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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Acute calculous cholecystitis: Review of current best practices

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Abstract

Acute calculous cholecystitis (ACC) is the most frequent complication of cholelithiasis and represents one-third of all surgical emergency hospital admissions, many aspects of the disease are still a matter of debate. Knowledge of the current evidence may allow the surgical team to develop practical bedside decision-making strategies, aiming at a less demanding procedure and lower frequency of complications. In this regard, recommendations on the diagnosis supported by specific criteria and severity scores are being implemented, to prioritize patients eligible for urgency surgery. Laparoscopic cholecystectomy is the best treatment for ACC and the procedure should ideally be performed within

72 h. Early surgery is associated with better results in comparison to delayed surgery. In addition, when to suspect associated common bile duct stones and how to treat them when found are still debated. The antimicrobial agents are indicated for high-risk patients and especially in the presence of gallbladder necrosis. The use of broad-spectrum antibiotics and in some cases with antifungal agents is related to better prognosis. Moreover, an emerging strategy of not converting to open, a difficult laparoscopic cholecystectomy and performing a subtotal cholecystectomy is recommended by adept surgical teams. Some authors support the use of percutaneous cholecystostomy as an alternative emergency treatment for acute Cholecystitis for patients with severe comorbidities.

Key words: Cholecystitis; Cholelithiasis; Biliary stones; Cholecystectomy; Laparoscopy

Core tip: This paper presented herein is a practical and comprehensive review of the acute cholecystitis. This common intra-abdominal infection can proceed to severe complications due to its natural history and requires operative treatment. Surgeons should keep in mind some basic concepts to allow them to make correct decisions about ideal operative strategy including timing.

Gomes CA, Junior CS, Di Saverio S, Sartelli M, Kelly MD, Gomes CC, Gomes FC, Corrêa LD, Alves CB, Guimarães SF. Acute calculous cholecystitis: Review of current best practices. *World J Gastrointest Surg* 2017; 9(5): 118-126 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i5/118.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i5.118

INTRODUCTION

Acute calculous cholecystitis (ACC) represents the second source of complicated intra-abdominal infection (18.5%), according to the World Society of Emergency Surgery complicated intra-abdominal infections Score study[1]. Biliary stones are the main etiology and are present in 6.5% of men and 10.5% of women[2]. The risk of complications, like ACC, gallstone pancreatitis, and choledocholithiasis is 1% to 4% per year. Furthermore, it is recognized that patients with symptomatic cholecystolithiasis will develop ACC more frequently than their asymptomatic counterparts; thereby, effectively raising the risk of complications to five times higher (*i.e.*, 20%)[3].

ACC is the most common complication of cholecystolithiasis accounting for 14% to 30% of cholecystectomies performed in many countries[4]. The disease can be diagnosed at any grade of severity including wall inflammation, local complication and systemic organ dysfunction. Moreover, complicated grades of the disease increase with age, with a peak between 70 and 75 years[5].

The aim is of this manuscript is to provide a practical and comprehensive review of the most important aspects of ACC and its complications. In parallel, to highlight the current evidence that helps the surgeons bedside decision making, on how best to manage the disease, to improve outcomes.

PATHOPHYSIOLOGY

ACC is caused by an inflammatory/infectious process involving the gallbladder wall, in many cases due to an impacted gallstone in the infundibulum or in the cystic duct[2]. The continued mucin production from epithelium and the gallbladder distention, results in micro and macro circulatory perfusion deficits. The subsequent events are serosa edema, mucosal sloughing, venous and lymphatic congestion, ischemia and necrosis with regional or diffuse peritonitis. Acute inflammation may be complicated by secondary bacterial infection, from the bile duct, *via* the portal lymphatic or vascular system. The microorganisms present in the gastrointestinal tract are the most common pathogens[5].

CLINICAL DIAGNOSIS

There is no unique marker capable of definitively indicating the diagnosis of ACC with high accuracy. The key aspects for diagnosis are upper left side signs of inflammation (pain and tenderness) and positive Murphy's sign, as well as clinical and biochemical indicators of systemic inflammatory response. These data must be nowadays supported with positive imaging such as abdominal ultrasound (AUS)[6,7].

Acute cholecystitis severity

The Tokyo Guidelines (TG13) is practical and in accordance with the pathophysiological aspects involved in the inflammation progression from gallbladder wall to regional and systemic complications. Therefore, the grade I represents a mild disease with only wall inflammation. The grade II is associated with local sign of complications such as palpable mass, pericholeystic fluid; onset of symptoms > 72 h; laboratory data showing leukocytosis > 18000/mm^3 and elevated C-reactive protein level. Finally, grade III is associated with organ dysfunction: Cardiovascular (refractory hypotension to volemic resuscitation at 30 mL/kg per hour), decrease of consciousness, respiratory failure (PaO2/FiO2: < 300), oliguria (creatinine: > 2.0 mg/dL), PTT/INR > 1.5 and platelets count below 100.000/mm^3[6].

The American Association of Surgery of Trauma proposes a uniform grading system for eight intra-abdominal infectious diseases including ACC. The grades range from I to V, considering the progressive anatomic inflammation severity (from mild to serious widespread

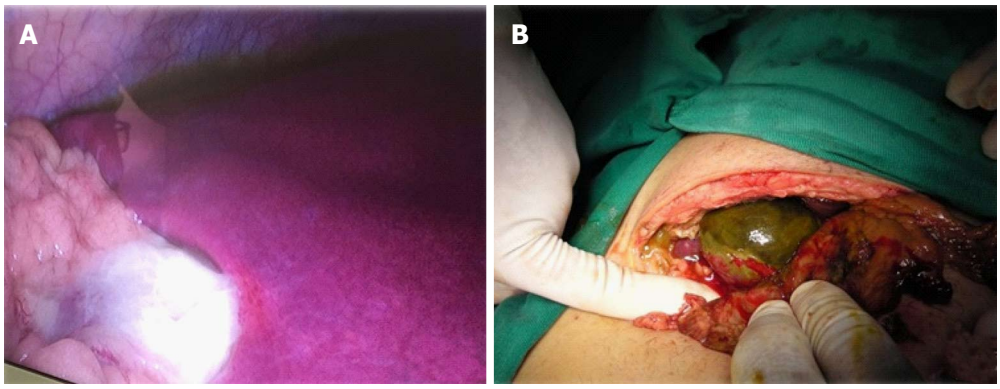

Figure 1 Complicated acute cholecystitis. A: Laparoscopic approach; B: Laparotomic approach.

complications)[8].

Yacoub *et al*[9] have developed five parameters to score and stratify patients under risk of gangrenous ACC (Figure 1). They are age > 45 years, heart beat > 90/min and gallbladder thickness > 4.5 mm (1 point for each parameter), leukocyte count > 13000 mm^3 (1.5 points) and male (2 points). Among their patients with ACC, 13% received 0-2 points (low probability), 33% received 2-4.5 points (intermediate probability) and 87% received > 4.5 points (high probability). The authors concluded that this fast bedside checklist could schedule patients for emergency cholecystectomy[9].

Currently the WSES is in the process of validating a new acute cholecystitis severity score. It takes into account the patient's clinical state, previous surgical intervention and intra-abdominal adhesions, degree of sepsis and regional inflammation[10]. While the paper highlights the initial operative severity score during laparoscopic cholecystectomy to help standardize reporting results of one of the most commonly performed surgeries worldwide, the score also assesses disease severity in the perioperative period and not exclusively in the preoperative period.

IMAGING DIAGNOSIS

Planar radiography is not so effective in the context of gallstones diagnosis, because they are radiolucent in the majority of cases (80%-85%)[11]. Instead, AUS is the first-line imaging requested in suggestive cases of ACC. It allows easy and practical bedside diagnosis due its compelling findings such as: Gallstones, lumen distension, three-phase wall thickening (Figure 2), sonographic Murphy's, perivisceral fluid and hyperemia on Color Dopller[12-15]. However, Kiewiet *et al*[12] have shown that AUS does not have the same accuracy in the diagnosis of ACC as it has in diagnosing cholecystolithiasis. The findings of gallstones, gallbladder wall thickness and Murphy's signal on AUS show high predictive value for ACC diagnosis (95%)[16]. However, not always all signals are present at the same time and gallbladder wall thickening may be observed in other systemic diseases, such as liver, renal and heart failure, probably because portal hypertension[17].

Computed tomography (CT) is useful for the diagnosis of complicated forms of ACC (emphysematous and gangrenous cholecystitis)[18,19], besides it is value in the differential diagnosis with other intra-abdominal diseases, especially in obese patients or when gaseous distention limits the use of AUS. In addition, CT cholangiography (when not jaundiced) in diagnosing common bile duct stones (CBDS) is less employed, with a reported sensitivity from 50% to 90%[20-22].

Cholescintigraphy is an excellent method to diagnose ACC, but it is limited to some centers. It uses the principle that radiopharmaceuticals (diisopropyl iminodiacetic acid) should fulfill the gallbladder content in half an hour. Therefore, if gallbladder is not contrasted, few hours later, the diagnosis of ACC is highly probable, because there is cystic duct obstruction. Shea *et al*[23] showed in their meta-analysis that cholescintigraphy is the imaging of choice in difficult cases and has the highest diagnostic accuracy (Figure 3).

ASSESSING ASSOCIATED CBDS

The presence of associated CBDS should be stratified in all cases of cholecystectomy into low, moderate and high risk. The American Society of Gastrointestinal Endoscopy, has recently confirmed that the presence of choledocholithiasis on AUS and/or bilirubin > 4 mg/dL + dilated CBD criteria had higher specificity (more than 50%) for the CBDS diagnosis[24]. Padda *et al*[25] found in a cohort study that patients with ACC and CBDS present changes in liver function tests. So, the alkaline phosphatase is increased in 77% of the times, bilirubin in 60% and aminotransferase levels in 90%.

In fact, the enzymes could be affected by gallbladder inflammation secondary the acute transient hepatocellular injury, and even their use alone is of limited value[26]. Patients of moderate risk for choledocholithiasis should be underwent a magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) in the preoperative period. The use of intra-operative cholangiography (IOC), and/or laparoscopic ultrasound are effective alternative

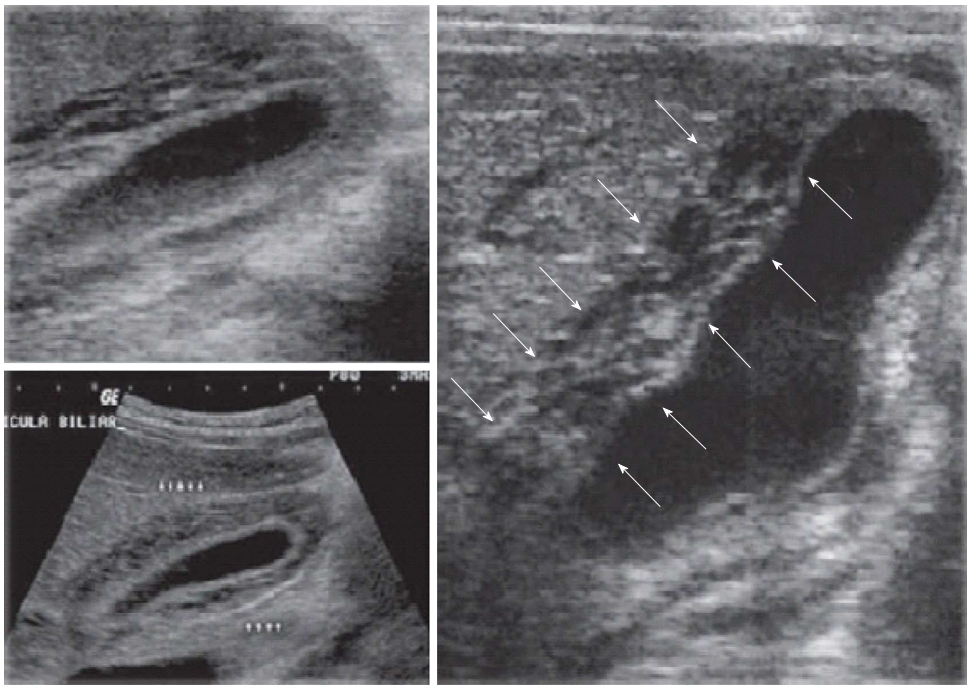

Figure 2 Transabdominal ultrasound in acute cholecystitis.

Figure 3 Cholescintigraphy in acute calculous cholecystitis.

for decrease the incidence of missing CBDS during cholecystectomy too. Therefore, the use of endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for patients that are stratified into the high-risk groups[24,27].

Giljaca *et al*[28], in the recent Cochrane meta-analysis, compared the level of diagnostic accuracy between MRCP and EUS and concluded that both tests are highly accurate and able to exclude the presence of CBDS with high sensibility and specificity (95%). They therefore recommend routinely avoiding the use of the more invasive ERCP, when possible, and instead reserving it for patients already graded as high risk for CBDS[24,28].

Amouyal *et al*[29] have shown that EUS is an excellent approach for detecting CBDS and could replace ERCP in many instances. It prevents the risk of overlooking them, when there are normal biochemical predictors and an absence of CBD enlargement on AUS. The exam is less invasive than ERCP, and has excellent sensitivity and specificity for the detection of CBDS including small stones (< 5 mm)[29].

HOW TO MANAGE ASSOCIATED COMMON BILE DUCT STONE

Patients with symptomatic ACC and CBDS detected during preoperative and/or intraoperative studies should be candidates to undergo CBDS extraction. The choice of treatment depends on the level of surgical expertise, equipment, and the availability of multidisciplinary facilities at each hospital[30]. The options include: open cholecystectomy (OC) with open common bile duct exploration; laparoscopic cholecystectomy (LC) with laparoscopic common bile duct extraction (LCBDE); and LC with endoscopic stone extraction (ESE) performed either preoperatively, intraoperative or post-operatively[31,32]. A systematic review of randomized controlled trials has shown that OC with open CBDE has the lowest incidence of retained stones, but is associated with high morbidity and mortality, especially in elderly patients[30,32]. In addition, there was no difference in the retained CBDS among preoperative or intra-operative ERCP and LCBDSE[30,31]. The procedure, either *via* the transcystic duct (more than 50% success), or *via* choledochotomy (considered to be the more difficult group) is safe and effective to perform in units that are set up for this type of intervention[33,34]. Therefore,

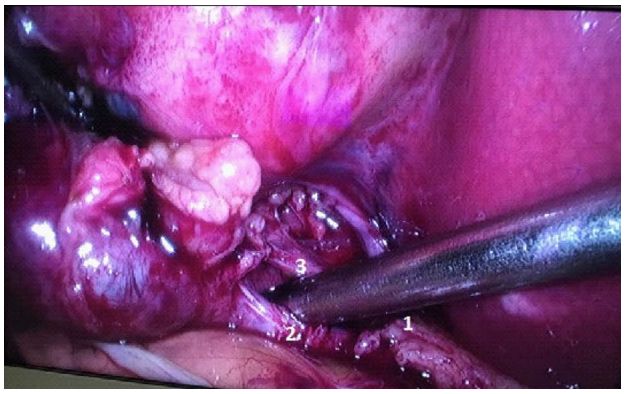

Figure 4 Laparoscopic cholecystectomy showing the critical view of safety. 1: Common hepatic duct; 2: Cystic duct; 3: Cystic artery.

LCBDE is a safe and effective approach for managing option CBDS, has been demonstrated to shorten the hospital stay and should be encouraged as a possible salvage procedure following cases of ESE failure[34].

As a rule, however, operations for severe ACC should focus on dealing with the problem at hand, as CBDS can be removed later. The severity of the local inflammatory process near the bile duct can mean that LCBDE would be difficult to perform. A temporary fenestrated transcystic catheter, inserted *via* the cystic duct into the duodenum (antegrade stent) is an option. Should this be considered, the definite treatment of CBDS would be postponed until the patient recovers and the catheter in the duodenum favors the ERCP. Nonetheless, this approach has not been tested yet prospectively and for coincidental CBDS that are not actively causing obstruction; critics have suggested it seems to be over-treatment, and complications from this technique have been known to occur.

LAPAROSCOPIC OR OPEN APPROACH

Laparoscopy has significant advantages over open surgery in managing septic patients. The immune response and the levels cytokines yielded, which are associated with systemic inflammatory response severity, are smaller and influence the clinical outcomes[35].

Recent systematic reviews and meta-analyses from the WSES concluded that in the setting of ACC post-operative morbidity, mortality, and hospital stay were significantly decreased after LC, as was the incidence of pneumonia and wound infection. Severe haemorrhage, bile leakage rates, and/or operative times were not significantly different between patients undergoing OC and LC. The group of experts concluded that cholecystectomy in ACC should be preferably managed by laparoscopy in the first instance[36]. Though other relevant treatment modalities include mini-cholecystectomy, reduced-port cholecystectomy, single-port cholecystectomy and robotic cholecystectomy, these were determined to be neither practical nor cost-effective in severe cases of ACC.

Because the surgeon's commitment is primarily to their patient and not to the laparoscopy procedure itself, the operation cannot be performed if the "critical view of safety" (CVS) is not obtained during cholecystic pedicle dissection, regardless of the chosen approach (*i.e.,* laparoscopy *vs* laparotomy). Failure to identify the CVS is a strong indication of IOC for the complete understanding of the biliary anatomy (Figure 4). The reported incidence of bile duct injury (CBDI) during LC ranges from 0.16% to 1.5%, and has not decreased over time. Stefanidis *et al*[37] studied how often surgeons resort to the consideration of the CVS during LC and their results were disappointed. Only 20% of observed surgeons achieved adequately the CVS during LC; that is, CVS criterion was not routinely used by majority of surgeons. Furthermore, one-fourth of those who claimed to obtain the CVS did so inadequately[37].

Retrograde laparoscopic cholecystectomy (RLC) or "fundus first" laparoscopic cholecystectomy, a procedure that sometimes utilizes a liver retractor, does have a role in cases in which the standard technique (*i.e.*, cephalad fundic traction and antegrade dissection) fails to provide good exposure[38]. Another emerging strategy that refrains from the need to convert to opening a difficult LC and performing a subtotal cholecystectomy (SCL) is also underway. There is increasing evidence about the feasibility and safety of this procedure, which employs a strategy of "calculated retreat is not defeat[39]. SCL procedures are nominated "fenestrating" and "reconstituting" types and are good alternative in difficult cases. Laparoscopic subtotal cholecystectomy has its advantages but may require advanced laparoscopic skills[39].

An alternative approach aimed at preventing bile duct injury (BDI) is laparoscopic partial cholecystectomy (LPC). A recent systematic review concluded that, when a difficult gallbladder is encountered during LC, LPC is a safe alternative to conversion and closing of the cystic duct, gallbladder remnant, or both seems to be preferable[40]. Currò *et al*[41] (2017) conducted a prospective randomized study comparing three-dimensional *vs* two-dimensional imaging for LC and, despite their small sample, concluded that three-dimensional approach does not improve the performance time of LC in experienced hands. Further study is necessary, however, to verify if it can reduce biliary complications[41].

TIMING OF SURGICAL TREATMENT

Gurusamy *et al*[42] (2010) in their meta-analysis compared early laparoscopic cholecystectomy (ELC - 1 wk of onset of symptoms) X delayed laparoscopic cholecystectomy (DLC - at least 6 wk after symptoms free) in patients with ACC. They concluded that the two groups presented similar results regarding bile duct injury and conversion rate, but the hospital stay was shorter by 4 d for ELC and recommend the approach[42].

Table 1 The choice of antibiotics for treatment of acute calculous cholecystitis according the WSES proposal in two different scenarious

Community acquired		Health care associated	
Infections situations	Drug	Infections situations	Drug
No severe Sepse ESBL -	Amoxicilin Clavulanate	No severe sepse	Piperacilin Tazobactan + Tigecicline + - Fluconazol
No severe Sepse ESBL +	Tigecicline		
Severe Sepse ESBL -	Piperacilin Tazobactan	Severe sepse	Piperacilin Tazobactan + Tigecicline + Echinocandin
Severe Sepse ESBL +	Piperacilin Tazobactan + Tigecicline + Fluconazole		or Carbapenen + Teiclopanin + Echinocandin

From: Campaline *et al*[47], 2014. WSES. ESBL: Extended spectrum β-lactamase.

Cao *et al*[43] (2015) in their meta-analyses studied if ELC is superior to DLC for ACC management. They showed that ELC group has presented reductions in mortality, bile duct complications and improvement in many other parameters analyzed.

Although the procedure should be performed within the first 72 h, patients still benefit from early surgery compared to delayed surgery. Therefore, the period of onset of symptoms should not influence the surgeons' willingness to perform an ELC. They suggest that ELC is the standard of care in the treatment of ACC[43].

According to TG13, for patients with grade Ⅰ disease, cholecystectomy at an early stage (*e.g.*, within 72 h of onset of symptoms) is recommended. If non-operative treatment (antimicrobial therapy) is chosen and no improvement is observed within 24-48 h, reconsider ELC first. For patients classified as grade Ⅱ (*i.e.*, they demonstrate local complications), emergency surgery must be expedited (*via* laparotomy or laparoscopy) and in the absence of adequate facilities, skilled personnel or technical equipment, patient transfer should be considered. For patients with grade Ⅲ and/or those unfit to undergo an emergency cholecystectomy, gallbladder drainage may be an attractive alternative. This therapy is typically complemented with antibiotics and intensive care; an interval cholecystectomy may also be performed at three months, following improvement in the patient's health status[6]. However, Amirthalingam *et al*[44] (2016) suggested that these recommendations are too restrictive, stating instead that patients with moderate and severe ACC can be managed by ELC and sometimes, even those that fall into the category of grade I should be managed using percutaneous drainage because of potential underlying.

In addition, the 2016 WSES guidelines on ACC identify two important aspects in the management. First of all, they conclude that "surgery is superior to observation of ACC in the clinical outcome and shows some cost-effectiveness advantages due to the gallstone-related complications (33% in relapse) and to the high rate of readmission and surgery in the observation group". Second, they confirm that "cholecystectomy is the gold standard for treatment of ACC"[45].

ANTIMICROBIAL TREATMENT

The role of therapeutic antibiotics in ACC is controversial, but seems appropriate in non-operative treatment, which should be reserved for patients with mild disease[6]. The use of preoperative prophylactic antibiotics is not suitable for low-risk patients undergoing LC. The main purpose of starting antibiotics in surgically managed cases of ACC is to prevent perioperative infectious complications[46], however, according to van Dijk *et al*[47] in recent systematic review, which assessed its effect in the course of ACC conclude: They are not effective for patients undergone to non-operative treatment neither in those one selected for cholecystectomy.

When antibiotics are indicated, the choice of antimicrobial agent is guided by the likely type of pathogen being targeted, taking into consideration whether it was acquired in the community or a healthcare setting, whether it is extended spectrum β-lactamase (ESBL) producing, the presence of sepsis, as well as the agent's pharmacodynamics and pharmacokinetics. Blood cultures are not always positive and many times the prescription is based on empiric approach. As we know, critically-ill patients need acute care measures and the intravenous antibiotics administration within the first hour. Microbiological data take at least 48 h for the identification of the microorganisms. In addition, the Hospital based Antibiotic Stewardship Programs should be involved to provide the most frequent pathogens and their susceptibility/resistance profiles[48].

The most important pathogens in ACC originate in the patient's indigenous flora and include Enterobacteriaceae: *E. coli* and *Klebsiella sp*, *Streptococcus sp*, and anaerobes such as *Bacteroides fragilis* group. In these cases, narrower spectrum activity antimicrobials targeting the previously mentioned pathogens are the best option. However, in patients with ESBL-producing Enterobacteriaceae infections, agents against ESBL-producing bacteria need to be warranted[48]. Campanile *et al*[49] (2014) recommend the use of antibiotics and antifungal agents in high-risk patients with gangrenous cholecystitis as their use is tied to lower incidence of infection at the surgical site and better prognosis. The Table 1 illustrates more clearly their antimicrobial recommendations[49].

COMPLICATIONS

Bile leak from a duct of Luschka is more common than true bile duct injury and occurs in 0.1%-0.5% of patients after cholecystectomy. Other complications include peritonitis (0.2%), hemorrhage and surgical site infection including spaces and organs. Operative complication rates are comparable between the laparoscopic and laparotomic approaches. In addition, there is less concern for contamination and lower rates of

wound infection when the gallbladder is taken out in a retrieval bag during laparoscopic cholecystectomy[50-53].

A recent systematic review assessed the associated factors linked to the conversion of LC to OC. The results showed that male patients, age 60-65 years, sclerotic gallbladder or wall thickness (4-5 mm) and acute cholecystitis, were significant risk factors for conversion[54].

WHEN TO PERFORM CHOLECYSTOSTOMY

Percutaneous cholecystostomy (PC) is an alternative to emergency cholecystectomy in complicated cases of high risk patients, however, there are yet no evidences supporting this claim[55,56]. Gurusamy *et al*[56] (2013) in a Cochrane Database systematic review included two trials with 156 participants. The first trial compared PC followed by ELC *vs* DLC (70 participants). The results showed that the mortality, morbidity and conversion rate were the same among the two groups[56].

The second trial (86 participants), compared PC *vs* conservative treatment (86 participants). Again, the result of the study showed no difference in the same parameters[56].

It has been difficult to establish the role of percutaneous gallbladder drainage because of the different existing definitions for the "high-risk patient"[42,54]. In an attempt to clarify the conflicting evidences, Yeo *et al*[57] 2017 in a retrospective review, studied 103 aged patients (median: 80 years), who had undergone PC procedures. The study results showed that the patients with higher APACHE Ⅱ scores, higher Charlson index, delay in diagnosis and carrying out the procedure had higher in-hospital mortality. On the other, the absence of these findings was associated with eventual cholecystectomy[57].

CONCLUSION

Presented herein is a practical and comprehensive review of the ACC. This common intra-abdominal infection can proceed to severe complications due to its natural history and requires operative treatment. Surgeons should keep in mind some basic concepts to allow them to make correct decisions about ideal operative strategy including timing.

The clinical diagnosis should be based on strictly criteria and the patient should be stratified according grade and the possibility of local and systemic complications. Laparoscopy is the suggested first approach for cholecystectomy guaranteeing significant advantages over open surgery. In select cases, percutaneous cholecystostomy may be used as a lifesaving manoeuvre. In addition, the possibility of choledocholithiasis should be kept in mind and its therapeutic alternatives considered. Finally, to recognize the basic principles that guide the antimicrobial use for prophylactic and therapeutic proposes.

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SYSTEMATIC REVIEWS

International scientific communications in the field of colorectal tumour markers

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Author contributions: Ivanov K designed the study; Donev I performed the information retrieval on the topic; Ivanov K drafted the manuscript; Ivanov K and Donev I were involved in the final approval of the manuscript.

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Abstract

AIM

To analyze scientometrically the dynamic science internationalization on colorectal tumour markers as reflected in five information portals and to outline the significant journals, scientists and institutions.

METHODS

A retrospective problem-oriented search was performed in Web of Science Core Collection (WoS), MEDLINE, BIOSIS Citation Index (BIOSIS) and Scopus for 1986-2015 as well as in Dervent Innovations Index (Derwent) for 1995-2015. Several specific scientometric parameters of the publication output and citation activity were comparatively analyzed. The following scientometric parameters were analyzed: (1) annual dynamics of publications; (2) scientific institutions; (3) journals; (4) authors; (5) scientific forums; (6) patents - number of patents, names and countries of inventors, and (7) citations (number of citations to publications by single authors received in WoS, BIOSIS Citation Index and Scopus).

RESULTS

There is a trend towards increasing publication output on colorectal tumour markers worldwide along with high citation rates. Authors from 70 countries have published their research results in journals and conference proceedings in 21 languages. There is considerable country stratification similar to that in most systematic investigations. The information provided to end users and scientometricians varies between these data-bases in terms of most parameters due to different journal coverage, indexing systems and editorial policy. The lists of the so-called "core" journals and most productive authors in WoS, BIOSIS, MEDLINE and Scopus along with the list of the most productive authors - inventors in Derwent present a particular interest to the beginners in the field, the institutional and national science managers

and the journal editorial board members. The role of the purposeful assessment of scientific forums and patents is emphasized.

CONCLUSION

Our results along with this problem-oriented collection containing the researchers' names, addresses and publications could contribute to a more effective international collaboration of the coloproctologists from smaller countries and thus improve their visibility on the world information market.

Key words: Colorectal tumour markers; Scientometrics; International scientific communications; Web of Science; MEDLINE; BIOSIS; Scopus; Derwent

Core tip: Colorectal tumour markers represent a promising option for the early diagnosis and prognostic evaluation of colorectal cancer patients. Dynamically changing environment of the communication infrastructure in this significant interdisciplinary field deserves comprehensive scientometric assessment. By means of this specific approach, valuable and relatively objective information about the trends and perspectives of research and publication output worldwide has been provided. The results obtained and the comprehensive collection of abstracts and full texts of relevant publications on colorectal tumour markers could contribute to the further improvement of the international visibility on the world information market of coloproctologists from smaller countries.

Ivanov K, Donev I. International scientific communications in the field of colorectal tumour markers. *World J Gastrointest Surg* 2017; 9(5): 127-138 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i5/127.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i5.127

INTRODUCTION

At present, primary colorectal cancer is diagnosed in > 1.4 million subjects annually and incidence is increasing[1]. Recently, much effort focuses on screening and earlier detection of colorectal cancer, which reduces the cancer-related mortality rate[2]. Several screening markers are currently applied to help diagnosing the early-stage colorectal cancer or even the premalignant lesions. They are divided into two different categories: stool markers, such as FOBT/FIT and blood-based markers as DNA/RNA and proteins[3]. DNA methylation-based biomarkers should be widely used to improve the current diagnosis, screening, prognosis and treatment prediction in colorectal cancer[4]. Detection of epigenetic and genetic alterations of circulating cell-free DNA as DNA methylation or DNA mutations and related ribonucleic acids improves cancer detection based on unique, colorectal cancer-specific patterns which serve as biomarkers in screening and diagnosis[5].

The analysis of a panel of 92 candidate cancer protein markers measured in 35 clinically identified colorectal cancer patients and 35 ones identified at screening colonoscopy proves the importance of the validation of the early detection markers in a true screening setting for limiting the number of false-positive findings[6]. Serum expression levels of miR-17, miR-21, and miR-92 represent valuable markers for recurrence after adjuvant chemotherapy in colon cancer patients[7].

A plasma-based protein marker panel for colorectal cancer detection was identified by multiplex targeted mass spectrometry using multiple reaction monitoring technology[8]. The usefulness of diagnostic marker panels was already suggested by us, too[9]. The measurement of metabolite porphyrin concentrations in urine could serve as a new screening and recurrence marker for colorectal cancer[10]. Better understanding and elucidation of the various influences provides a more accurate picture of the segmental distribution of some common molecular markers in colorectal cancer such as KRAS, EGFR, Ki-67, Bcl-2, and COX-2, potentially allowing the application of a novel patient's stratification for treatment based on particular molecular profiles in combination with tumour location[11].

The main objectives of this article were to comparatively analyze by means of scientometric methods the dynamic science internationalization in the actual topic of colorectal tumour markers as reflected in five information portals (data-bases), to outline the most significant primary information sources, scientists and institutions in this interdisciplinary field and thus attempt at contributing to the further improvement of the international scientific communications in smaller countries.

MATERIALS AND METHODS

In July 2016, a retrospective problem-oriented search on this topic using the term of "colorectal marker(s)" in publication titles only was performed. Information retrieval covered the following information portals (data-bases): Web of Science Core Collection (WoS), MEDLINE and BIOSIS Citation Index (BIOSIS) (Thomson Reuters, Philadelphia, PA, United States) as well as Scopus (Elsevier, the Netherlands) for the period from January 1st, 1986 till December 31st, 2015. Information about patents indexed in Dervent Innovations Index (Derwent) (Thomson Reuters, Philadelphia, PA, United States) between 1995 and 2015 was analyzed, too.

The following scientometric parameters were analyzed: (1) annual dynamics of publications - total number and thematic belonging of abstracted publications as well as languages and types of primary publications; (2) scientific institutions - number of abstracted publications and country belonging; (3) journals - total number and number of abstracted articles

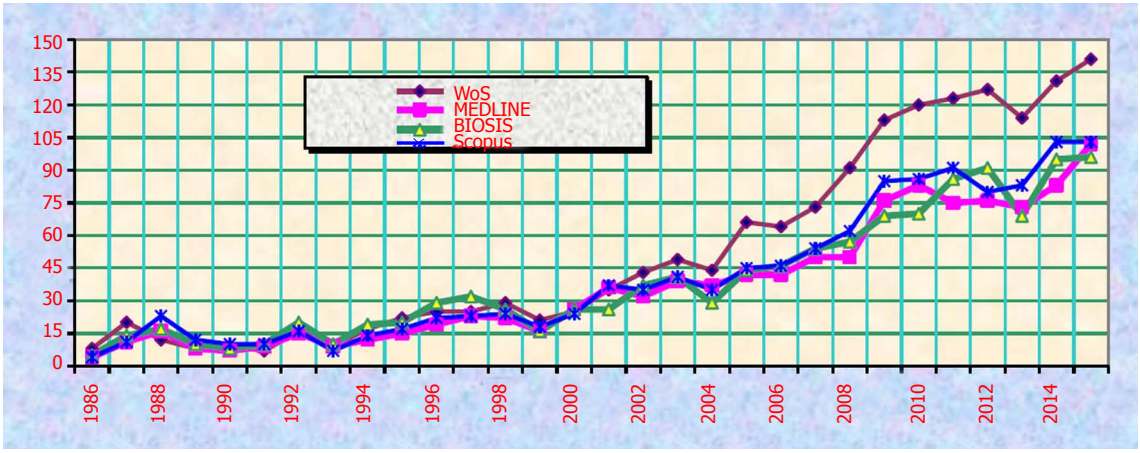

Figure 1 Annual dynamics of the number of publications on the topic abstracted in four data-bases.

Table 1 General bibliometric characteristics of four data-bases concerning the topic

Parameter	WoS	BIOSIS	MEDLINE	Scopus
Total number of publications	1587	1172	1108	1221
Total number of journals	334	265	364	N/A
Total number of journals with one article only	163	140	201	N/A
Total number of languages (n = 21)	5	11	17	19
Total number of countries of authors (n = 70)	63	55	N/A	63
Total number of research areas (WoS categories)	48	42	49	21

N/A: Not available.

from single journals as well as narrow-profile specialized journals containing the term of "(bio)marker(s)" in their titles; (4) authors - number of unique names and number of publications; (5) scientific forums - titles and publications in them; and (6) patents - number of patents, names and countries of inventors and assignees as well number of claims in single patents, and (7) citations - number of citations to publications by single authors received in WoS, BIOSIS Citation Index and Scopus. Purposeful combinations of such quantitative parameters enabled a comprehensive assessment of the unity of the institutionalization, interdisciplinarity and internationalization of modern science in this narrow field of rising socio-medical importance[12].

RESULTS

Our results revealed several essential peculiarities of the dynamic structure of the publication and citation output on this topic during these three decades.

The amounts of relevant papers, journals containing them, and countries of authors varies between the data-bases (Table 1). There are 106 patents indexed in Derwent during the period of the observation

The annual dynamics of the number of publications on this topic which have been abstracted in WoS, BIOSIS, MEDLINE and Scopus and that of the patents abstracted in Derwent are illustrated on Figures 1 and 2. There is a considerable recent increase of the publication output, especially in WoS.

The distribution of some leading countries according to the number of publications in WoS, BIOSIS, and Scopus indicates a considerable stratification typical of most scientometric investigations (Figure 3). The corresponding figures for the United States are 314, 228, and 223 publications; for Canada - 36, 17, and 21; for Switzerland - 34, 21, and 20; for Poland - 17, 13, and 24; for Bulgaria - only five, three, and three, respectively, etc. Meanwhile, the aforementioned paper of ours[8] has received six citations in WoS.

The distributions of document types (Table 2) and languages (Table 3) display an obvious variability between these four data-bases. This is mainly due to the strict restrictions of journal coverages permanently applied by the editors of WoS.

The lists of the so-called "core" journals containing the greatest number of relevant papers on the topic (Table 4) and the most productive authors in WoS, BIOSIS, MEDLINE and Scopus (Table 5) along with the list of the most productive authors - inventors in Derwent (Table 6) represent a particular interest not only to the beginners in the field but also to the institutional and national science managers and the journal editorial board members as well. It should be added that among the top 20 journals, there are two titles equally represented in four data-bases, three titles are omitted in one data-base but one title, Lab Invest is omitted in both MEDLINE and Scopus. On the other hand, most journals in the scientometric "tail", *i.e.*, presenting with one article abstracted only, are

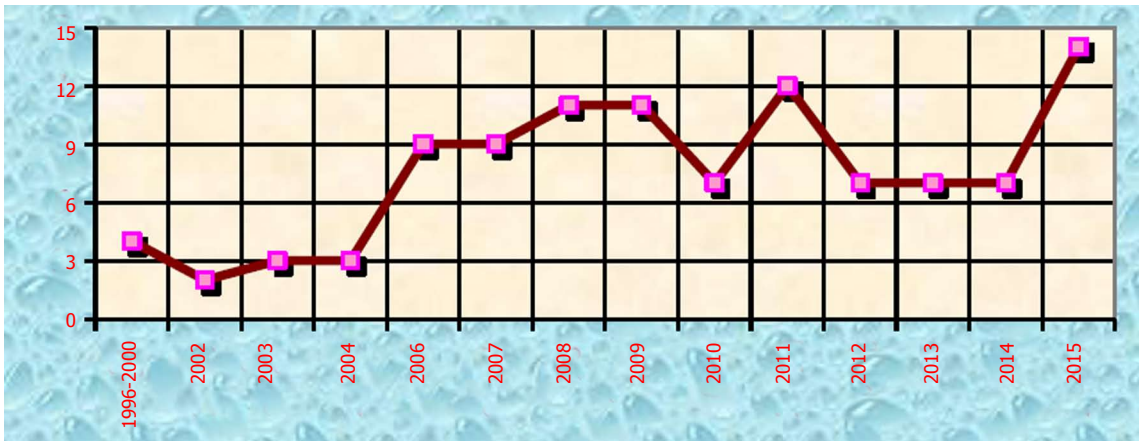

Figure 2 Annual dynamics of patents on the topic.

Table 2 Document type distribution in four data-bases

Document type	WoS	BIOSIS	MEDLINE	Scopus
Journal article	870	700	1057	970
Review	63	38	118	114
Congress proceedings	57	6	1	39
Meeting abstract	543	313	0	0
Editorial	34	6	17	18
Letter-to-the-editor	37	9	28	32
Book chapter	6	9	0	8
Evaluation study	0	0	28	0
Multicenter study	0	0	19	0
Randomized controlled trial	0	0	15	0
Meta-analysis	0	0	13	0
Validation study	0	0	11	0
Patent	0	19	0	0

Table 3 Language distribution of publications on the topic abstracted in four data-bases

Language	WoS	BIOSIS	MEDLINE	Scopus
English	1545	1136	1017	1095
German	17	5	10	17
French	14	9	12	14
Spanish	9	2	9	12
Japanese	0	7	17	21
Chinese	0	6	11	27
Italian	2	1	6	7
Polish	0	0	5	7
Czech	0	1	4	5
Danish	0	0	4	4
Other (11)	0	3 (5)	7 (15)	9 (15)

Table 4 "Core" journals on the topic in four data-bases

Rank	Journal title	WoS	BIOSIS	MEDLINE	Scopus
1	*Gastroenterology*	115	100	15	15
2	*J Clin Oncol*	96	4	12	13
3	*Br J Cancer*	52	47	45	47
4	*Anticancer Res*	46	54	39	39
5	*Cancer Res*	43	45	14	14
6	*Eur J Cancer*	38	36	20	20
7	*Clin Cancer Res*	36	9	34	34
8	*Dis Colon Rectum*	33	4	24	19
9	*Oncol Rep*	28	28	28	28
10	*Int J Cancer*	27	25	26	26
Total "core" journals - *n* (%)		10 (2.99)	10 (3.76)	10 (2.75)	10 (N/A)
Total publications - *n* (%)		514 (32.39)	352 (30.03)	255 (23.01)	257 (21.05)

N/A: Not available.

Table 5 Most productive authors on the topic in four data-bases

Rank	Author's name	WoS	BIOSIS	MEDLINE	Scopus
1	Ahlquist DA	25	31	10	8
2	Mori M	22	14	16	20
3	Doki Y	17	11	13	16
4	Nielsen HJ	17	12	2	11
5	Lugli A	16	14	5	6
6	Mimori K	16	10	11	14
7	Zlobec I	16	14	5	6
8	Inoue Y	14	4	10	10
9	Ishi H	14	8	11	14
10	Mahoney DW	14	11	1	2

almost equally indexed in these four data-bases thus confirming Bradford's law of journal scattering in any research field. In this case, these journals amount to 48.80% in WoS, to 52.83% in BIOSIS, and to 55.22% in MEDLINE (their absolute counts are shown in Table 1).

Only a small number of most productive scientific institutions in WoS and Scopus (Table 7) and institutions - assignees in Derwent (Table 8) is provided in order to indicate their undoubtedly high relative share on the world information market.

The computerized analysis published online by Thomson Reuters of the main research areas (in BIOSIS and MEDLINE) and of the Web of Science categories (in WoS itself) has identified significant differences concerning several indexing results between there three data-bases, Table 9). We would like only to mention the figures for "gastroenterology and hepatology", "biochemistry and molecular biology", and "immunology" and to emphasize the achievements in these interdisciplinary fields in clinical medicine and

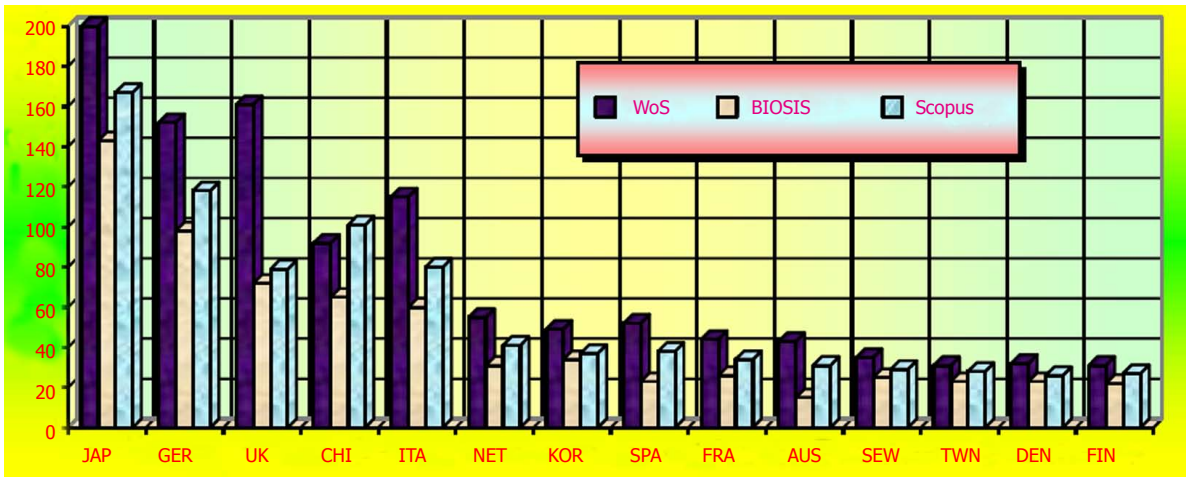

Figure 3 Country distribution according to the number of publications on the topic abstracted in three data-bases.

Table 6 Most productive authors - inventors on the topic in Derwent

Name	Country	City	Institution	Patents
Karl J	Germany	Penzberg	Roche Diagnostic GmbH	9
Choquet-Kastylevsky G	France	Nancy Letoile	Biomerieux SA	9
Charrier JP	France	Nancy Letoile	Biomerieux SA	9
Ataman-Oenal Y	France	Nancy Letoile	Biomerieux SA	6
Beaulieu C	France	Nancy Letoile	Biomerieux SA	6
Ahlquist DA	United States	Rochester	Mayo Clinic	4

Table 7 Most productive institutions on the topic in WoS and in Scopus

Rank	Institution	WoS	Scopus
1	German Cancer Research Center	29	26
2	Mayo Clinic	29	17
3	Harvard University	28	14
4	Osaka University	25	25
5	Kyushu University	22	22
6	Universität Heidelberg	25	19
7	Ludwig-Maximilians-Universität München	21	23
8	Memorial Sloan-Kettering Cancer Center	20	12
9	Kaohsiung Medical University	15	22
10	University of Copenhagen	23	9

Table 8 Most productive institutions - assignees on this topic in Derwent

Nomination	Country	Patents
Biomerieux SA	France	9
Hoffmann La Roche	Switzerland	9
Mayo Medical Education and Research	United States	4
Ruiqu Biotechnology Shanghai Co. Ltd	China	3
Signature Diagnostics GmbH	Germany	3
Shimadzu Corporation	Japan	3
Ver Christelijk Wetenschappel Onderw	The Netherlands	3
Fudan University	China	3

Table 9 Dominant research areas (WoS categories) on the topic in three data-bases

Rank	Research area (WoS category)	WoS	BIOSIS	MEDLINE
1	Oncology	834	1153	1034
2	Gastroenterology and hepatology	297	1084	166
3	Surgery	301	55	132
4	Pathology	169	55	74
5	Cell biology	47	42	231
6	Biochemistry and molecular biology	42	266	703
7	Medical laboratory technology	33	393	48
8	Pharmacology and pharmacy	27	144	190
9	Radiology, nuclear medicine and medical imaging	25	15	30
10	Genetics and heredity	24	402	490
11	Public, environmental and occupational health	23	22	29
12	Immunology	10	77	454
13	Hematology	7	22	43
14	Nutrition and dietetics	5	16	17
15	Endocrinology and metabolism	3	98	22

biomedicine.

The distributions of the number of authors according to the number of their patents (Figure 4) and that of the declared claims in their patents (Figure 5) demonstrate a significant research activity on the topic of colorectal tumour markers. This specific scientometric evaluation contributes to the identification of the players at the fore-front of clinical medicine-related technological progress.

Several common citation patterns on this topic as reflected in WoS and BIOSIS are listed in Table 10. The percentages of the times cited without self-citations and of the citing articles without self-citations are extraordinarily high, indeed. The so-called "h-index" introduced by Hirsch[13] is very high - 75 and 57 in WoS and in BIOSIS, respectively.

The comparative assessment of ten articles which have been most cited in WoS, in BIOSIS, and in Scopus (Table 11)[14-23] identifies two weird discrepancies. The

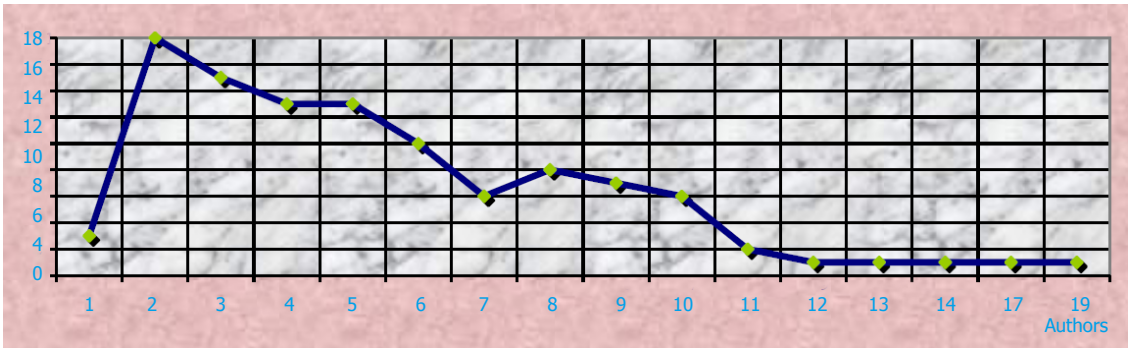

Figure 4 Distribution of the number of authors according to the number of their patents on the topic.

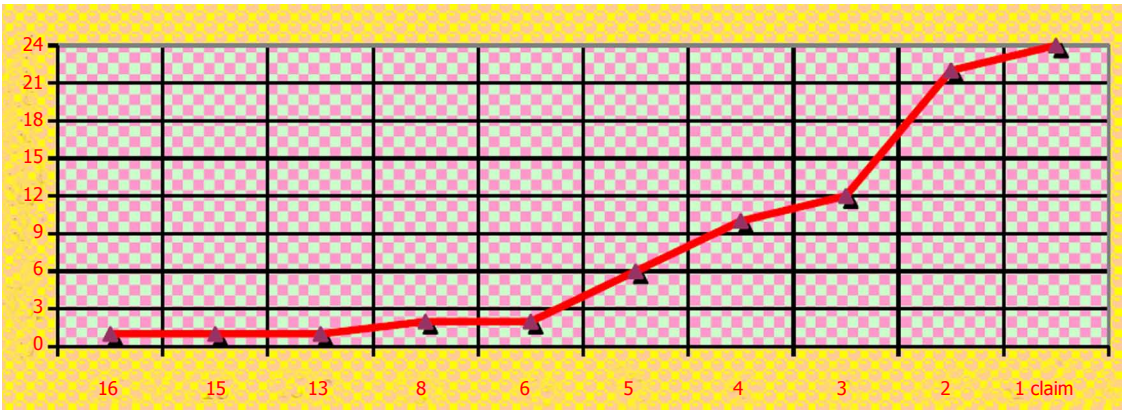

Figure 5 Distribution of the number of declared claims in the patents on the topic.

Table 10 Cumulative citation patterns on the topic in WoS and BIOSIS

Citation parameter	WoS	BIOSIS
Total number of publications	1587	1172
Sum of the times cited	25116	13297
Sum of the times cited without self-citations	24092	12777
Percentage of these times cited	95.92	96.09
Citing articles	19607	11061
Citing articles without self-citations	19120	10779
Percentage of these citing articles	97.52	97.45
Average citations per item	15.83	11.35
Average citations per year	810.19	443.23
Articles cited at least once	961	643
Percentage of these articles	60.55	54.86
H-index	75	57

article published in the "core" journal *J Clin Oncol*[17] has not been indexed in Scopus at all (as opposed to the other 13 articles in this journal) as well as the article co-authored by Sturgeon *et al*[22] and published in the journal *Clin Chem* has not been indexed in BIOSIS at all (as opposed to the other nine articles in this journal ranked 15th among a total of 265 journals).

The comprehensive scientometric analysis of the bibliographic information about the congresses, symposia, meetings, and conferences held in many countries which proceedings have been abstracted in WoS and in BIOSIS clearly outlines the rising role of these forums for the intensive development of the international scientific communications and science advancement as well (Tables 12 and 13).

In WoS and in BIOSIS, we have identified six scientific forums containing the terms of "tumour or cancer (bio) markers" in their titles (Table 14) and, in four data-bases, we have found out eight specialized journals meeting this criterion (Table 15). The annual dynamics of these 51 articles is characterized by two peak values (in 2010 and in 2014) (Figure 6). The considerable relative share (78.43%) of the papers published in foreign specialized journals stresses, indeed (Figure 7) and testifies to the substantial role of this particular aspect of science internationalization.

DISCUSSION

Our results convincingly outline the rising publication output on colorectal tumour markers worldwide and the significant citation activity as substantial features of quality and international prestige under the conditions of science globalization.

Modern colorectal tumour markers are used either for diagnostic, or for prognostic purposes. In addition, they could be applied for therapeutic evaluations.

The combined detection of two tumour markers, serum p53 antibody and carcinoembryonic antigen (CEA), improves the diagnostic sensitivity and prognosis

Table 11 Ten most cited articles on the topic in three data-bases

Ref.	Journal title, volume, year and pages	WoS	BIOSIS	Scopus
Ng *et al*[14]	*Gut* 2009; 58: 1375-1381	593	447	656
Bast *et al*[15]	*J Clin Oncol* 2001; 19: 1865-1878	552	314	670
Cui *et al*[16]	*Science* 2003; 299: 1753-1755	472	400	530
No author list[17]	*J Clin Oncol* 1996; 14: 2843-2877	388	234	Absent
Walther *et al*[18]	*Nat Rev Cancer* 2009; 9: 489-499	315	243	348
Duffy[19]	*Clin Chem* 2001; 47: 624-630	253	141	289
Duffy *et al*[20]	*Eur J Cancer* 2007; 43: 1348-1360	245	160	276
Nakamori *et al*[21]	*Gastroenterology* 1994; 106: 353-361	234	179	219
Sturgeon *et al*[22]	*Clin Chem* 2008; 54: E11-E79	211	Absent	255
Duffy *et al*[23]	*Eur J Cancer* 2003; 39: 718-727	202	120	235

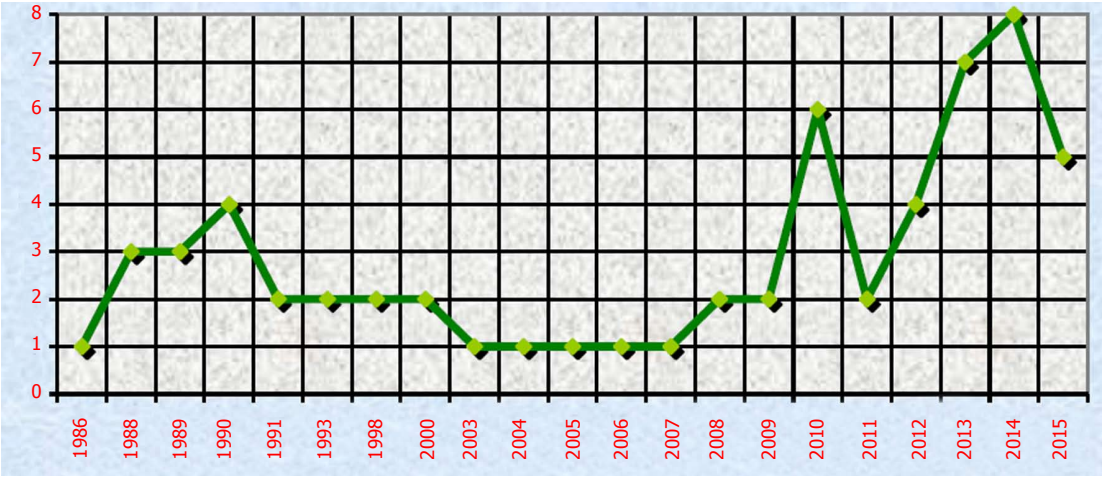

Figure 6 Annual dynamics of papers on the topic in specialized journals.

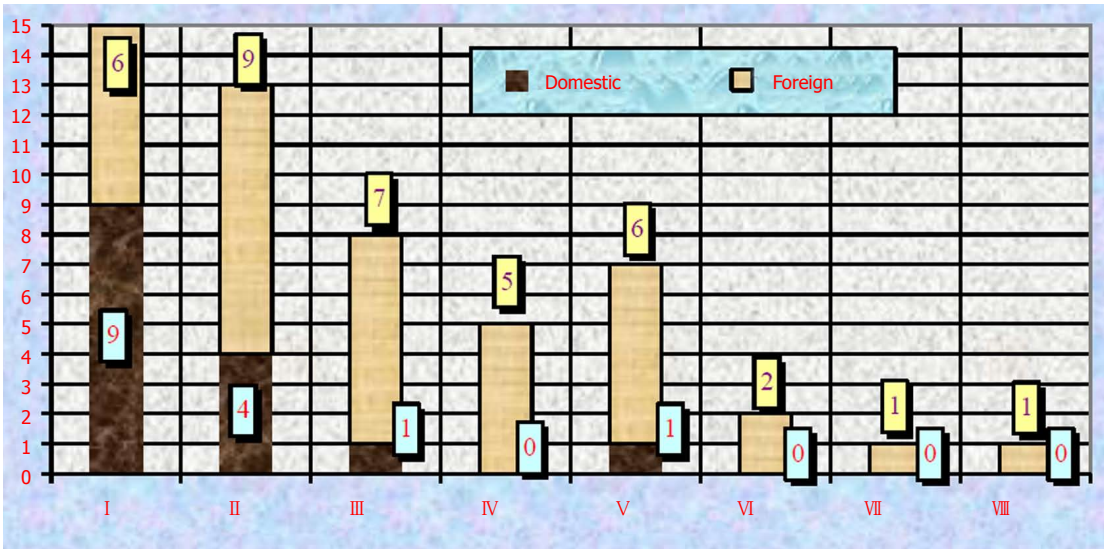

Figure 7 Papers on the topic published in domestic and foreign specialized journals. I: Cancer Epidemiol Biomarkers Prev; II: Int J Biol Markers; III: Cancer Biomarkers; IV: Disease Markers; V: J Tumor Marker Oncol; VI: Biomarkers; VII: Biomarkers Med; VIII: Genet Testing Mol Biomarkers.

of early-stage colorectal cancer patients[24].

A diagnosis strategy of serum tumour markers, an artificial intelligent algorithm, provides decision support for physicians on the usage of different tumour markers and diagnosis of colorectal cancer[25].

CEA containing macrophages combined with C-reactive protein possesses diagnostic potential in early colorectal cancer[26]. The diagnostic models based on the logistic regression analysis, support vector machine and back-propagation neural network demonstrate

Table 12 Bibliometric characteristics of scientific forums on the topic in WoS and BIOSIS

Parameter	WoS	BIOSIS
Number of forum titles	95	73
Number of unique forums	170	203
Number of publications	377	432
Number of forums with a single event only	71	52
Number of forums with two events	9	5
Number of forums with three events	5	2
Number of forums with one publication only	57	117
Number of forums with two publications	10	34
Number of forums with three publications	5	16
Maximal number of events of a unique forum	12	27
Maximal number of publications in a unique forum	58	102

Table 13 Scientific forums with most events and papers in them on the topic in WoS and BIOSIS

Scientific forum title	WoS		BIOSIS	
	Events	Papers	Events	Papers
Digestive Disease Week	12	58	25	90
Annual Meeting of the American Association for Cancer Research	4	17	27	102
Annual Meeting of the United States and Canadian Academy of Pathology	10	34	11	29
Annual Meeting of the American Society of Clinical Oncology	8	49	0	0
European Society for Medical Oncology Congress	7	17	1	5
World Congress of Gastrointestinal Cancer	7	24	0	0
Meeting of the International Society for Oncodevelopmental Biology and Medicine	3	6	9	16
Meeting of the Pathological Society of Great Britain and Ireland	5	5	11	11
European Congress of Pathology	0	0	11	22
Annual Meeting of the American College of Gastroenterology	4	5	5	6

Table 14 Scientific forums with "tumour or cancer (bio)markers" in their titles in WoS and BIOSIS

Scientific forum title	WoS		BIOSIS	
	Events	Papers	Events	Papers
Hamburg Symposium on Tumor Markers	2	3	5	8
Congress (Meeting) of the International Society of Oncology and Biomarkers	3	4	2	2
Annual Meeting of the EORTC/NCI/ASCO on Molecular Markers in Cancer	1	2	1	2
Annual Conference on Diet and Cancer: Markers, Prevention, and Treatment	1	1	0	0
International Symposium on Tumor Markers - From Biology to Therapy	1	1	0	0
Joint Meeting on Markers in Cancer of ASCO, EORTC and NCI	0	0	1	1

a higher early diagnostic value of the combination of serum tumour markers, *e.g.*, CEA, cancer antigen (CA) such as CA 19-9, CA 242, CA 125, and CA 15-3 for colorectal cancer[27]. SATB2 protein is a diagnostic marker for tumours of colorectal origin and provides a new and advantageous supplement for clinical differential diagnostics[28]. In combination with CK7 and CK20, its specificity increases from 77% up to 100%. The most common markers for such tumours include the expression of CK20, often along with lack of CK7, *i.e.*, the $CK20^{+}/CK7^{-}$ phenotype[28].

MYBL2 gene is an independent prognostic marker with tumour-promoting functions in colorectal cancer and its overexpression may play an important role in tumourigenesis[29]. HLA class Ⅱ antigen expression in colorectal cancer is a reliable prognostic marker as it is related with a favourable clinical course of the disease[30]. The combined high levels of some inflammatory cytokines such as CXCL8, vascular endothelial growth factor and Pentraxin3 are potential prognostic markers as they are associated with increased risk of colorectal cancer recurrence independently of TNM staging and with worse survival[31]. The circulating microRNAs markers miR-122 and miR-200 family members could be used in the development of a multi-marker blood test for colorectal cancer prognosis and survival[32]. The decreased erythropoietin expression, high vascular endothelial growth factor levels and elevated cyclin B1 expression, predominant moderate tumour differentiation, absence of metastasis, and negative lymph node status are reliable proliferation and differentiation markers indicating the low level of aggressiveness, better prognosis, and longer colorectal adenocarcinoma patient's survival[33]. By means of solid-phase proximity ligation assay, 35 protein markers were simultaneously analyzed in a small amount of blood of stage Ⅰ to Ⅳ colorectal cancer patients, however, these markers did not give better prognostic information than CEA[34].

An outlined correlation exists between the differentiation degree and expression of aldehyde dehydrogenase 1, a stem cell marker, in colorectal carcinoma cells[35]. Low-stage tumours exhibit a higher expression of aldehyde dehydrogenase 1 or CD133 compared with high-stage tumours while CD133 expression is associated with lymph node metastasis-positive cases thus predicting the disease prognosis. Aldehyde dehydragenase 1 and Nodal are important prognostic markers in colorectal cancer as there is a significant correlation between their expression and the differentiation degree, metastasis, number of tumour-positive lymph nodes and disease stage[36].

Science internationalization includes not only direct research interaction between single scientists from different countries and their teams organized through official contracts or within informal collectives but also several essential components[12]: (1) continuous creation of new international scientific societies and international associations of national societies, of new international scientific journals and international publishers or publish-

Table 15 Specialized journals with the term of "(bio)markers" in their titles in four data-bases

Rank	Journal title	WoS	Scopus	MEDLINE	BIOSIS	Total
1	*Cancer Epidemiol Biomarkers Prev*	0	0	0	15	15
2	*Int J Biol Markers*	5	0	11	9	13[1]
3	*Cancer Biomarkers*	7	8	7	8	8[1]
4	*Disease Markers*	5	5	5	5	5[1]
5	*J Tumor Marker Oncol*	0	3	0	6	6[1]
6	*Biomarkers*	2	0	2	2	2[1]
7	*Biomarkers Med*	0	0	1	0	1
8	*Genet Testing Mol Biomarkers*	1	0	1	0	1[1]
Total number of publications		20	16	27	45	51[1]
Total number of journals		5	3	6	6	8[1]
Countries of authors		19	13	20	20	25[1]
Countries of journals		5	2	4	5	5[1]
Articles in domestic journals		2	1	2	14	11[1]
Articles in journals published abroad		18	15	25	31	40[1]

[1]The sum of unique items is smaller than the total amount of single items due their duplication in several data-bases.

ing houses; (2) publishing of scientific papers, reviews and book reviews in foreign journals and periodicals; (3) translation and publishing of monographs by foreign authors; (4) organization of international scientific forums and participation in them of authors from numerous foreign countries; (5) enrichment of the forms of immediate exchange of scientists from other countries; (6) unlimited dissemination of new scientific information through modern information-communication technologies; (7) modernization and automatization of scientific libraries; and (8) introduction of electronic journals and monographs; and (9) overcoming of the traditional barriers for interpersonal communication between scientists from different countries.

Similarly to other authors[37], we face not only advantages but also disadvantages in the comprehensive activity of both editors and staff in these two widely recognized information centres in the United States and in the Netherlands. There is user-friendly uninterrupted online access to the information portals providing a rising amount of full-text articles. The computerized data processing facilitates automated problem-oriented information retrievals and large-scale scientometric analyses as well. However, several unfavorable features deserve a special attention. Some author's affiliations are incomplete, even within one and the same scientific institution. Single significant publications are missing in at least one of these four data-bases although the corresponding journals are covered. The incorporation of proceedings from congresses, conferences and symposia is insufficient. The indexing of primary document types and research areas should be further improved, too.

There is a stable research interests in the issues of a variety of peculiarities of the modern international scientific communications and collaboration worldwide.

Publication coverage in Scopus or WoS, English as a specific international language, and journal articles as a specific type of publication, are indicators of research quality and internationalization in the social sciences and humanities[38]. There is a different extent of internationalization of peer reviewed and non-peer reviewed book publications in the social sciences and humanities in Belgium[39].

The analysis of the dynamics of journal internationality using using 1398 journals and 2557229 papers during 1991-2014 demonstrates that journals' papers and references have become more globalized over time[40]. For both national and multinational publishers, most of the changes in journal internationalization occur between the fourth and sixth year of indexing in *WoS*. Natural sciences as well as engineering and technology have the most international papers but the journals in medical and health sciences, natural sciences, and agricultural sciences contain the most international references.

The emergence of a new transnational demand in health research dealing with global regenerative medicine and parallel markets is analyzed according to relevant theoretical dilemmas in medical anthropology and the sociology of science and health[41].

The investigation of the international and domestic coauthorship relations of all citable items in the Social Sciences Citation Index 2011 demonstrates that the international networks in the social sciences have grown during the last decades in addition to the national ones but not by replacing them[42]. The comparison of the internationalization of more than one thousand academic journals in six fields of science indicates that social sciences literature is still nationally and linguistically fragmented more than natural sciences one[43].

A standardization method that transforms all fractions of internationally coauthored papers from a dataset of the National Science Foundation into a comparable framework is applied to examine the evolution and convergence of the patterns of international scientific collaboration between 1973 and 2012[44]. The convergence of these long-run collaboration patterns between the applied and basic sciences might be a contributing factor that supports the evolution of modern

scientific fields.

The promises and challenges of international collaboration in achieving success towards poverty, environment, education, science, and medicine are reviewed comprehensively[45]. A model for sustainable university-based international plastic surgery collaboration between plastic surgery consultants from abroad and a hospital in a developing country is implemented[46]. The analysis of China's international publications on healthcare science and services research identifies a rapid recent increase[47]. Collaboration among countries, institutions and authors increase, too. The academic impact of publications with partners from European and American countries is relatively higher than of those with partners from Asia. The most prominent actors are Peking University, Fudan University, Chinese University of Hong Kong, and University of Hong Kong. The significance of the international scientific collaboration in the field of minimally invasive general surgery is highlighted[48].

The bibliometric analysis of Cuban scientific publications listed in PubMed during the period between 1990 and 2010 proves that Cuban science policy and practice ensure the application of science for social needs by harnessing human resources through national and international collaboration, building stronger scientific capacity[49]. The research output and impact of 479 Mexican researchers working abroad and included in the Mexican National System of Researchers are investigated in terms of production, mobility and scientific collaboration[50]. Mobility exerts a strong effect on scientists' international collaboration.

The dynamic internationalization of modern science is analyzed by Bulgarian authors in different interdisciplinary fields such as haemorrhagic stroke prevention[51], paediatric sleep apnea[52], applications of the geographical information systems in health planning[37], *etc.*

In conclusion, contemporary colorectal tumour markers are more and more widely studied and routinely applied in clinical coloproctology worldwide thus promoting the further improvement of individualized patient's management. We have revealed a series of discrepancies in the coverage and computerized processing of the recent scientific literature on colorectal tumour markers by these powerful information centres that necessitates refinements in their editorial policy. The creation of this comprehensive problem-oriented collection with purposefully systematized files containing the researchers' names, addresses and publications is designed mainly for specialists in coloproctology from smaller countries who strive for a more effective collaboration with colleagues from eminent centres abroad and, in this way, to achieve an improved international visibility on the world information market.

COMMENTS

Background

A summary of the increasing role of screening and early detection of colorectal cancer with a variety of specific colorectal serum markers that is reflected in five modern information portals covering world literature on this hot topic during the recent decades.

Research frontiers

Nowadays, science stratification in terms of individual researchers, teams, institutions, journals, and countries deserves a special attention to be paid by the comprehensive scientometric approach to the structure and dynamics of international scientific communications in the field of colorectal tumour markers. Such a particular analysis is capable of identifying the most productive authors representing a true interest to the beginners in oncological coloproctology and related fields, the institutional and national science managers and the journal editorial board members. By providing systematized factual information to end users, the scientometric results outline the emerging opportunities for fruitful interdisciplinary and international collaboration.

Innovations and breakthroughs

Under the conditions of enormous globalization and competition in contemporary science, timely orientation in and awareness of the promising advances in colorectal tumour markers can substantially contribute to new scientific achievements not only by leaders working in powerful countries but also by the scientists from the rest of the world. Thus the collaboration trends can be further empowered and expanded.

Applications

In the era of telecommunication technologies, the new scientific information on colorectal tumour markers published in the ocean of journals, conference proceedings, monographs, patents and other primary literature sources is very easy to access in case one could be trained in information science and applied scientometrics. Besides science policy managers at different levels and journal editors could successfully apply these scientometric results, too.

Terminology

At the first glance, the particular terminology used in this article looks nearly strange to gastrointestinal surgeons, coloproctologists, and oncologists. On the other hand, there is a rising amount of meta-analyses, systematic reviews and scientometric papers on different topics recently published in various journals. All these publications make specific contributions to the uninterrupted world science advancement of benefit to patients.

Peer-review

The authors explored five information portals for the topic of colorectal tumour markers and outlined the significant journals, scientists and institutions. The authors made tremendous efforts on searching and comparing the five information portals, and showed the detailed results. This paper is interesting.

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