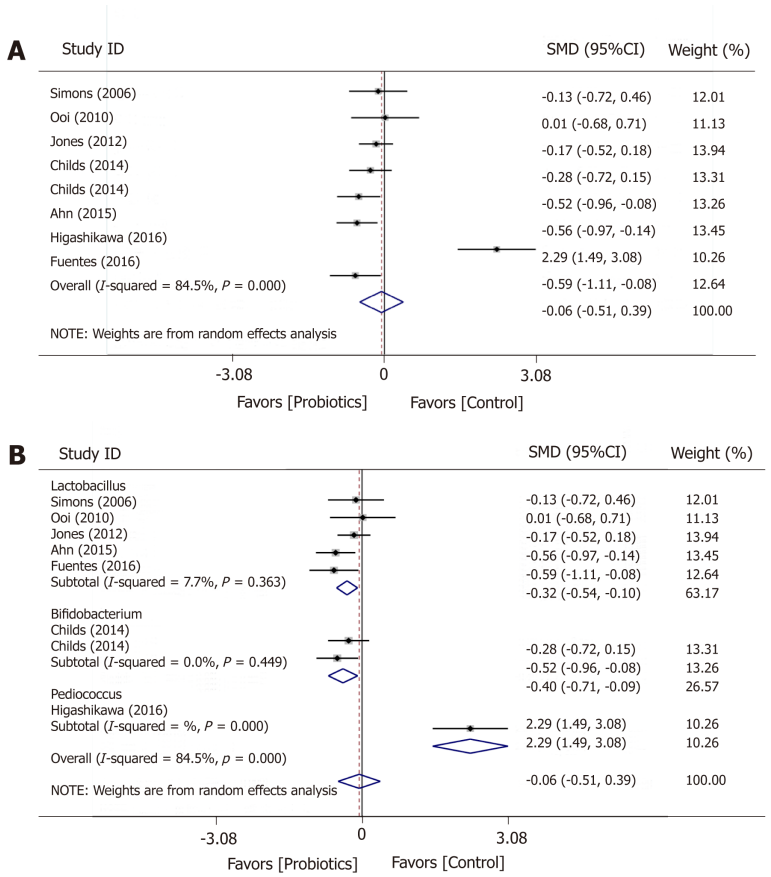

Figure 6 Meta-analysis forest plot concerning triglycerides (A) and triglycerides by genus (B).

Figure 7 Risk of bias of the included studies.

ARTICLE HIGHLIGHTS

Research background

An imbalance of the microorganisms could lead to many human diseases including dyslipidemia, fatty liver, and obesity. Probiotic supplementation has been considered an alternative treatment.

Research motivation
Variety of probiotics has been available as 'healthy' products to consumers for many health purposes. These over-the-counter probiotics usually comprised of multiple probiotic strains with some health claims. Given limited evidence on the isolated effect of each probiotic strain, a systematic approach to synthesize current scientific evidence is essential.

Research objectives
This study was aimed to identify clinical trials on the use of single probiotics alone or in combination with prebiotics for improving fatty liver, obesity, and dyslipidemia.

Research methods
This systematic review and meta-analysis was conducted using a rigorous methodology and supported by the use of systematic review management software. Titles and abstracts of the primary studies listed in PubMed and Embase databases were screened by two assessors using standard sets of inclusion and exclusion criteria. Data from the included articles were extracted in order to synthesize the effect of single probiotics on specific outcome measures.

Research results
A total of 13 randomized controlled trials were included. Three probiotics were included: *Lactobacillus* (10 studies), *Bifidobacterium* (2 studies), and *Pediococcus* (1 study). Probiotics significantly reduced BMI, reduced total cholesterol, reduced low-density lipoprotein, and increased high-density lipoprotein, compared to placebo; high study heterogeneities were observed. Only Lactobacillus could decrease triglyceride level with low heterogeneity. No included studies reported fibrosis score, liver functions, or subcutaneous fat outcomes.

Research conclusions
This systematic review emphasizes the effects of single genus non-food-based probiotics on decreasing BMI, total cholesterol and low-density lipoprotein as well as increasing high-density lipoprotein levels.

Research perspectives
Evidence on single genus probiotics is still limited. Additional clinical trials are needed for each of the single probiotics before combining two or more probiotics could be investigated.

REFERENCES

1 **Dethlefsen L**, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 2007; **449**: 811-818 [PMID: 17943117 DOI: 10.1038/nature06245]
2 **Yoo JY**, Kim SS. Probiotics and Prebiotics: Present Status and Future Perspectives on Metabolic Disorders. *Nutrients* 2016; **8**: 173 [PMID: 26999199 DOI: 10.3390/nu8030173]
3 **Reis SA**, Conceição LL, Rosa DD, Siqueira NP, Peluzio MCG. Mechanisms responsible for the hypocholesterolaemic effect of regular consumption of probiotics. *Nutr Res Rev* 2017; **30**: 36-49 [PMID: 27995830 DOI: 10.1017/S0954422416000226]
4 **Manson JE**, Tosteson H, Ridker PM, Satterfield S, Hebert P, O'Connor GT, Buring JE, Hennekens CH. The primary prevention of myocardial infarction. *N Engl J Med* 1992; **326**: 1406-1416 [PMID: 1533273 DOI: 10.1056/NEJM199205213262107]
5 **Ma J**, Zhou Q, Li H. Gut Microbiota and Nonalcoholic Fatty Liver Disease: Insights on Mechanisms and Therapy. *Nutrients* 2017; **9**: pii: E1124 [PMID: 29035308 DOI: 10.3390/nu9101124]
6 **NCD Risk Factor Collaboration (NCD-RisC)**. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet* 2016; **387**: 1377-1396 [PMID: 27115820 DOI: 10.1016/S0140-6736(16)30054-X]
7 **Nieuwdorp M**, Gilijamse PW, Pai N, Kaplan LM. Role of the microbiome in energy regulation and metabolism. *Gastroenterology* 2014; **146**: 1525-1533 [PMID: 24560870 DOI: 10.1053/j.gastro.2014.02.008]
8 **Bäckhed F**, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. *Science* 2005; **307**: 1915-1920 [PMID: 15790844 DOI: 10.1126/science.1104816]
9 **Cotillard A**, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P; ANR MicroObes consortium, Doré J, Zucker JD, Clément K, Ehrlich SD. Dietary intervention impact on gut microbial gene richness. *Nature* 2013; **500**: 585-588 [PMID: 23985875 DOI: 10.1038/nature12480]
10 **Borgeraas H**, Johnson LK, Skattebu J, Hertel JK, Hjelmesaeth J. Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2018; **19**: 219-232 [PMID: 29047207 DOI: 10.1111/obr.12626]
11 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
12 **Ahn HY**, Kim M, Ahn YT, Sim JH, Choi ID, Lee SH, Lee JH. The triglyceride-lowering effect of supplementation with dual probiotic strains, Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032: Reduction of fasting plasma lysophosphatidylcholines in nondiabetic and hypertriglyceridemic subjects. *Nutr Metab Cardiovasc Dis* 2015; **25**: 724-733 [PMID: 26044516 DOI: 10.1016/j.numecd.2015.05.002]
13 **Childs CE**, Röytiö H, Alhoniemi E, Fekete AA, Forssten SD, Hudjec N, Lim YN, Steger CJ, Yaqoob P, Tuohy KM, Rastall RA, Ouwehand AC, Gibson GR. Xylo-oligosaccharides alone or in synbiotic

combination with Bifidobacterium animalis subsp. lactis induce bifidogenesis and modulate markers of immune function in healthy adults: a double-blind, placebo-controlled, randomised, factorial cross-over study. *Br J Nutr* 2014; **111**: 1945-1956 [PMID: 24661576 DOI: 10.1017/S0007114513004261]

14 **Costabile A**, Buttarazzi I, Kolida S, Quercia S, Baldini J, Swann JR, Brigidi P, Gibson GR. An in vivo assessment of the cholesterol-lowering efficacy of Lactobacillus plantarum ECGC 13110402 in normal to mildly hypercholesterolaemic adults. *PLoS One* 2017; **12**: e0187964 [PMID: 29228000 DOI: 10.1371/journal.pone.0187964]

15 **Fuentes MC**, Lajo T, Carrión JM, Cuñé J. Cholesterol-lowering efficacy of Lactobacillus plantarum CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. *Br J Nutr* 2013; **109**: 1866-1872 [PMID: 23017585 DOI: 10.1017/S000711451200373X]

16 **Fuentes MC**, Lajo T, Carrión JM, Cuñé J. A randomized clinical trial evaluating a proprietary mixture of Lactobacillus plantarum strains for lowering cholesterol 1. *Mediterr J Nutr Metab* 2016; **9**: 125-135 [DOI: 10.3233/MNM-160065]

17 **Higashikawa F**, Noda M, Awaya T, Danshiitsoodol N, Matoba Y, Kumagai T, Sugiyama M. Antiobesity effect of Pediococcus pentosaceus LP28 on overweight subjects: a randomized, double-blind, placebo-controlled clinical trial. *Eur J Clin Nutr* 2016; **70**: 582-587 [PMID: 26956126 DOI: 10.1038/ejcn.2016.17]

18 **Inoue T**, Kobayashi Y, Mori N, Sakagawa M, Xiao JZ, Moritani T, Sakane N, Nagai N. Effect of combined bifidobacteria supplementation and resistance training on cognitive function, body composition and bowel habits of healthy elderly subjects. *Benef Microbes* 2018; 1-12 [PMID: 30198326 DOI: 10.3920/BM2017.0193]

19 **Jones ML**, Martoni CJ, Prakash S. Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. *Eur J Clin Nutr* 2012; **66**: 1234-1241 [PMID: 22990854 DOI: 10.1038/ejcn.2012.126]

20 **Kim M**, Kim M, Kang M, Yoo HJ, Kim MS, Ahn YT, Sim JH, Jee SH, Lee JH. Effects of weight loss using supplementation with Lactobacillus strains on body fat and medium-chain acylcarnitines in overweight individuals. *Food Funct* 2017; **8**: 250-261 [PMID: 28001147 DOI: 10.1039/C6FO00993J]

21 **Ooi LG**, Ahmad R, Yuen KH, Liong MT. Lactobacillus gasseri [corrected] CHO-220 and inulin reduced plasma total cholesterol and low-density lipoprotein cholesterol via alteration of lipid transporters. *J Dairy Sci* 2010; **93**: 5048-5058 [PMID: 20965319 DOI: 10.3168/jds.2010-3311]

22 **Rajkumar H**, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. *J Cardiovasc Pharmacol Ther* 2015; **20**: 289-298 [PMID: 25331262 DOI: 10.1177/1074248414555004]

23 **Sanchez M**, Darimont C, Drapeau V, Emady-Azar S, Lepage M, Rezzonico E, Ngom-Bru C, Berger B, Philippe L, Ammon-Zuffrey C, Leone P, Chevrier G, St-Amand E, Marette A, Doré J, Tremblay A. Effect of Lactobacillus rhamnosus CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women. *Br J Nutr* 2014; **111**: 1507-1519 [PMID: 24299712 DOI: 10.1017/S0007114513003875]

24 **Simons LA**, Amansec SG, Conway P. Effect of Lactobacillus fermentum on serum lipids in subjects with elevated serum cholesterol. *Nutr Metab Cardiovasc Dis* 2006; **16**: 531-535 [PMID: 17126768 DOI: 10.1016/j.numecd.2005.10.009]

25 **Sun J**, Buys N. Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. *Ann Med* 2015; **47**: 430-440 [PMID: 26340330 DOI: 10.3109/07853890.2015.1071872]

26 **Guo Z**, Liu XM, Zhang QX, Shen Z, Tian FW, Zhang H, Sun ZH, Zhang HP, Chen W. Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis* 2011; **21**: 844-850 [PMID: 21930366 DOI: 10.1016/j.numecd.2011.04.008]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com