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Short Report

Evidence mapping of randomized clinical trials in hepatobiliary surgery

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Introduction

Surgery is the best therapeutic option for improving the quality of life of most patients with benign and malignant lesions of the liver as well as diseases of the gallbladder and bile duct[1]. Technological advances in surgical techniques and early diagnosis of hepatobiliary tumours have improved surgical interventions[2,3]. As the number of surgical interventions has increased, so has the number of clinical studies investigating these interventions[3]. RCTs are considered to provide the best evidence for estimating the efficacy of a therapy[4,5]. However, RCTs are more challenging in surgical fields because of practical and ethical issues[2,5], so there are fewer surgical RCTs and those that have been published have a lower methodological and reporting quality than non-surgical RCTs. Therefore, only a minor part of surgical decision-making can be based on high-quality evidence from RCTs[6,7].

Despite the increased demand for evidence-based approaches, there is no systematic review of all RCTs published in the field of hepatobiliary surgery. The aim of the present study was to undertake a systematic review of RCTs in hepatobiliary surgery published in the past five decades, and to assess the trends of these trials over time, including where the studies were conducted, and also providing an evidence map based on the primary diseases they investigated.

Methods

This systematic review complies with the PRISMA statement. MEDLINE and Web of Science were searched for RCTs published until December 2021 that evaluated surgical therapy in hepatobiliary disease or perioperative interventions (including nutritive and pharmaceutical therapies), and that compared surgical with non-surgical therapies. Studies that assessed only neoadjuvant or adjuvant therapies without considering surgical interventions, those that investigated pancreatic biliary tract diseases, and studies that evaluated liver transplantation were excluded.

Two investigators independently evaluated the titles and abstracts of all included articles in a primary screening, after which the full texts of selected articles were evaluated for eligibility. The following data were then extracted from the included RCTs: publication year, region in which study was conducted, sample size, follow-up duration, and type of disease (hepatobiliary stones, primary malignant liver tumours, metastases to the liver, primary benign liver tumours, biliary tract lesions, liver cystic diseases, bile duct obstruction due to tumour, cirrhosis, portal hypertension, hepatobiliary trauma, and infections).

Details of the search strategy and statistical analysis are available in the *supplementary material*.

Results

MEDLINE and Web of Science searches yielded 33 057 records. After removing 8711 duplicate records, 24 346 references were included in the primary screening of titles and abstracts, 1887 of which were then included in the full-text evaluation for eligibility. In the end, 1102 RCTs were included in the systematic review.

The number of RCTs published in the field of hepatobiliary surgery increased between 1970 and 2021; only 13 RCTs were published between 1970 and 1979, increasing to 72 in 1980–1989, 187 in 1990–1999, 257 in 2000–2009, and 573 in 2010–2021 (*Fig. 1*). Most included RCTs were published in Asia (487 of 1102, 44.2 per cent), followed by Europe (418 of 1102, 37.9 per cent), North America (133 of 1102, 12.1 per cent), Africa (34 of 1102, 3.1 per cent), Australia and New Zealand (19 of 1102, 1.7 per cent), and South America (11 of 1102; 1.0 per cent). Most of the included RCTs were reported in English (94.3 per cent).

The medical journals publishing the largest number of the included RCTs in hepatobiliary surgery were *Surgical Endoscopy* (73 RCTs, 6.6 per cent), *Annals of Surgery* (72 RCTs, 6.5 per cent), *British Journal of Surgery* (68 RCTs, 6.2 per cent), *Hepatogastroenterology* (35 RCTs, 3.2 per cent), *American Journal of Surgery* (35 RCTs, 3.2 per cent), *World Journal of Surgery* (27 RCTs, 2.5 per cent), *Surgery* (27 RCTs, 2.5 per cent), and *Archives of Surgery* (*JAMA Surgery*) (23 RCTs, 2.1 per cent).

The included RCTs reported on a total of 136 313 patients and individual studies included a median of 88 (range 11–1113) participants. Concerning the sample size, 609 studies (55.8 per cent) had fewer than 100 participants, 337 (30.6 per cent) had 100–200 participants, and 150 (13.6 per cent) had more than 200 patients. Duration of follow-up was reported in 1024 of the 1102 RCTs (92.9 per cent), and was less than 1 month in 41.8 per cent of studies, 1–12 months in 397 (38.8 per cent), and more than 12 months in 198 (19.4 per cent).

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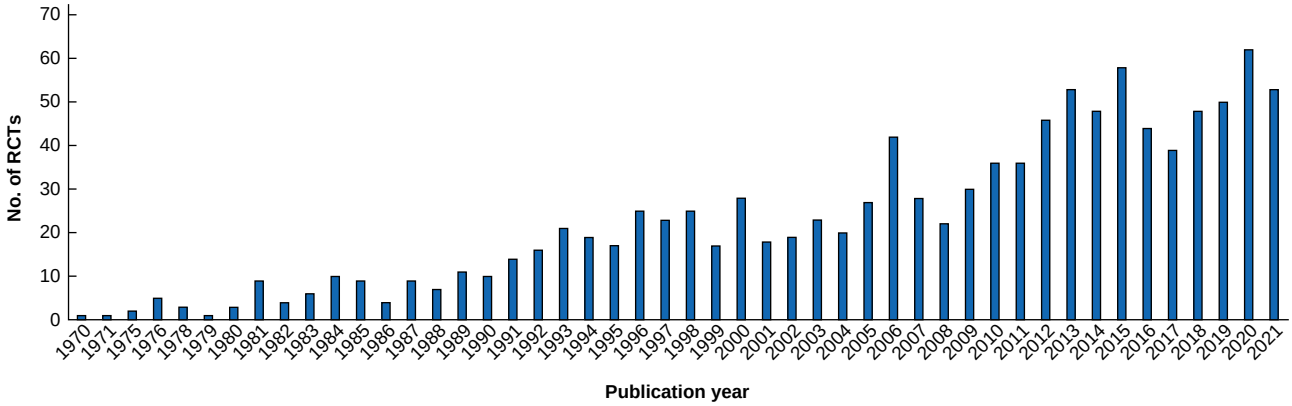

Fig. 1 Number of RCTs according to year of publication

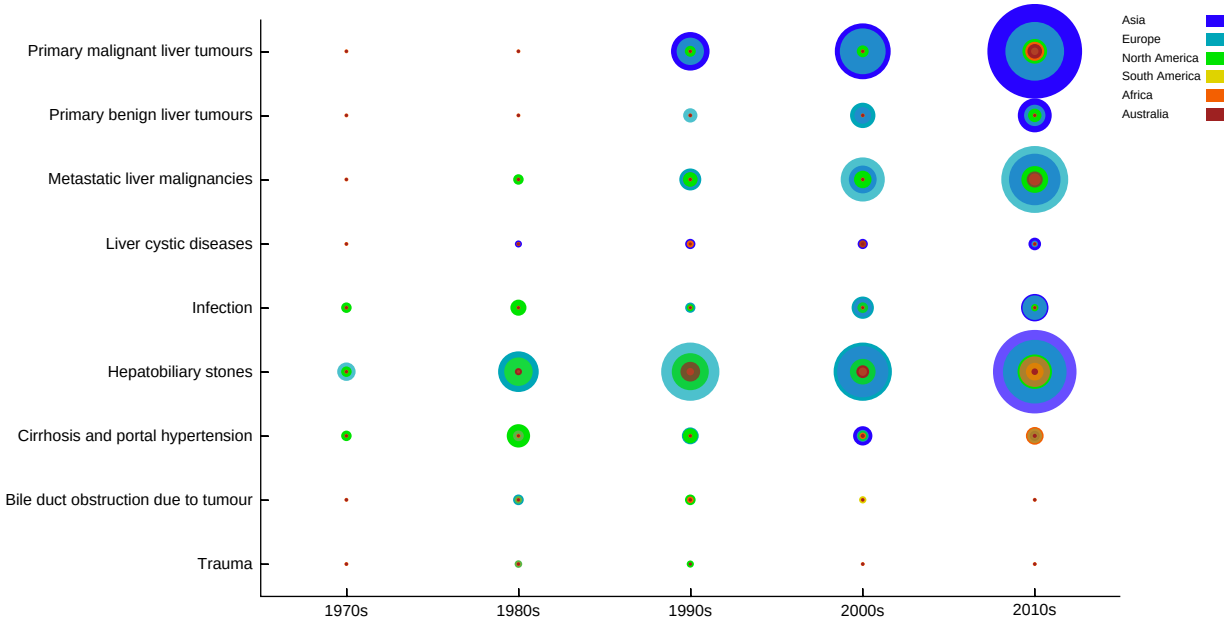

Fig. 2 Bubble plot showing types of disease in relation to date of publication, by region

The colour of the bubbles and circles represents the region in which the study was conducted, and the frequency of trials is indicated by the size.

Regarding disease type, 856 RCTs reported on one type of hepatobiliary disease, 218 reported on two types, and 28 on three types. The most common primary diseases investigated in the included trials were hepatobiliary lithiasis (550 RCTs, 49.9 per cent), primary malignant liver tumours including hepatocellular carcinoma and cholangiocarcinoma (396 RCTs, 35.9 per cent), liver metastases from other malignancies (228 RCTs, 20.6 per cent), cirrhosis (54 RCTs, 4.9 per cent), portal hypertension (54 RCTs, 4.9 per cent), hepatobiliary infection (54 RCTs, 4.9 per cent), benign liver tumours (55 RCTs, 5.0 per cent), biliary tract lesions (68 RCTs, 6.2 per cent), cystic liver disease (12 RCTs, 1.1 per cent), and liver trauma (2 RCTs, 0.2 per cent) (*Fig. 2*).

Discussion

This study evaluated the trends in RCTs published in the field of hepatobiliary surgery over the past five decades. It identified a significant increase in the number of RCTs published in hepatobiliary surgery over time. Most RCTs investigated malignant liver diseases (primary and metastatic) and hepatobiliary lithiasis. In contrast, some diseases were not adequately investigated, including hepatic infections, benign liver tumours, and cystic hepatic diseases.

The number of RCTs evaluating hepatobiliary lithiasis has increased over the years, and the resulting increase in knowledge and insights has advanced the standard of surgical techniques for treating hepatobiliary lithiasis, such as laparoscopic cholecystectomy[1,8]. Although the number of RCTs published in the field of hepatobiliary surgery has increased over the past five decades as a whole, the rate has decreased from 77.2 per cent in the 1970s to 41.4 per cent in the last 12 years. The number of trials evaluating liver resection has also increased, which may be explained by dramatic improvements in diagnostic technologies, better interdisciplinary perioperative management and postoperative care, and the development of novel intraoperative modalities, devices, and techniques[9].

The literature search revealed substantial research on malignant liver tumours and hepatobiliary stones, likely because these diseases have a higher prevalence and a greater impact on the health system than diseases that can be treated non-surgically. Surgery is required only if symptoms are acute or the patient's condition is worsening.

Surgical RCTs have more limitations and lower methodological quality than pharmaceutical RCTs[3], so the quality of RCTs published in the field of hepatobiliary surgery needs to be evaluated[2,10,11]. The methodological quality and risk of bias should be assessed in several domains, including randomization, concealment, and blinding, similar to studies published in other surgical fields[2,12–20]. Surgical RCTs evaluate not only the intraoperative surgical techniques and devices but also perioperative management of patients, including pharmaceutical and nutritional therapies and care protocols. Therefore, future studies should evaluate the types of intervention investigated and their trends.

In conclusion, the overall number of RCTs published in the field of hepatobiliary surgery has increased over time, and considerable interest has been paid to liver tumours and hepatobiliary stones. However, there is a lack of evidence from other fields of hepatobiliary surgery. Future studies are needed to investigate the quality of RCTs and how quality changes with time. Comprehensive studies are also required to identify evidence gaps in the field.

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Author contributions

Ali Majlesara (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Writing—original draft, Writing—review & editing), Ehsan Aminizadeh (Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Ali Ramouz (Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Elias Khajeh (Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing—review & editing), Filipe Borges (Data curation, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing), Gil Goncalves (Data curation, Methodology, Resources, Supervision, Writing—review & editing), Carlos Carvalho (Formal analysis, Investigation, Resources, Writing—review & editing), Mohammad Golriz (Formal analysis, Investigation, Supervision, Writing—review & editing), and Arianeb Mehrabi (Conceptualization, Project administration, Resources, Supervision, Writing—review & editing).

Disclosure

The authors declare no conflict of interests.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data used for this study can be made available upon request to the corresponding author.

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