frontiers | Research Topics

Reviews in surgical oncology

Edited by
Cesare Ruffolo and Andrea Laurenzi

Published in
Frontiers in Surgery
Frontiers in Oncology

ISSN 1664-8714
ISBN 978-2-8325-2602-6
DOI 10.3389/978-2-8325-2602-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Reviews in surgical oncology

Topic editors

Cesare Ruffolo — University Hospital of Padua, Italy

Andrea Laurenzi — IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

Citation

Ruffolo, C., Laurenzi, A., eds. (2023). *Reviews in surgical oncology*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2602-6

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 20 July 2023
DOI 10.3389/fonc.2023.1242530

OPEN ACCESS

EDITED AND REVIEWED BY
Francesco Giovinazzo,
Agostino Gemelli University Polyclinic (IRCCS), Italy

*CORRESPONDENCE
Andrea Laurenzi
andrea.laurenzi@aosp.bo.it

RECEIVED 19 June 2023
ACCEPTED 28 June 2023
PUBLISHED 20 July 2023

CITATION
Radi G, Ruffolo C and Laurenzi A (2023) Editorial: Reviews in surgical oncology. *Front. Oncol.* 13:1242530. doi: 10.3389/fonc.2023.1242530

Editorial: Reviews in surgical oncology

Giorgia Radi[1], Cesare Ruffolo[2] and Andrea Laurenzi[1]*

[1]Hepatobiliary Surgery and Organ Transplantation, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]Chirurgia Generale 3, Azienda Ospedaliero-Universitaria di Padova, Padova, Italy

KEYWORDS

surgical oncology, training, high volume center, surgery, tumors

Editorial on the Research Topic
Reviews in surgical oncology

In the next decades, the oncological impact will progressively increase. In fact, it's expected that within 2035 there will be 23,9 million of new oncological patients and 14,6 million of death related to cancer, however the distribution of mortality will not be homogeneous with a major rate in less developed countries (1).

Almost 80% of oncological patients will require a surgical intervention that are estimated to be 45 million within 2030 (2).

It's well known that most of oncological patients does not have an immediate access to a proper oncological surgery in high volume centers.

Although there are several reasons to this problem, one of the leading causes is the lack of surgeons properly trained in the management of oncological patients.

Surgical oncology is defined as a subspecialty of surgery applied to oncology, from diagnosis to treatment. It's still under debate if surgical oncology could be considered as a specialty itself, but there is almost full agreement on the fact that a single surgeon could not be skilled in the management of all type of cancers.

The surgeon operates within multidisciplinary teams together with oncologists, radiologists, radiation oncologists, pathologists etc. to plan the best diagnostic and therapeutic project for each patient. There are several evidence that show how this approach can modify patients' management and lead to better outcomes (3), moreover also high-volume hospitals have shown to lead to reduction in postoperative mortality and morbidity (4).

In surgical oncology, surgeons can act in different phases: diagnostic and staging performing biopsies; in the treatment either with curative intent removing organs affected by tumor or in the palliative treatment leading to tumor reduction volume for reduced quality of life or in the context of emerging complications (i.e. bleeding, perforations etc). Moreover, surgeons can also intervene in the setting of prevention removing organs and/or tissues at high risk of degeneration in patients with genetic mutations or in the reconstructive phase such as breast cancer.

From the surgical point of view there are three pillars in the surgical oncology: patients' selection, minimally invasive surgery and quality of oncological resections.

Patients' selection has a double meaning; the first is associated to check if the patient is fit in half to undergo surgical procedures due to an older population with different types of comorbidities, the second is if the patient really benefits from a surgical intervention or if a neoadjuvant treatment could be envisaged to improve long-term outcomes.

Minimally invasive surgery had a widespread impact on surgical oncology during the last two decades, improving post-operative outcomes with comparable oncological outcomes, allowing faster access to adjuvant treatment, and improving quality of life.

The quality of oncological resections, either minimally invasive or conventional, remains one of the main goals of surgical oncology, since complete excision of tumor with adequate lymph-nodes removal and without residual micro-macroscopic tumor foci is associated to better long-term outcomes.

Considering the importance of this discipline and the impact of cancer on population, it would be of paramount importance to develop a strong educational process that allows training in all different oncological fields, considering the differences between type of cancers, their incidence, and available resources.

There are several limits to the development of such model from the lack of consciousness of such disease to the shortage of proper personnel and facilities.

For this reason it's our opinion that evidence based medicine with the use of reviews represents a useful tool to promote a homogeneous level in cancer management, sharing good clinical practice with an adequate level of training, trying to minimize the differences between different health regions.

Author contributions

GR wrote the article. CR critical view and correction. AL conceived and wrote the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Cancer fact sheets. International Agency for Research on Cancer. *GLOBOCAN* (2012). Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (Accessed 12/19/2015).

2. Sullivan R, Alatis OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol* (2015) 16(11):1193–224. doi: 10.1016/S1470-2045(15)00223-5

3. Pillay B, Wootten AC, Crowe H, Corcoran N, Tran B, Bowden P, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: a systematic review of the literature. *Cancer Treat Rev* (2016) 42:56–72. doi: 10.1016/j.ctrv.2015.11.007

4. Ratnayake B, Pendharkar SA, Connor S, Koea J, Sarfati D, Denne E, et al. Patient volume and clinical outcome after pancreatic resecection: a contemporary systematic review and meta-analysis. *Surgery* (2022) 172:273–83. doi: 10.1016/j.surg.2021.11.029

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 22 July 2022
DOI 10.3389/fonc.2022.935640

OPEN ACCESS

EDITED BY
Ignazio Gaspare Vetrano,
Carlo Besta Neurological Institute Foundation (IRCCS), Italy

REVIEWED BY
Jacopo Falco,
Carlo Besta Neurological Institute Foundation (IRCCS), Italy
Enrico Gambatesa,
University of Milan, Italy

*CORRESPONDENCE
Jin Ke
22013493@qq.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 06 May 2022
ACCEPTED 27 June 2022
PUBLISHED 22 July 2022

CITATION
Shu M and Ke J (2022) The surgical management of osteoid osteoma: A systematic review.
Front. Oncol. 12:935640.
doi: 10.3389/fonc.2022.935640

The surgical management of osteoid osteoma: A systematic review

Man Shu[1] and Jin Ke[2]*

[1]Department of Orthopaedics, General Hospital of Southern Theater Command, Southern Medical University, Guangzhou, China, [2]Department of Orthopaedics, ZhuJiang Hospital of Southern Medical University, Southern Medical University, Guangzhou, China

Background: Osteoid osteoma (OO) comprises approximately 11%-14% of benign bone tumors. The main symptom of OO is localized pain accompanied by nighttime aggravation. Surgical treatment is frequently used in clinic, including open surgery and percutaneous ablation, the latter including radiofrequency ablation, cryoablation, and microwave ablation, but there is no consensus on when and how to choose the best treatment for OO.

Purpose: We did a systematic review of the literature on existing surgical treatments of OO to assess the safety and efficacy of surgical treatments of OO and to evaluate the surgical options for different locations of OO.

Methods: The inclusion criteria in the literature are 1. Patients diagnosed with osteoid osteoma and treated surgically; 2. Include at least five patients; 3. Perioperative visual analogue scale (VAS), postoperative complications, and recurrence were recorded; 4. Literature available in PubMed from January 2014 to December 2021.

Results: In the cohort, 1565 patients (mainly adolescents) with OO received 1615 treatments. And there are 70 patients with postoperative recurrence and 93 patients with postoperative complications (minor: major=84:9). The results of Kruskal-Wallis examination of each experimental index in this experiment were clinical success rate $H=14.818$, $p=0.002$, postoperative short-term VAS score $H=212.858$, $p<0.001$, postoperative long-term VAS score $H=122.290$, $p<0.001$, complication rate $H=102.799$, $p<0.001$, recurrence rate $H=17.655$, $p<0.001$, the technical success rate was $H=45.708$, $p<0.001$, according to the test criteria of $\alpha=0.05$, H_0 was rejected. The overall means of the outcome index in each group were not completely equal.

Conclusion: Percutaneous ablation and open surgery are safe and reliable for OOs, and the technical success rate of percutaneous ablation is higher than that of open surgery. Open surgery and cryoablation can be selected for OOs close to the nerve and atypical sites, while radiofrequency ablation and microwave ablation can be selected for OOs in most other sites.

KEYWORDS

radiofrequency ablation, surgery, cryoablation, microwave ablation, meta-analysis, osteoid osteoma (OO)

Introduction

Jaffe first described osteoid osteoma (OO) in 1935 as a benign isolated osteogenic tumor (1). It accounts for 11%-14% of benign bone tumors (2). OO is most common in the femurs and tibias of adolescents, with 6% spinal lesions (3–5). The main symptom of OO is localized pain that worsens at night. The reason for this is that OO produces a lot of prostaglandin (PG), and PGE increases pain sensitivity (6–9). It recovers on its own, but it takes a long time (10, 11).

Medicines and surgery are used in the medical treatment of OO. The medications used are mostly non-steroidal anti-inflammatory drugs (NSAIDS), which not only provide symptomatic relief but also shorten the time it takes for the body to heal itself (4, 12, 13). On the other hand, long-term use of NSAIDs causes side effects such as bleeding, gastrointestinal reactions, and nephrotoxicity (4).

Open surgery and percutaneous ablation are two surgical options for treating OO. Nonetheless, percutaneous ablation is becoming more popular in hospitals; it is not a replacement for open surgery (14). However, in open surgery, the inexact location and the large surgical incision cause several bone defects that may require bone grafting or internal fixation, increasing the discomfort and expense of the patient (4, 15).

In 1992, D. Rosenthal described the use of radiofrequency ablation (RFA) (16), and since then, percutaneous ablation has become the 'gold standard treatment' for OO (17–20). RFA causes tumor cell necrosis due to resistive electrothermal effects and has been shown in clinical trials to be a safe, efficient, and low-cost treatment for OO (18, 21). For the first time, in 2010, the cryoablation was presented to treat OO, which involved freezing and thawing cycles to kill tumor cells (22). This therapy can be ablated in the eccentric position of the lesion, avoiding bone drilling (23, 24), removing the risk of permanent nerve damage, and eventually improving the safety of atypical OO sites (24, 25). Microwave ablation (MWA), another treatment method for OO, was first reported in 2014. Microwave needles emit magnetic fields that generate heat, causing tumor cell necrosis through vibrations generated in surrounding polar molecules (20, 26). MWA has several advantages over RFA, including a faster heating rate, a higher intratumor temperature, a larger ablation range, little effect on tissue, and carbonization (20, 27, 28).

There is no agreement on when and how to select the best treatment for OO. Therefore, this study aims to assess the safety and efficacy of OO surgical treatments. A systematic review of the existing literature on surgical treatments for OO was also used to evaluate the surgical options for different locations of OO.

Materials and methods

Selection of studies

The inclusion criteria in the literature are 1. Patients diagnosed with OO and treated surgically; 2. Include at least five patients; 3. Preoperative and postoperative visual analogue scale (VAS), postoperative complications, and recurrence were recorded; 4. Literature available in PubMed from January 2014 to December 2021. Exclusion criteria: 1. Includes ambiguous clinical data. 2. Patients misdiagnosed as OO. 3. Systematic reviews and meta-analysis.

Since the PubMed database described the first case of treating OO by MWA in 2014, we searched the literature published from January 2014 to December 2021. A search algorithm was developed based on a combination of keywords ('osteoid osteoma' [All Fields] AND ('cryoablation' [All Fields] OR 'radiofrequency' [All Fields] OR 'microwave' [All Fields] OR 'surgery *' [All Fields] OR 'resection' [All Fields]) AND (2014: 2021 [update]).

Two authors reviewed the literature (Man Shu and Jin Ke). First, the titles and abstracts of the literature were divided and organized. Furthermore, their full texts were filtered using the aforementioned criteria. The data were extracted by two authors (Man Shu and Jin Ke), and any content disagreements were

resolved by a third author. The screening steps are depicted in Figure 1 of the PRISMA flow diagram. We collected a few parameters as a whole data set, including the total number of patients, patient age and sex, treatment methods, clinical success rate (mean [SD]), changes in perioperative VAS (mean [SD]), complications, and recurrence during follow-up.

Data analysis

Technical success is defined as 'cases without any technical failure, such as failure of the range to penetrate the nidus, machine failure during surgery, etc.', while clinical success is defined as 'resolution of the patient's symptoms throughout the follow-up period'. The recurrence rate is the percentage of cases that relapse. The total number of technical successes is divided by the total number of cases reported by each study to calculate the technical success rate. The total number of clinical successes is divided by the total number of cases reported by each study to get the clinical success rate. The 'short-term postoperative VAS' is defined as the most recent postoperative VAS, while the 'long-term postoperative VAS' is defined as the last postoperative follow-up VAS. The second treatment after treatment failure was counted as one patient and two surgeries, and if the second other treatment was received, in each of the two treatment modalities, there was one patient and one operation in each method.

The primary endpoints for this study were postoperative VAS scores and clinical success rate, with complications and recurrences as secondary endpoints. We compared VAS scores and clinical success rates between groups to assess the efficacy of each surgical method. The rate of complications was calculated after complications were classified using the Society of Interventional Radiology (SIR) classification system for complications (29). The mean and standard deviations (SD) of perioperative VAS and clinical success rates were calculated, and data for each patient were recorded separately if they were not reported in this study. We used SPSS 25.0 for Kruskal-Wallis testing and the Kruskal-Wallis one-way ANOVA method for postmortem multiple comparisons to assess differences between groups.

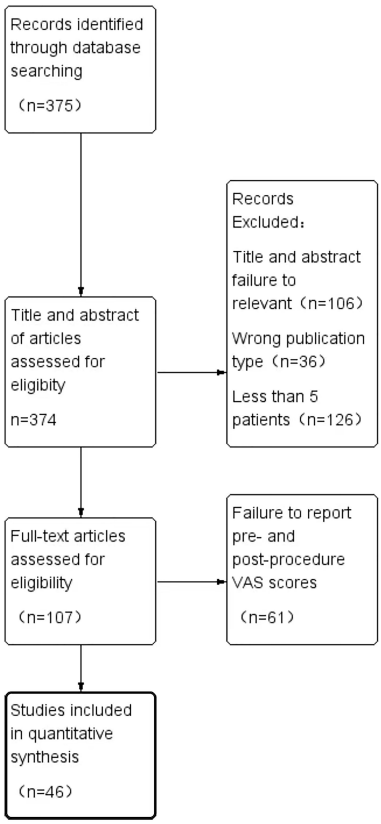

FIGURE 1
PRISMA flow diagram demonstrating the selection process of articles.

Results

Study selection

Approximately 375 articles were chosen from the PubMed database. According to the abstract screening, 106 articles were not related to the purpose of the current study, 36 articles belonged to a review, and 126 articles had fewer than five patients. The full texts of the remaining 107 articles were reviewed, excluding the 61 articles that did not include a perioperative VAS score. The PRISMA flow diagram depicts the process of screening for inclusion (Figure 1).

Patient population

A total of 1615 treatments were administered to 1565 patients with OO. The included patients ranged in age from 3 to 68 years, with the majority being adolescents. Figure 2 shows the anatomical distribution of OO. Table 1 lists the outcome indicators for each study. Individual OO of the spine (RFA: surgery = 7:2, population ratio was 185:30) was recorded in nine of the included studies. OO of atypical sites was performed separately in three studies (RFA: surgery = 2:1, population ratio was 89:26), and four studies included pediatric patients (RFA: surgery: cryoablation = 2:1:1, population ratio was 40:47:29).

Outcomes

Table 2 describes the characteristics of the patients and each endpoint. Table 3 shows the total clinical success rate in studies that recorded atypical sites alone [excluding femur and tibia (64,

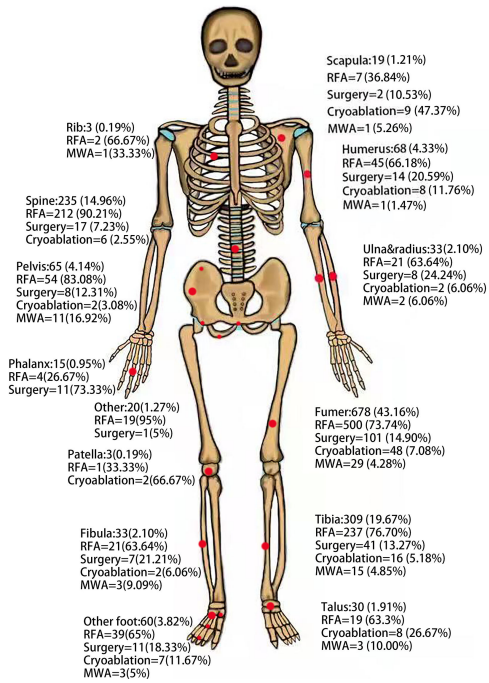

FIGURE 2
Anatomic distribution of osteoid osteomas in the patient cohort based on technology.

69)] of OO. This study included 70 patients with postoperative recurrence and 93 patients with postoperative complications (minor: major=84:9).

Among the 54 patients who relapsed after RFA, 43 were cured after secondary RFA, nine with open surgery, one with MWA, and one with laser ablation. Nine patients relapsed after open surgery, three were cured by secondary surgery, one by RFA, and five were not recorded. One of the four patients who relapsed after cryoablation was cured with RFA, while the other three were cured with secondary cryoablation. While three patients relapsed after MWA, one underwent surgical resection, one was cured by secondary MWA, and one was not recorded. The overall rate of recurrence in 12 cases of atypical OO (including spine) was 5.5% (n = 18), of which the rate of recurrence after RFA was 6.2% (n = 17), six were cured by RFA again after relapse, three were cured by open surgery, and others were not recorded; the rate of recurrence after open surgery was 1.8% (n = 1), and one case was cured with RFA 2 years later.

The SIR system was used to classify complications. Among postoperative complications of RFA (minor: major=51:8), 21 were grade A (five transient pain and paresthesia, one muscle hematoma, one soft-tissue edema, one skin erythema, one needle tip rupture, 12 abnormalities of the transient blood biochemical index), 29 were grade B (21 burns, six infection, one fasciitis, one herniated lumbar disc herniation), and eight were grade D (three of osteomyelitis, two fractures, one thigh abscess, one pulmonary edema, one peroneal nerve injury). Postoperative complications of open surgery (minor: major =16:1), four of grade A (four of temporary dysfunction), 12 of grade B (six of infection, three of neurovascular injury, two of limited activity induced by pain, and one of delayed healing), and one of grade D (fracture). Among the post-cryoablation complications (minor = 12), four were of grade A (transient pain and soft tissue swelling), two were of grade B (mild burns), and the data of six were not recorded in detail. All postoperative complications of MWA (minor = 5) were grade A (two paresthesia, two mild burns, and one hypofunction).

The Kruskal-Wallis test results for each outcome in this experiment are provided below. According to the test criteria of α= 0.05, the clinical success rate was H=14.818, p=0.002, the postoperative short-term VAS score was H=212.858, p<0.001, the postoperative long-term VAS score was H=122.290, p<0.001, rate of complication was H=102.799, p<0.001, rate of recurrence was H=17.655, p=0.001, the technical success rate was H=45.708, p<0.001, H_0 was rejected, and it can be considered that the overall mean of each outcome index in each group was not completely equal. Table 4 shows pairwise comparisons of the outcome measures in each group.

Ablation process and follow-up

Table 5 shows the operating and hospitalization times of the patients in each group. The average intraoperative control temperature of 826 patients in 24 studies of RFA treatment was 90°C and continuously heated for 6.7 ± 3.3 min. A freezing-thawing cycle was used to treat the 100 patients with cryoablation. The average freeze time was 10 min, and the average thaw time was 7.3 min. In the three MWA studies, the power of 16W, 80°C ablation was used for 76 ± 53.26s; 20W, 80° C ablations for 2 min; and 50W ablation for 1 min or 60W ablation for 1.7 min.

RFA, MWA, and surgical resection were found, respectively, only in one patient with recurrence after 2 years of follow-up.

Discussion

In this study, the technical success rate of each surgical method was positively correlated with clinical success. Prud'Homme et al. (5) documented a clinical failure of a patient with OO at the ankle due to slight intraoperative movement; Le Corroller et al. (24) documented two failed cases, one of which was due to the unsatisfactory position of the freezing probe. Chahal et al. (45) documented postoperative recurrence in nine patients with poor localization. The current study found that percutaneous ablation had a higher technical success rate than open surgery. The main reasons for the failure of each technology were positioning issues and puncturing issues. Therefore, it also demonstrates that technological

TABLE 1 Characteristics of the results of each study.

Study	Reference no.	Mean follow-up time (m)	Mean lesion size (mm)	VAS pre-procedure	VAS recent post-procedure	VAS last post-procedure	Clinical success	Complication rate	Recurrence rate
Basile, A	(26)	8.7	7.3	6	0	0.3	100.0%	0.0%	0.0%
Coupal, T. M	(23)	6	9.9	7.4	1.5	0.3	100.0%	0.0%	0.0%
Morassi, L. G	(30)	23.2	NA	8.6	1	0	86.7%	0.0%	15.4%
Regev, G. J	(31)	18	14	7.7	2.8	0	100.0%	0.0%	0.0%
Yu, F	(32)	15.5	NA	3.4	0.8	0.1	100.0%	0.0%	0.0%
Alemdar, C	(33)	53.5	NA	8.1	0.8	1.6	77.4%	7.6%	9.4%
Arıkan, Y	(34)	15.8	6.9	7.2	0.64	0.64	82.4%	11.8%	17.7%
Filippiadis, D	(35)	6	9.1	8.9	0	0	100.0%	0.0%	0.0%
Gökalp, M. A	(36)	12	NA	8.3	0.5	0	100.0%	0.0%	0.0%
Guo, X	(37)	20	NA	6.5	1.5	0	100.0%	0.0%	0.0%
Karagöz, E	(38)	26.5	8.1	9	0	0	94.4%	11.1%	5.6%
Lin, N	(39)	16	1~5	4.7	1.4	0	100.0%	0.0%	0.0%
Masciocchi, C	(40)	24	NA	8.5	1.5	0	100.0%	6.7%	0.0%
Miyazaki, M	(41)	15.1	9.9	7.1	1.6	0.2	86.0%	57.1%	0.0%
Outani, H	(42)	18	9	7.3	0	0	96.8%	9.4%	3.1%
Whitmore, M. J	(43)	18.3	6.7	10	0	0	90.5%	20.7%	3.5%
Albisinni, U	(44)	41.5	11.4	8	0	0	93.4%	3.3%	6.6%
Chahal, A	(45)	15.4	8.5	7	0	0	86.2%	2.3%	13.8%
Costanzo, A	(46)	84.3	10	7.4	0.3	0	100.0%	0.0%	0.0%
Erol, B	(47)	59	NA	7.7	0.3	0	100.0%	0.0%	0.0%
Faddoul, J	(48)	12~84	9.9	7.6	2.56	0	87.5%	0.0%	12.5%
Kulkarni, S. S	(49)	48	NA	7.8	0.4	0	97.7%	7.0%	2.3%
Nöel, M. A	(50)	12	9.9	8.8	2	0	85.7%	0.0%	14.3%
Prudhomme,C	(5)	1	5.7	6.46	0.85	0.46	92.3%	15.4%	7.7%
Wang, B	(51)	46.6	10.3	7.6	0	0.3	100.0%	0.0%	0.0%
Wu, H	(52)	12	8	3.2	4.5	2.2	72.2%	27.8%	8.3%
Hage, A. N	(53)	93.1	9.4	8	0	0	91.3%	2.2%	6.5%
Santiago, E	(54)	21	7.8	8	0	0	95.2%	14.3%	4.8%
Ankory, R	(55)	36	NA	7.7	0.5	0	94.2%	1.9%	5.8%
Beyer, T	(56)	28.5	NA	6.2	0.71	0	89.7%	2.6%	9.1%
Fujiwara, T	(14)	25	NA	7	2.2	0	100.0%	0.0%	0.0%
Kaptan, M. A	(57)	17.8	11.84	8.6	0.1	0	100.0%	25.0%	0.0%
Kostrzewa, M.	(58)	36	5.3	6.9	1.25	0	91.7%	4.2%	4.2%
Neyisci, C	(59)	16	NA	8.3	1.23	0	100.0%	9.5%	0.0%
Sahin, C	(60)	23	7~15	8	0~1	0	98.0%	6.0%	1.7%
Yu, X	(61)	55.5	11.3/13	8/6.5	1/2	0.75/0	100%/93.8%	0.0%/18.8%	0.0%/6.3%
Ayas, M. S	(62)	12	NA	4.8	0.2	0.2	100.0%	18.8%	6.3%
Reis, J.	(63)	12	10/11	7/8	0/0.2	0.4/0.8	93.3%/93.3%	13.3%/0.0%	6.7%/6.7%
Tanrıverdi, B	(64)	46	NA	7.2	1.3	0	100.0%	0.0%	0.0%
Yuce, G	(65)	22	3.6	8.4	3.2	3.2	96.4%	1.8%	3.6%
Arrigoni, F	(66)	26	NA	9.1	0	0	98.4%	1.6%	1.6%
Filippiadis, D	(67)	23.3	8.28	9.1	0	0	100.0%	0.0%	0.0%
Le Corroller, T	(24)	18~90	6	8	0	0	96.0%	6.0%	4.0%
Lorenc, T	(68)	90	5.6	8.5	0	0	87.5%	7.7%	15.4%
Niazi, G. E	(69)	24	6.1	8.6	0	0	100.0%	2.9%	0.0%
Somma, F	(70)	24	NA	8.3	1.5	0.47	96.1%	5.9%	3.9%

TABLE 2 Patient characteristics and outcomes.

	RFA	Surgery	Cryoablation	MWA	Total
Patients (n)	1161	235	110	59	1565
Male : female	804 : 357	161 : 74	69 : 41	37 : 22	1071:494
Age (mean ± SD)	20.6 ± 4.6	17.1 ± 6.1	22.1 ± 6.1	22.8 ± 4.5	20.3 ± 5.2
lesion size (mm)	9.0 ± 2.2	9.2 ± 3.8	6.9 ± 1.2	6.8 ± 2.0	8.6 ± 2.4
VAS scores					
Preoperative	7.8 ± 1.1	6.5 ± 1.8	8.5 ± 0.9	6.7 ± 0.3	7.6 ± 1.3
postoperative short-term	0.7 ± 0.8	1.5 ± 1.5	1.4 ± 0.4	0.7 ± 0.6	0.8 ± 1.0
postoperative long-term	0.2 ± 0.7	0.7 ± 0.9	0.3 ± 0.1	0.2 ± 0.2	0.3 ± 0.7
Clinical success (95%CI)	94.8% (94.5%, 95.1%)	90.1% (88.6%,91.7%)	94.9% (94.4%,95.4%)	93.3% (92.6%,93.9%)	94.0% (93.7%,94.3%)
Recurrences (95%CI)	4.8% (4.5%, 5.1%)	3.7% (3.1%, 4.2%)	3.6% (3.3%, 3.8%)	5.1% (4.5%, 5.8%)	4.5% (4.3%,4.8%)
Technical success (95%CI)	98.1% (97.9%, 98.3%)	95.8% (95.1, 96.6%)	99.1% (98.9%,99.3%)	100% (100%,100%)	97.9% (97.7%, 98.1%)
Complications (95%CI)	5.1% (4.7%, 5.6%)	7.4% (6.1%, 8.7%)	10.9% (9.6%, 12.3%)	8.3% (6.8%, 9.8%)	6.0% (5.6%, 6.4%)
Follow-up (mean ± SD)	32.4 ± 22.4	35.1 ± 21.0	33.9 ± 18.8	18.9 ± 14.8	32.4 ± 21.8
Biopsy	68.6% (393/573)	82.9% (165/199)	52.8% (19/36)	72.9% (10/13)	71.5% (587/821)

failure is a major cause of clinical failure and recurrence. To improve the effectiveness of surgery, we can choose to perform it under computer tomography (CT) guidance multiple times, and we can combine it with 3D reconstruction to design the puncturing process.

Outani et al. (42) recorded two postoperative fractures and one postoperative osteomyelitis among the major complications in this study. A case of fibula fracture occurred 10 days later as a result of the addition of two additional holes at the ablation site by 3D navigation that increased bone defect; one case was fracture caused by intense exercise 5 weeks after the operation, and one case had osteomyelitis at the ablation site 2 weeks later. Alemdar et al. (33) recorded incomplete fractures caused by exercise within 3 months after the operation. Yuce et al. (65) reported osteomyelitis caused by burn infection caused by needle overheating. Kaptan et al. (57) documented a case of local osteomyelitis without cause. Based on the foregoing, several measures can be implemented to prevent the occurrence of serious complications and thus improve the safety of surgical treatment, such as preoperative iodine coating to prevent postoperative infection (71), reducing bone defects during operation, limiting exercise within 3 months after the operation, using sterile ice packs to cool the surrounding skin during percutaneous ablation or inserting additional needles to infuse saline to protect peripheral nerves (72, 73), or multiple low power ablations.

Surgical modalities

This study demonstrated that open surgery and percutaneous ablation are safe and reliable procedures (18, 21).

RFA has become the most widely used method for treating OO in recent years and is considered the gold standard. RFA was used to treat approximately 74.2% of the cases in this study. Even for the OO near nerve sites and other atypical sites, the success rate was 91.5% and 97.8%, demonstrating the success of RFA in OO treatment. However, the use of ground pads in RFA increases the risk of skin burns.

The success rate of open surgery for OO adjacent to important neurovascular sites and atypical sites was 96.7% and 100%, respectively. Therefore, open surgery remains a viable option for OO near neurovascular and atypical sites. Open surgery is also constantly evolving: CT-guided drilling resection (33) and CT-guided Kirschner wire positioning (36). Nevertheless, patients suffer more trauma in open surgery.

Compared to RFA, conscious patients tolerated cryoablation well, which can significantly reduce postoperative pain and hospitalization time (54). Cryoablation has the potential to reduce the risk of permanent nerve damage. Le Corroller et al. (24) found no neurological damage following spinal OO cryoablation. Therefore, cryoablation is preferred for OO near atypical sites. The procedure is so time-consuming that it lengthens the duration of the operation and thus increases the likelihood of complications (71).

In this study, 74.6% (44/59) of OO occurred in the MWA group at typical sites (femur and tibia). Budrevicius et al. (74) reported successful MWA treatment in one of the OO cases at the joint site L3 (not included in this study). MWA of OO in atypical sites (including the spine) is theoretically equally effective. MWA had less power than RFA in this study, had a shorter ablation time, and had no infection or serious

TABLE 3 The clinical success rate of OO in the atypical sites.

	Surgical resection	RFA	Total
clinical success rate of OO in the spine	96.7% (95.5%, 97.9%)	91.5% (91.0%, 92.1%)	92.2% (91.7%, 92.8%)
clinical success rate of atypical sites	100%	97.8% (97.4%, 98.2%)	98.3% (97.9%, 98.6%)

TABLE 4 Results of pairwise comparison of outcome measures in each group.

	RFA-Cryoablation	RFA-MWA	RFA-surgery	MWA-Cryoablation	MWA-surgery	Cryoablation-surgery
Clinical success rates	H=78.30 P=0.471	H=201.44 P=0.004	H=-15.91 P=1.000	H=-123.14 P=0.523	H=-217.35 P=0.005	H=94.212 P=0.405
Recurrence rate	H=28.72 P=1.000	H=-139.23 P=0.114	H=103.03 P=0.007	H=167.95 P=0.116	H=242.26 P=0.001	H=-74.31 P=0.889
Complication rates	H=-384.50 P<0.001	H=-294.89 P<0.001	H=47.65 P=0.810	H=-89.602 P=1.000	H=342.55 P<0.001	H=-432.15 P<0.001
Postoperative short-term VAS	H=415.06 P<0.001	H=-63.59 P=1.000	H=-316.59 P<0.001	H=478.65 P<0.001	H=-252.97 P=0.001	H=731.62 P<0.001
Postoperative long-term VAS	H=116.28 P=0.006	H=-229.84 P<0.001	H=-231.86 P<0.001	H=346.13 P<0.001	H=-2.02 P=0.001	H=348.14 P<0.001
Technical success rate	H=40.62 P=1.000	H=-229.38 P<0.001	H=115.94 P<0.001	H=270.00 P<0.001	H=345.32 P<0.001	H=-75.32 P=0.465

The P-value in the table is adjusted.

TABLE 5 Mean length of surgery and hospital stay.

		Patients	Mean	SD	SEM
operation time(minutes)	RFA	358	72.7	20.19	1.07
	Surgery	149	70.1	45.26	3.71
	Cryoablation	71	80.0	0.00	0.00
	Total	578	72.9	28.03	1.17
length of stay(days)	RFA	548	1.3	2.02	0.09
	Surgery	166	2.1	1.36	0.11
	Cryoablation	50	0.4	0.50	0.07
	Total	764	1.4	1.87	0.07

complications after ablation. Therefore, it is concluded that MWA is a reliable therapy for OO at common sites. However, in this study, the incidence of burns in MWA (3.4%) is higher than that of RFA (1.8%), which may be due to the rapid heating of MWA (75).

Biopsy and follow-up

Although tumor pathology is usually the gold standard, some doctors insisted that a biopsy was unnecessary due to the typical symptoms and imaging characteristics of OO. However, in the study of Regev et al. (31), one patient with Ewing's sarcoma was misdiagnosed as OO, and in the Reis et al. (63) study, a patient with suspected OO was pathologically diagnosed with osteosarcoma (this patient was not included in the study). In any case, while a biopsy is not always necessary for the diagnosis of OO, it is significant to rule out other diseases.

OO recurrence is most common within the first 2 years after surgery (76, 77). After 24 months, approximately three of 72 recurrences occurred in this experiment. This reflects the importance of follow-up as well as the reference significance of at least a 24-month follow-up period.

Limitations

This study has several limitations. First, there was the impact of systematic and random errors on the validity of the study results. Second, the article only included studies with five or more patients from 2014 to 2021, resulting in a limited number of original articles in the literature. Third, fewer cases of cryoablation and MWA for

the treatment of OO were reported, limiting the ability to compare different treatment methods.

Conclusion

In conclusion, open surgery and percutaneous ablation, such as RFA, MWA, and cryoablation, are appropriate and safe. Percutaneous ablation has been found to have a higher technical success rate than open surgery. Open surgery and cryoablation are effective for OO near nerve sites and in atypical sites, whereas RFA and MWA are beneficial for OO in most typical sites.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Author contributions

JK contributed to conception and design of the study. MS and JK screened and extracted data. MS wrote the first draft of the manuscript. MS and JK contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by The Natural Science Foundation of Guangdong Province, China (No. 2020A1515010625)

Acknowledgment

We are grateful for the support from The Natural Science Foundation of Guangdong Province.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Jaffe HL. "Osteoid-Osteoma" a Benign Osteoblastic Tumor Composed of Osteoid and Atypical Bone. *Arch surg* (1935) 31(5):709–28. doi: 10.1001/archsurg.1935.01180170034003

2. Unni KK. Dahlin's bone tumors: General aspects and data on 11,087 cases. *5th Ed* (1996) 106:693. doi: 10.1093/ajcp/106.5.693

3. Kan P, Schmidt MH. Osteoid osteoma and osteoblastoma of the spine. *Neurosurg Clinics North America* (2008) 19:65–70. doi: 10.1016/j.nec.2007.09.003

4. Boscainos PJ, Cousins GR, Kulshreshtha R, Oliver TB, Papagelopoulos PJ. Osteoid osteoma. *Orthopedics* (2013) 36:792–800. doi: 10.3928/01477447-20130920-10

5. Prud'homme C, Nueffer J-P, Runge M, Dubut J, Kastler B, Aubry S, et al. Prospective pilot study of CT-guided microwave ablation in the treatment of osteoid osteomas. *Skeletal Radiol* (2017) 46:315–23. doi: 10.1007/s00256-016-2558-5

6. Schulman L, Dorfman HD. Nerve fibers in osteoid osteoma. *J Bone Joint Surg Am* (1970) 52:1351–6. doi: 10.2106/00004623-197052070-00008

7. Makley JT, Dunn MJ. Prostaglandin synthesis by osteoid osteoma. *Lancet* (1982) 2:42. doi: 10.1016/S0140-6736(82)91174-6

8. O'Connell JX, Nanthakumar SS, Nielsen GP, Rosenberg AE. Osteoid osteoma: The uniquely innervated bone tumor. *Mod Pathol* (1998) 11:175–80.

9. de Chadarevian JP, Katsetos CD, Pascasio JM, Geller E, Herman MJ. Histological study of osteoid osteoma's blood supply. *Pediatr Dev Pathol* (2007) 10:358–68. doi: 10.2350/06-07-0133.1

10. Moberg E. The natural course of osteoid osteoma. *J Bone Joint Surg Am* (1951) 33:A, 166–70. doi: 10.2106/00004623-195133010-00015

11. Golding JS. The natural history of osteoid osteoma; with a report of twenty cases. *J Bone Joint Surg Br* (1954) 36-B:218–29. doi: 10.1302/0301-620X.36B2.218

12. Bottner F, Roedl R, Wortler K, Grethen C, Winkelmann W, Lindner N, et al. Cyclooxygenase-2 inhibitor for pain management in osteoid osteoma. *Clin Orthop Relat Res* (2001) 2001(393)258–63. doi: 10.1097/00003086-200112000-00029

13. Carpintero-Benitez P, Aguirre MA, Serrano JA, Lluch M. Effect of rofecoxib on pain caused by osteoid osteoma. *Orthopedics* (2004) 27:1188–91. doi: 10.3928/0147-7447-20041101-17

14. Fujiwara T, Kunisada T, Takeda K, Hasei J, Nakata E, Mochizuki Y, et al. Mini-open excision of osteoid osteoma using intraoperative O-Arm/Stealth navigation. *J Orthopaedic Sci* (2019) 24:337–41. doi: 10.1016/j.jos.2018.09.017

15. Çakar M, Esenyel CZ, Seyran M, Tekin AÇ, Adaş M, Kürşad Bayraktar M, et al. Osteoid osteoma treated with radiofrequency ablation. *Adv Orthop* (2015) 2015:807274. doi: 10.1155/2015/807274

16. Rosenthal DI, Alexander A, Rosenberg AE, Springfield D. Ablation of osteoid osteomas with a percutaneously placed electrode: A new procedure. *Radiology* (1992) 183:29–33. doi: 10.1148/radiology.183.1.1549690

17. Noordin S, Allana S, Hilal K, Nadeem N, Lakdawala R, Sadruddin A, et al. Osteoid osteoma: Contemporary management. *Orthopedic Rev* (2018) 10:7496. doi: 10.4081/or.2018.7496

18. Lindquester WS, Crowley J, Hawkins CM. Percutaneous thermal ablation for treatment of osteoid osteoma: A systematic review and analysis. *Skeletal Radiol* (2020) 49:1403–11. doi: 10.1007/s00256-020-03435-7

19. Benyass Y, Chafry B, Koufagued K, Chagar B. Osteoid osteoma of the acetabular roof: A case report. *J Med Case Rep* (2016) 10:232. doi: 10.1186/s13256-016-1016-2

20. Kostrzewa M, Diezler P, Michaely H, Rathmann N, Attenberger UI, Schoenberg SO, et al. Microwave ablation of osteoid osteomas using dynamic MR imaging for early treatment assessment: Preliminary experience. *J Vasc Interventional Radiol JVIR* (2014) 25:106–11. doi: 10.1016/j.jvir.2013.09.009

21. Shanmugasundaram S, Nadkarni S, Kumar A, Shukla PA. Percutaneous ablative therapies for the management of osteoid osteomas: A systematic review and meta-analysis. *Cardiovasc Interventional Radiol* (2021) 44:739–49. doi: 10.1007/s00270-021-02804-6

22. Liu DM, Kee ST, Loh CT, McWilliams J, Ho SG, Brower JS, et al. Cryoablation of osteoid osteoma: Two case reports. *J Vasc Interv Radiol* (2010) 21:586–9. doi: 10.1016/j.jvir.2009.12.389

23. Coupal TM, Mallinson PI, Munk Pl Liu D, Clarkson P, Ouellette H. CT-guided percutaneous cryoablation for osteoid osteoma: Initial experience in adults. *AJR Am J Roentgenol* (2014) 202:1136–9. doi: 10.2214/AJR.13.11336

24. Le Corroller T, Vives T, Mattei J-C, Pauly V, Guenoun D, Rochwerger A, et al. Osteoid osteoma: Percutaneous CT-guided cryoablation is a safe, effective, and durable treatment option in adults. *Radiology* (2022) 302(2):211100. doi: 10.1148/radiol.2021211100

25. Aarts BM, Klompenhouwer EG, Rice SL, Imani F, Baetens T, Bex A, et al. Cryoablation and immunotherapy: An overview of evidence on its synergy. *Insights Imaging* (2019) 10:53. doi: 10.1186/s13244-019-0727-5

26. Basile A, Failla G, Reforgiato A, Scavone G, Mundo E, Messina M, et al. The use of microwaves ablation in the treatment of epiphyseal osteoid osteomas. *Cardiovasc Interventional Radiol* (2014) 37:737–42. doi: 10.1007/s00270-013-0722-z

27. Brace CL. Radiofrequency and microwave ablation of the liver, lung, kidney, and bone: What are the differences? *Curr Probl Diagn Radiol* (2009) 38:135–43. doi: 10.1067/j.cpradiol.2007.10.001

28. Moser T, Buy X, Goyault G, Tok CH, Irani F, Gangi A. Ablation des tumeurs osseuses sous contrôle de l'imagerie : Revue des techniques actuelles. *J Radiol* (2008) 89:461–71. doi: 10.1016/S0221-0363(08)71449-5

29. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of interventional radiology clinical practice guidelines. *J Vasc Interv Radiol* (2003) 14:S199–202. doi: 10.1097/01.RVI.0000094584.83406.3e

30. Morassi LG, Kokkinis K, Evangelopoulos DS, Karargyris O, Vlachou I, Kalokairinou K, et al. Percutaneous radiofrequency ablation of spinal osteoid osteoma under CT guidance. *Br J Radiol* (2014) 87:20140003. doi: 10.1259/bjr.20140003

31. Regev GJ, Salame K, Keynan O, Lidar Z. Resection of benign vertebral tumors by minimally invasive techniques. *Spine J* (2015) 15:2396–403. doi: 10.1016/j.spinee.2015.07.002

32. Yu F, Niu X-H, Zhang Q, Zhao H-T, Xu L-H, Deng Z-P. Radiofrequency ablation under 3D intraoperative iso-c c-arm navigation for the treatment of osteoid osteomas. *Br J Radiol* (2015) 88:20140535. doi: 10.1259/bjr.20140535

33. Alemdar C, Çaçan MA, Dusak A, Özkul E, Atiç R, Kapukaya A. A comparison of percutaneous trephine excision and open surgery in the treatment of osteoid osteoma. *Int Orthopaedics* (2016) 40:1481–7. doi: 10.1007/s00264-015-3044-8

34. Arıkan Y, Yavuz U, Lapcin O, Sökücü S, Özkan B, Kabukçuoğlu Y. Percutaneous radiofrequency ablation for osteoid osteoma under guidance of threedimensional fluoroscopy. *J Orthopaedic Surg (Hong Kong)* (2016) 24:398–402. doi: 10.1177/1602400326

35. Filippiadis D, Gkizas C, Kostantos C, Mazioti A, Reppas L, Brountzos E, et al. Percutaneous biopsy and radiofrequency ablation of osteoid osteoma with excess reactive new bone formation and cortical thickening using a battery-powered drill for access: A technical note. *Cardiovasc Interventional Radiol* (2016) 39:1499–505. doi: 10.1007/s00270-016-1366-6

36. Gökalp MA, Gözen A, Ünsal S, Önder H, Güner S. An alternative surgical method for treatment of osteoid osteoma. *Med Sci Monitor* (2016) 22:580–6. doi: 10.12659/MSM.896988

37. Guo X, Li X, Li Z, Peng D, Zhang X, Zhang Q. [Therapeutic effect analysis for open resection in osteoid osteoma around lesser trochanter of femur]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban J Cent South Univ Med Sci* (2016) 41:1291–6. doi: 10.11817/j.issn.1672-7347.2016.12.007

38. Karagöz E, Özel D, Özkan F, Duran Özel B, Özer Ö, Ünsal Coşkun Z. Effectiveness of computed tomography guided percutaneous radiofrequency ablation therapy for osteoid osteoma: Initial results and review of the literature. *Polish J Radiol* (2016) 81:295–300. doi: 10.12659/PJR.896475

39. Lin N, Ye Z-M, Qu H, Yan X-B, Pan W-B, Huang X, et al. Open surgery for osteoid osteoma with three dimensional c-arm scan under the guidance of computer navigation. *Orthopaedic Surg* (2016) 8:205–11. doi: 10.1111/os.12233

40. Masciocchi C, Zugaro L, Arrigoni F, Luca Gravina G, Mariani S, La Marra A, et al. Radiofrequency ablation versus magnetic resonance guided focused ultrasound surgery for minimally invasive treatment of osteoid osteoma: A propensity score matching study. *Eur Radiol* (2016) 26:2472–81. doi: 10.1007/s00330-015-4111-7

41. Miyazaki M, Arai Y, Myoui A, Gobara H, Sone M, Rosenthal DI, et al. Phase I/II multi-institutional study of percutaneous radiofrequency ablation for painful osteoid osteoma (JIVROSG-0704). *Cardiovasc Interventional Radiol* (2016) 39:1464–70. doi: 10.1007/s00270-016-1438-7

42. Outani H, Hamada K, Takenaka S, Imura Y, Oshima K, Sotobori T, et al. Radiofrequency ablation of osteoid osteoma using a three-dimensional navigation system. *J Orthopaedic Sci* (2016) 21:678–82. doi: 10.1016/j.jos.2016.05.005

43. Whitmore MJ, Matthew Hawkins C, David Prologo J, Marshall KW, Fabregas JA, Yim DB, et al. Cryoablation of osteoid osteoma in the pediatric and adolescent population. *J Vasc Interventional Radiol JVIR* (2016) 27:232–7. doi: 10.1016/j.jvir.2015.10.005

44. Albisinni U, Facchini G, Spinnato P, Gasbarrini A, Bazzocchi A. Spinal osteoid osteoma: Efficacy and safety of radiofrequency ablation. *Skeletal Radiol* (2017) 46:1087–94. doi: 10.1007/s00256-017-2662-1

45. Chahal A, Rajalakshmi P, Khan SA, Rastogi S, Srivastava DN, Gamanagatti S. CT-guided percutaneous radiofrequency ablation of osteoid osteoma: Our experience in 87 patients. *Indian J Radiol Imaging* (2017) 27:207–15. doi: 10.4103/ijri.IJRI_260_16

46. Costanzo A, Sandri A, Regis D, Trivellin G, Pierantoni S, Samaila E, et al. CT-guided radiofrequency ablation of osteoid osteoma using a multi-tined expandable electrode system. *Acta Bio-med Atenei Parmensis* (2017) 88:31–7. doi: 10.23750/abm.v88i4-S.6791

47. Erol B, Topkar MO, Tokyay A, Sofulu O, Caliskan E, Okay E. Minimal invasive intralesional excision of extremity-located osteoid osteomas in children. *J Pediatr Orthopedics Part B* (2017) 26:552–9. doi: 10.1097/BPB.0000000000000294

48. Faddoul J, Faddoul Y, Kobaiter-Maarrawi S, Moussa R, Rizk T, Nohra G, et al. Radiofrequency ablation of spinal osteoid osteoma: A prospective study. *J Neurosurg Spine* (2017) 26:313–8. doi: 10.3171/2016.8.SPINE16462

49. Kulkarni SS, Shetty NS, Polnaya AM, Janu A, Kumar S, Puri A, et al. CT-guided radiofrequency ablation in osteoid osteoma: Result from a tertiary cancer centre in India. *Indian J Radiol Imaging* (2017) 27:318–23. doi: 10.4103/ijri.IJRI_30_17

50. Nöel MA, Segura MJ, Sierre S, Francheri Wilson IA, Tello CA, Galaretto E, et al. Neurophysiological monitoring in radiofrequency ablation of spinal osteoid osteoma with a progressive time and temperature protocol in children. *Spine Deformity* (2017) 5:351–9. doi: 10.1016/j.jspd.2017.03.001

51. Wang B, Bo Han S, Jiang L, Shu Yuan H, Liu C, Zhu B, et al. Percutaneous radiofrequency ablation for spinal osteoid osteoma and osteoblastoma. *Eur Spine J* (2017) 26:1884–92. doi: 10.1007/s00586-017-5080-0

52. Wu H, Lu C, Chen M. Evaluation of minimally invasive laser ablation in children with osteoid osteoma. *Oncol Lett* (2017) 13:155–8. doi: 10.3892/ol.2016.5417

53. Hage AN, Chick JFB, Gemmete JJ, Grove JJ, Srinivasa RN. Percutaneous radiofrequency ablation for the treatment of osteoid osteoma in children and adults: A comparative analysis in 92 patients. *Cardiovasc Interventional Radiol* (2018) 41:1384–90. doi: 10.1007/s00270-018-1947-7

54. Santiago E, Pauly V, Brun G, Guenoun D, Champsaur P, Le Corroller T. Percutaneous cryoablation for the treatment of osteoid osteoma in the adult population. *Eur Radiol* (2018) 28:2336–44. doi: 10.1007/s00330-017-5164-6

55. Ankory R, Kadar A, Netzer D, Schermann H, Gortzak Y, Dadia S, et al. 3D imaging and stealth navigation instead of CT guidance for radiofrequency ablation of osteoid osteomas: A series of 52 patients. *BMC Musculoskeletal Disord* (2019) 20:579. doi: 10.1186/s12891-019-2963-8

56. Beyer T, van Rijswijk CSP, Martel Villagrán J, Rehnitz C, Muto M, von Falck C, et al. European Multicentre study on technical success and long-term clinical outcome of radiofrequency ablation for the treatment of spinal osteoid osteomas and osteoblastomas. *Neuroradiology* (2019) 61:935–42. doi: 10.1007/s00234-019-02226-9

57. Kaptan MA, Acu B, Öztunalı Ç, Çalışır C, İnan U, Bilgin M. Correlation of 3-T MRI and CT findings with patient symptoms and treatment outcome in radiofrequency ablation of osteoid osteoma. *Acta Orthopaedica Traumatol Turcica* (2019) 53:239–47. doi: 10.1016/j.aott.2019.04.015

58. Kostrzewa M, Henzler T, Schoenberg SO, Diehl SJ, Rathmann N. Clinical and quantitative MRI perfusion analysis of osteoid osteomas before and after microwave ablation. *Anticancer Res* (2019) 39:3053–7. doi: 10.21873/anticanres.13439

59. Neyisci C, Erdem Y. Safe and effective treatment choice for osteoid osteoma: Computed tomography-guided percutaneous radiofrequency ablation. *Cureus* (2019) 11:e5526. doi: 10.7759/cureus.5526

60. Sahin C, Oc Y, Ediz N, Altınay M, Bayrak AH. The safety and the efficacy of computed tomography guided percutaneous radiofrequency ablation of osteoid osteoma. *Acta Orthopaedica Traumatol Turcica* (2019) 53:360–5. doi: 10.1016/j.aott.2019.06.001

61. Yu X, Wang B, Yang SM, Han SB, Jiang L, Liu XG, et al. Percutaneous radiofrequency ablation versus open surgical resection for spinal osteoid osteoma. *Spine J* (2019) 19:509–15. doi: 10.1016/j.spinee.2018.07.013

62. Ayas MS, Gül O, Emin Okutan A, Kerimoğlu S, Yıldız M, Uğur Turhan A, et al. Effectiveness and reliability of traditional open surgery in atypical localizations of osteoid osteoma. *Joint Dis Related Surg* (2020) 31:541–7. doi: 10.5606/ehc.2020.74333

63. Reis J, Chang Y, Sharma AK. Radiofrequency ablation vs microwave ablation for osteoid osteomas: Long-term results. *Skeletal Radiol* (2020) 49:1995–2000. doi: 10.1007/s00256-020-03518-5

64. Tanrıverdi B, Erbahçeci Salık A, Çetingök H, Edipoğlu E, Gökhan Bilgili M, Güven K, et al. Multidisciplinary approach in the treatment of osteoid osteoma with radiofrequency ablation. *Joint Dis Related Surg* (2020) 31:255–9. doi: 10.5606/ehc.2020.71413

65. Yuce G, Aytekin N, Eren S, Genç B, Faruk Ateş Ö, Canyiğit M. Is radiofrequency ablation safe and effective in treating osteoid osteomas? a prospective single-center study with atypical cases. *J Orthopaedic Surg (Hong Kong)* (2020) 28:2309499020960555. doi: 10.1177/2309499020960555

66. Arrigoni F, Spiliopoulos S, de Cataldo C, Reppas L, Palumbo P, Mazioti A, et al. A bicentric propensity score matched study comparing percutaneous computed tomography-guided radiofrequency ablation to magnetic resonance-guided focused ultrasound for the treatment of osteoid osteoma. *J Vasc Interventional Radiol JVIR* (2021) 32:1044–51. doi: 10.1016/j.jvir.2021.03.528

67. Filippiadis D, Stefanou D, Mazioti A, Foti L, Tsochatzis A, Kelekis N, et al. Computed tomography guided radiofrequency ablation of osteoid osteoma in children: A single center's experience. *Skeletal Radiol* (2021). doi: 10.1007/s00256-021-03904-7

68. Lorenc T, Kocoń H, Gołębiowski M. Computed tomography-guided percutaneous radiofrequency and laser ablation for the treatment of osteoid osteoma - long-term follow-up from 5 to 10 years. *Polish J Radiol* (2021) 51 (4):855–61. doi: 10.5114/pjr.2021.102678

69. Niazi GE, Basha MAA, Elsharkawi WFA, Zaitoun MMA. Computed tomography-guided radiofrequency ablation of osteoid osteoma in atypical sites: Efficacy and safety in a Large case series. *Acad Radiol* (2021) 28:68–76. doi: 10.1016/j.acra.2020.01.028

70. Somma F, Stoia V, D'Angelo R, Fiore F. Imaging-guided radiofrequency ablation of osteoid osteoma in typical and atypical sites: Long term follow up. *PloS One* (2021) 16:e0248589. doi: 10.1371/journal.pone.0248589

71. Miwa S, Shirai T, Yamamoto N, Hayashi K, Takeuchi A, Tada K, et al. Risk factors for surgical site infection after malignant bone tumor resection and reconstruction. *BMC Cancer* (2019) 19:33. doi: 10.1186/s12885-019-5270-8

72. Hoffmann RT, Jakobs TF, Kubisch CH, Trumm CG, Weber C, Duerr H-R, et al. Radiofrequency ablation in the treatment of osteoid osteoma-5-Year experience. *Eur J Radiol* (2010) 73:374–9. doi: 10.1016/j.ejrad.2008.11.018

73. Gangi A, et al. Osteoid osteoma: Percutaneous laser ablation and follow-up in 114 patients. *Radiology* (2007) 242:293–301. doi: 10.1148/radiol.2421041404

74. Budrevicius K. Microwave ablation as a minimally invasive surgical option for the posterior spinal elements osteoid osteoma: A case report %J journal of spine. *J Spine* (2021) 10:1–3.

75. Kastler A, Krainik A, Sakhri L, Mousseau M, Kastler B. Feasibility of real-time intraprocedural temperature control during bone metastasis thermal microwave ablation: A bicentric retrospective study. *J Vasc Interv Radiol* (2017) 28:366–71. doi: 10.1016/j.jvir.2016.09.030

76. Bourgault C, Vervoort T, Szymanski C, Chastanet P, Maynou C. Percutaneous CT-guided radiofrequency thermocoagulation in the treatment of osteoid osteoma: A 87 patient series. *Orthopaedics Traumatol Surg Res OTSR* (2014) 100:323–7. doi: 10.1016/j.otsr.2014.02.001

77. Rimondi E, Mavrogenis AF, Rossi G, Ciminari R, Malaguti C, Tranfaglia C, et al. Radiofrequency ablation for non-spinal osteoid osteomas in 557 patients. *Eur Radiol* (2012) 22:181–8. doi: 10.1007/s00330-011-2240-1

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 05 August 2022
DOI 10.3389/fonc.2022.972498

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Giovanni Cristalli,
Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Italy
Fabio Ferreli,
Humanitas University, Italy

*CORRESPONDENCE
Yiwen Jia
tbjyw1990@126.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 18 June 2022
ACCEPTED 13 July 2022
PUBLISHED 05 August 2022

CITATION
Yin S, Han Y, Liu Y, Chen B, Fu Z, Sheng S, Wang J, Shen C, Wang X and Jia Y (2022) Comparison of various surgical incisions in parotidectomy: A systematic review and network meta-analysis.
Front. Oncol. 12:972498.
doi: 10.3389/fonc.2022.972498

Comparison of various surgical incisions in parotidectomy: A systematic review and network meta-analysis

Siyue Yin[1,2†], Yanxun Han[2,3†], Yuchen Liu[2,3†], Bangjie Chen[1,2], Ziyue Fu[2], Shuyan Sheng[2], Jianpeng Wang[2], Chuanlu Shen[2], Xinyi Wang[2] and Yiwen Jia[4*]

[1]Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [2]Anhui Medical University, Hefei, China, [3]Department of Otolaryngology, Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [4]Department of Gastroenterology, The Third Affiliated Hospital of Anhui Medical University (Hefei first people's Hospital), Hefei, China

Background: This network meta-analysis aimed to comprehensively compare the operative and postoperative outcomes of different parotidectomy incisions.

Methods: Embase, PubMed, Web of Science, and Cochrane Central Register of Controlled Trials were searched up to April 2022. A complete Bayesian network meta-analysis was performed using the Markov Monte Carlo method in OpenBUGS.

Results: Seventeen studies with 1609 patients were included. Thirteen were retrospective cohort studies, three were prospective cohort studies, and one was a randomized controlled study. The quality of evidence was rated as very low in most comparisons. The incision satisfaction score of the modified facelift incision (MFI), retroauricular hairline incision (RAHI), V-shaped incision (VI) were higher than that of the modified Blair incision (MBI) (MBI vs. MFI: mean difference [MD] -1.39; 95% credible interval [CrI] -2.23, -0.57) (MBI vs. RAHI: MD -2.25; 95% CrI -3.40, -1.12) (MBI vs. VI: MD -2.58; 95% CrI -3.71, -1.46); the tumor size treated by VI was smaller than that by MBI (MD 5.15; 95% CrI 0.76, 9.38) and MFI (MD 5.16; 95% CrI 0.34, 9.86); and the risk of transient facial palsy in the MFI was lower than that in the MBI (OR 2.13; 95% CrI 1.28, 3.64). There were no differences in operation time, drainage volume, wound infection, hematoma, salivary complications, Frey syndrome, or permanent facial palsy between incision types.

Conclusion: The traditional MBI is frequently used for large tumor volumes, but the incision satisfaction score is low and postoperative complication control is poor. However, emerging incisions performed well in terms of incision satisfaction scores and control of complications. More randomized controlled trials are needed to compare the different parotidectomy incisions. Patients should be fully informed about the characteristics of each incision to make the most informed decision, along with the physician's advice.

Systematic Review Registration: PROSPERO, identifier CRD42022331756

KEYWORDS

parotidectomy, surgical incision, Bayesian network meta-analysis, modified Blair incision, modified facelift incision, retroauricular hairline incision, V-shaped incision

1 Introduction

The parotid glands, being the largest pair of salivary glands in the human body, are the location of approximately 80% of salivary gland cancer (1). According to the International Agency for Research on Cancer, there were 53,583 new cases of salivary gland cancer globally in 2020, accounting for 0.3% of all cancers (2). Most parotid tumors are benign, and parotidectomy is the preferred treatment option because of recurrence and potential malignant transformation (3, 4). Since the classic cervicomastoidfacial incision was proposed by Blair in 1912, the operative approach for parotid gland resection has undergone continuous improvement and innovation (5). Endoscopy- and robot-assisted parotidectomy techniques have also progressed in recent years, but their safety and ease of use need to be further proven in practice.

Currently, four incision types are commonly used for parotidectomy. The modified Blair incision (MBI) is the most widely used surgical incision in the clinic, while the modified facelift incision (MFI), retroauricular hairline incision (RAHI), and V-shaped incision (VI) are becoming increasingly prevalent. A large-scale surgical incision allows for full exposure of the parotid gland tissue to minimize facial nerve injury, but the ensuing huge facial scar inevitably inflicts a psychological load on the patient (6, 7). In contrast, smaller incisions with better cosmetic results require persuasive data representation to control complications.

There has been ongoing discussion regarding the different incision types for parotidectomy. Unfortunately, the number of relevant meta-analyses is limited (8). This study compared four incision options for parotidectomy based on a Bayesian network meta-analysis with the aim of providing evidence for surgical and patient incision selection.

2 Methods

2.1 Search strategy

This study was registered *a priori* with PROSPERO (CRD42022331756). We conducted a systematic literature search of Embase, PubMed, Web of Science, and Cochrane Central Register of Controlled Trials in April 2022 and were not restricted with regard to publication language and date. The complete search strategy is presented in Supplementary Material. We also reviewed the references of the included articles to identify additional potential studies. Because all analyses were based on previously published studies, ethical approval and patient consent were not required.

2.2 Study selection

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, studies were included based on the population, intervention, comparison, outcome, and study design (PICOS). The PICOS components of this study were as follows: P (patients who underwent parotidectomy with speculated benign parotid tumors on preoperative examination), I (use of MBI [Figure 1A], MFI [Figure 1B], RAHI [Figure 1C], or VI [Figure 1D] in parotidectomy), C (pairwise comparisons between the four incisions), O (intraoperative and postoperative parameters, including operation time, incision satisfaction score, drainage volume, permanent facial palsy, bleeding volume, transient facial palsy, Frey syndrome, salivary complications, wound infection, and hematoma), and S (randomized clinical trials [RCTs] or original research articles with prospective or retrospective designs).

The inclusion criteria were as follows: 1) RCTs or original research articles with prospective or retrospective designs, 2) articles that included patients who underwent parotidectomy and who had speculated benign parotid tumors by preoperative examination, and 3) studies that reported the outcome of parotidectomy and included at least one required outcome measure. The exclusion criteria were as follows: 1) studies using endoscopes or robots to assist with surgery, 2) studies with no control group, 3) studies related to flap or fascia reconstruction, 4) articles not published in English, and 5) review articles, short reports, and letters to the editor.

2.3 Data extraction and quality assessment

Data were independently extracted by two investigators. All divergences that arose throughout the procedure were reviewed

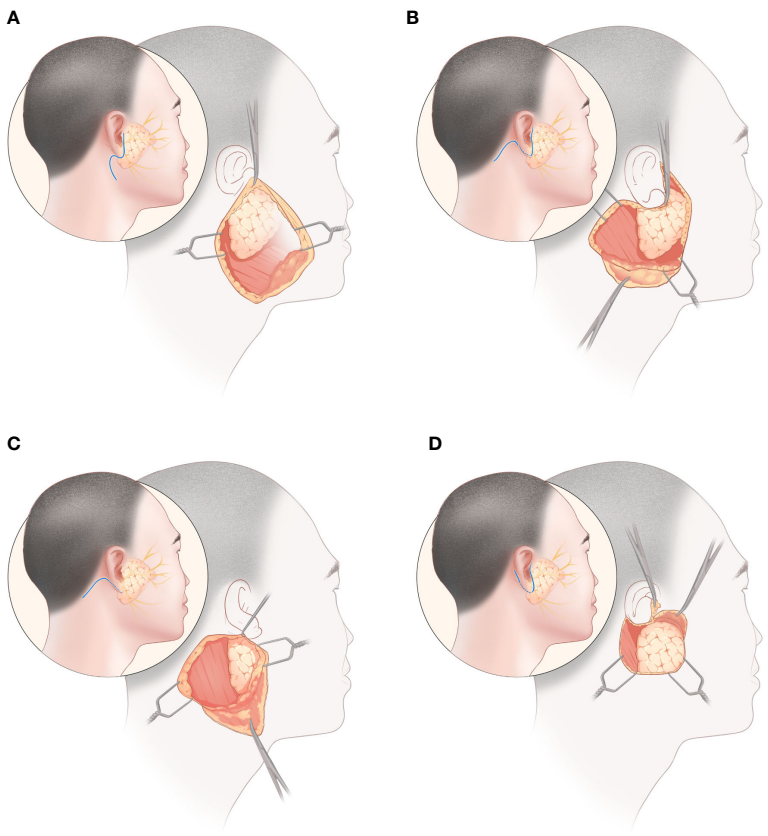

FIGURE 1
Parotidectomy *via* four incisions: **(A)** modified Blair incision, **(B)** modified facelift incision, **(C)** retroauricular hairline incision, **(D)** V-shaped incision.

by a third investigator, and a decision was made. The extracted data included the name of the first author, year of publication, country, study type, age, sex, duration of follow-up, surgical approach, tumor size, operation time, and postoperative outcomes. The primary outcomes were incision satisfaction score, operation time, drainage volume, and permanent facial palsy. Secondary outcomes were tumor size, transient facial palsy, Frey syndrome, salivary complications, wound infection, and hematoma. If relevant data were missing, an approximate formula was used for the calculation. The quality of the included RCTs was evaluated using the Cochrane Collaboration Tool, while the Newcastle-Ottawa scale (NOS) and the risk of bias in non-randomized studies of interventions (ROBINS-I) were used to assess the quality of the cohort studies. The evaluation criteria for the RCT tool included the randomization procedure, allocation concealment, baseline comparability of the research groups, blinding, and completeness of follow-up (9). NOS evaluates and scores study bias out of 9 points, including 4 for patient selection, 2 for research group comparability, and 3 for outcome evaluation. The ROBINS-I assesses bias due to confusion, subject selection, intervention classification, deviations from expected interventions, missing data, outcome measures, and reported outcome selection.

2.4 Statistical analysis

This network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (10). For continuous variables, the mean difference (MD) was calculated. As the variables in the categorical data were all adverse event outcomes and the positive rate was low, the odds ratio (OR) was used to calculate the effect size. For zero positive event outcomes, 0 was replaced by 0.5 to prevent a large confidence interval (11). A pairwise comparison meta-analysis was performed to obtain direct comparison results. To visualize all head-to-head comparisons for each outcome, we created network plots. Our study was based entirely on the random effects of the Bayesian approach and was analyzed using the Monte Carlo Markov chain (MCMC) method in OpenBUGS Version 3.2.3. The auxiliary statistical analysis and mapping were performed

using software R 4.1.3 (main packages including gemtc and rjags) and Stata V.14. The fit of the model was verified using totresdev, and convergence was ensured using trace plots, Autocorr, Brooks-Gelman-Rubin diagnostic diagrams, and Potential Scale Reduction Factor (PSRF). The deviance information criterion (DIC) of the consistent and inconsistent models was compared to select a better model (12). If the inconsistent model had a better fit (low DIC value), the results were interpreted with caution (13). League tables were used to show the pooled comparisons for each outcome. We tested the overall heterogeneity of the outcomes and compared local inconsistencies using the node-splitting method. The evaluation criteria for statistical heterogeneity were as follows: I^2 index values below 25% were considered as low heterogeneity, 50% as moderate heterogeneity, and 75% as high heterogeneity. Statistical significant was set at $P<0.05$. The surface under the cumulative ranking (SUCRA) was used to rank the inspected interventions (14). Furthermore, we evaluated publication bias using a funnel plot for outcomes in more than 10 studies. Finally, we used the network meta-analysis recommendations for grading and developed GRADE to assess the certainty of evidence (15).

3 Results

3.1 Search results and methodological quality

The selected databases were searched for 334 potentially related articles. Following the removal of duplicate studies, the titles and abstracts of 166 selected studies were examined and 121 unqualified papers were eliminated. After reading the full text, 1609 patients were included across 17 qualified articles, including one RCT, 13 retrospective cohort studies, and three prospective cohort studies. Figure 2 shows literature selection procedure in this study.

The baseline characteristics of the 17 types of research included in the network meta-analysis are presented in Table 1 (16–32). In our analysis, 14 of the studies were two-arm trials and three were three-arm trials involving four different surgical procedures. Nine cohort studies were considered to be of high quality, with NOS scores of 7 or greater. Specific scores are presented in Table 1. Table 2 shows the findings of the bias risk assessment for cohort studies using the ROBINS-I, with eight studies having a low overall bias. The results of RCT evaluated by the Cochrane Collaboration Tool are shown in Table 3.

3.2 Traditional meta-analyses

Figures 3, 4 summarize the direct comparison results of the pairwise meta-analyses of continuous and dichotomous outcomes from the 17 studies, respectively. The MFI, RAHI and VI had significantly higher incision satisfaction scores than the MBI; the RAHI and VI had significantly higher incision satisfaction scores than the MFI; however, no study has directly compared the RAHI and VI. VI required substantially longer time to operate than MBI, whereas MFI lasted significantly longer than RAHI. MBI had a significantly larger tumor size than MFI, whereas VI was significantly smaller than the other three incisions. The incidence of transient facial palsy was significantly higher only in the MBI group when compared with the MFI group, and there was no statistical significance in a pairwise direct comparison of other complications. Overall, the heterogeneity was low, although several groups had high values, reflecting differences in surgical skills among physicians or the small number of studies included in these pairwise comparisons.

3.3 Bayesian network meta-analyses

Figure 5 shows the network relationships between the different incisions. The area of each circle denotes the number of patients included, and the thickness of the lines linking the two surgical incisions represents the number of articles. Table 4 displays the pooled comparison findings, with the statistically significant values highlighted in bold.

3.3.1 Incision satisfaction score

Nine studies including 585 patients provided data on incision satisfaction scores. Meta-analysis of pooled network showed similar MDs when comparing MFI vs. RAHI (MD -0.85; 95% credible interval [CrI] -2.00, 0.28), MFI vs. VI (MD -1.18; 95% CrI -2.49, 0.11), RAHI vs. VI (MD -0.33; 95% CrI -1.88, 1.23), while MBI vs. MFI (MD -1.39; 95% CrI -2.23, -0.57), MBI vs. RAHI (MD -2.25; 95% CrI -3.40, -1.12), and MBI vs. VI (MD -2.58; 95% CrI -3.71, -1.46) were signifificant (Table 4A). No statistical difference was observed between direct and indirect comparisons (MFI vs. MBI, p=0.08; RAHI vs. MBI, p=0.36; RAHI vs. MFI, p=0.21; VI vs. MFI, p=0.14). The overall heterogeneity was low (I^2 = 6%). The SUCRA rankings were 0.1% for MBI, 36% for MFI, 75% for RAHI, and 88% for VI.

3.3.2 Operation time

Eleven studies involving 957 patients reported the operation time. Meta-analysis of the pooled network showed similar MDs when comparing MBI vs. MFI (MD -1.67; 95% CrI -11.49, 10.39), MBI vs. RAHI (MD -0.40; 95% CrI -13.52, 14.08), MBI vs. VI (MD -3.53; 95% CrI -17.91, 9.81), MFI vs. RAHI (MD 1.30; 95% CrI -12.60, 14.16), MFI vs. VI (MD -1.86; 95% CrI -18.42, 11.48), RAHI vs. VI (MD -3.12; 95% CrI -21.20, 12.57) (Table 4B). No statistical difference was observed between the direct and indirect comparisons (MFI vs. MBI, p=0.09; RAHI vs. MBI, p=0.52; VI vs. MBI, p=0.09; RAHI vs. MFI, p=0.29; VI vs.

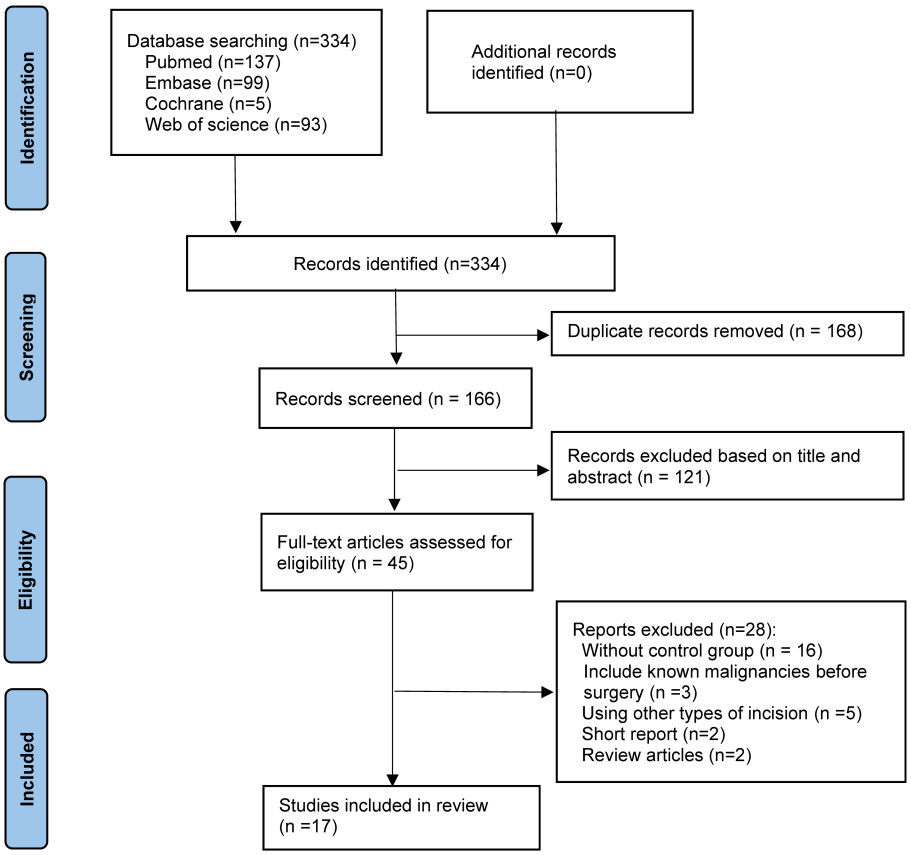

FIGURE 2
The Preferred Reporting Items for Systematic Reviews and network meta-analyses checklist (PRISMA-NMA) diagram.

MFI, p=0.35; VI vs. RAHI, p=0.40). The overall heterogeneity was low (I^2 = 13%). The SUCRA rankings were 63% for MBI, 46% for MFI, 58% for RAHI, and 33% for VI.

3.3.3 Drainage volume

Seven studies with a total of 960 patients reported the drainage volume. Meta-analysis of the pooled network showed similar MDs when comparing MBI vs. MFI (MD -3.22; 95% CrI -15.16, 5.55), MBI vs. RAHI (MD 7.54; 95% CrI -13.56, 22.30), MBI vs. VI (MD 0.36; 95% CrI -10.68, 11.63), MFI vs. RAHI (MD 10.99; 95% CrI -6.35, 24.47), MFI vs. VI (MD 3.67; 95% CrI -7.12, 17.53), RAHI vs. VI (MD -7.15; 95% CrI -22.19, 14.14) (Table 4C). No statistical difference was observed between the direct and indirect comparisons (MFI vs. MBI, p=0.41; V vs. MBI, p=0.35; VI vs. MFI, p=0.92; VI vs. RAHI, p=0.70). The overall heterogeneity was low (I^2 = 14%). The SUCRA rankings were 50% for MBI, 15% for MFI, 84% for RAHI, and 51% for VI.

3.3.4 Permanent facial palsy

Eleven studies of 969 patients reported permanent facial palsy. Meta-analysis of the pooled network showed similar ORs when comparing MBI vs. MFI (OR 1.04; 95% CrI 0.30, 7.49), MBI vs. RAHI (OR 0.56; 95% CrI 0.11, 25.13), MBI vs. VI (OR 0.60; 95% CrI 0.13, 11.98), MFI vs. RAHI (OR 0.37; 95% CrI 0.07, 18.85), MFI vs. VI (OR 0.36; 95% CrI 0.07, 10.17), RAHI vs. VI (OR 0.15; 95% CrI 0.03, 20.62) (Table 4D). No statistical difference was observed between the direct and indirect comparisons (MFI vs. MBI, p=0.71; RAHI vs. MBI, p=0.90; V vs. MBI, p=0.61; RAHI vs. MFI, p=0.40; VI vs. MFI, p=0.60; VI vs. RAHI, p=0.65). The overall heterogeneity was low (I^2 = 0%). The SUCRA rankings were 7% for MBI, 57% for MFI, 61% for RAHI, and 76% for VI.

3.3.5 Secondary outcomes

Tables 5 and 6 provide a mixed comparison and SUCRA rankings of the secondary outcomes, respectively. Meta-analysis of the pooled network did not show statistically significant OR comparing MBI vs. MFI, MBI vs. RAHI, MBI vs. VI, MFI vs. RAHI, MFI vs. VI, and RAHI vs. VI in terms of hematoma (OR 1.22, 95% CrI 0.35, 9.09; OR 0.52, 95% CrI 0.10, 33.33; OR 0.33, 95% CrI 0.07, 12.50; OR 0.28, 95% CrI 0.05, 16.67; OR 0.15, 95% CrI 0.03, 9.09; OR 0.08, 95% CrI 0.02, 16.67, respectively). The

TABLE 1 Characteristics and NOS quality assessment of the included studies.

Author, year, country	Study design	Surgical procedure	No. of patient	Age (years)	Gender (M/F)	Follow-up (months)	Tumor size (mm)	Newcastle-Ottawa Scale			
								Selection	Comparability	Outcome	Total (9☆)
Terris (16), USA	RCS	MBI	15	40.3 ± 24.6	5/10	7.7 ± nr	nr	☆☆☆	☆	☆☆	6
		MFI	17	40.3 ± 12.3	1/16	8.1 ± nr					
Roh (17) Korea	RCS	MBI	49	50.5 ± 15.7	23/26	48 ± 23	29 ± 19	☆☆☆☆	☆☆	☆☆☆	9
		MFI	52	48.4 ± 14.6	24/28	47 ± 22	27 ± 18				
Wasson (18), UK	RCS	MBI	59	51 ± nr	29/30	≥6	nr	☆☆☆☆	☆	☆	6
		MFI	20	44 ± nr	11/9						
Bianchi (19), Italy	RCS	MBI	35	nr	nr	≥18	nr	☆☆☆	☆	☆☆☆	7
		MFI	48								
Lee (20), Korea	RCS	MBI	162	45.82 ± 18.44	90/72	8.98 ± nr	26.49 ± 11.94	☆☆☆☆	☆	☆☆	7
		MFI	182	44.12 ± 16.76	51/131		23.76 ± 9.98				
Zhi (21), China	RCS	MBI	20	49 ± nr	nr	36 ± 0	nr	☆☆☆	☆	☆☆☆	7
		MFI	18	45 ± nr							
Graciano (22) Brazil	RCS	MBI	30	47.3 ± nr	21/9	nr	48.12 ± nr	☆☆☆	☆	☆☆	6
		MFI	30	34.93 ± nr	11/19		34.29 ± nr				
Kim (23), Korea	RCS	MBI	16	45 ± nr	6/10	29 ± NA	27.1 ± nr	☆☆☆	☆☆	☆☆☆	8
		MFI	24	51 ± nr	9/15		27.4 ± nr				
		RAHI	33	46 ± nr	14/19		27.8 ± nr				
Bulut (24) Germany	RCS	MBI	24	43 ± nr	5/19	97 ± NA	31 ± nr	☆☆☆☆	☆	☆☆☆	8
		MFI	24	43 ± nr	5/19		29 ± nr				
Wu (25), China	RCS	MBI	28	47.2 ± 14.1	14/14	25 ± 0	22 ± 9	☆☆☆	☆☆	☆☆	7
		RAHI	36	48.1 ± 18.0	22/14		24 ± 9				
Xu (26), China	PCS	MBI	35	41.66 ± 13.18	17/18	48 ± nr	37.2 ± 6.9	☆☆☆	☆	☆☆☆	7
		MFI	36	39.46 ± 11.18	14/22		35.7 ± 6.5				
Zheng (27), China	PCS	MBI	23	37.5 ± 8.9	11/12	19.2 ± 2.8	25.1 ± 5	☆☆☆	☆	☆☆	6
		VI	23	36.2 ± 8.7	10/13	18.7 ± 2.6	23 ± 6				
Jo, Korea	PCS	MBI	40	51.1 ± 17	19/21	nr	24.7 ± 7.9	☆☆☆☆	☆	☆	6
		VI	34	46.3 ± 13.4	13/21		21.4 ± 5.8				
Ahn (28), Korea	RCS	MFI	122	53.5 ± 14.8	71/51	nr	28 ± 11	☆☆☆☆	☆	☆☆	7
		RAHI	50	51.8 ± 17.7	24/26		27 ± 10				
		VI	41	42.1 ± 14.5	12/29		19 ± 5				
Li (29), China	RCT	MBI	20	43.35 ± 8.83	15/5	nr	22.5 ± nr	–	–	–	–

(Continued)

TABLE 1 Continued

Author, year, country	Study design	Surgical procedure	No. of patient	Age (years)	Gender (M/F)	Follow-up (months)	Tumor size (mm)	Newcastle-Ottawa Scale			
								Selection	Comparability	Outcome	Total (9☆)
		MFI	20	45.95 ± 8.16	16/4		17 ± nr				
		VI	20	43.40 ± 9.89	16/4		18 ± nr				
Zhang, China	RCS	MBI	36	nr	23/13	6	nr	☆☆☆	☆☆	☆	6
		MFI	32		nr						
Chen (30), China	RCS	MFI	29	56 ± 11.86	16/13	nr	27.7 ± 9.9	☆☆☆	☆	☆☆	6
		RAHI	19	39 ± 14.49	6/13		24.3 ± 9				
Matsumoto (21), Japan	RCS	MBI	97	50.71 ± 15.08	35/62	nr	26.36 ± 10.77	☆☆☆	☆☆	☆☆	7
		MFI	78	51.99 ± 13.53	29/49	nr	25.78 ± 11.85				

RCS, retrospective cohort study; PCS, prospective cohort study; RCT, randomized controlled trial; MBI, modified Blair incision; MFI, modified facelift incision; RAHI, retroauricular hairline incision; VI, V-shaped incision; nr, not reported. The number of * corresponds to the score.

SUCRA rankings were 40% for MBI, 67% for MFI, 56% for RAHI, and 37% for VI. Comparisons of the OR between MBI vs. MFI, MBI vs. RAHI, MBI vs. VI, MFI vs. RAHI, MFI vs. VI, and RAHI vs. VI were also not statistically significant for wound infection (OR 0.84, 95% CrI 0.21, 10.13; OR 0.26, 95% CrI 0.07, 98.14; OR 0.12, 95% CrI 0.09, 17.69; OR 0.10, 95% CrI 0.04, 80.26; OR 0.03, 95% CrI 0.04, 22.54; OR 0.001, 95% CrI 0.01, 49.00, respectively). The SUCRA rankings were 37% for MBI, 54% for MFI, 60% for RAHI, and 49% for VI. In addition, the pooled network meta-analysis did not find statistically significant ORs comparing MBI vs. MFI, MBI vs. RAHI, MBI vs. VI, MFI vs. RAHI, MFI vs. VI, and RAHI vs. VI in terms of salivary complications and Frey syndrome (salivary complications: OR 1.36, 95% CrI 0.73, 2.83; OR 1.60, 95% CrI

TABLE 2 Risk of bias assessment in cohort studies by ROBINS-I.

Study	Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intendedinterventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Terris	16	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Roh	17	Low	Low	Low	Low	Low	Low	Low	Low
Wasson	18	Critical	Low	Low	Low	Low	Low	Low	Critical
Bianchi	19	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Lee	20	Low	Low	Low	Low	Low	Low	Low	Low
Zhi	21	Low	Low	Low	Low	Low	Low	Low	Low
Graciano	22	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Kim	23	Low	Low	Low	Low	Low	Low	Low	Low
Bulut	24	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Wu	25	Low	Low	Low	Low	Low	Low	Low	Low
Xu	26	Low	Low	Low	Low	Low	Low	Low	Low
Zheng	27	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Jo		Low	Low	Low	Low	Low	Low	Low	Low
Zhang		Critical	Moderate	Low	Low	Low	Low	Low	Critical
Ahn	28	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Chen	30	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Matsumoto	21	Low	Low	Low	Low	Low	Low	Low	Low

Comparisons	No. of Studies	No. of Patients	Mean difference (95% Crl)	I^2
Incision satisfaction score				
MBI vs. MFI	5	300	1.32(1.07,1.58)	83.50%
MBI vs. RAHI	2	113	2.72(1.62,3.83)	77.00%
MBI vs. VI	3	160	1.92(0.68,3.17)	89.90%
MFI vs. RAHI	2	105	1.45(1.01,1.89)	0.00%
MFI vs. VI	1	40	1.62(0.90,2.34)	0.00%
RAHI vs. VI	0	0		
Operation time				
MBI vs. MFI	6	459	0(−0.37,0.37)	71.00%
MBI vs. RAHI	2	113	0.31(−0.07,0.69)	0.00%
MBI vs. VI	3	160	0.43(0.03,0.83)	35.90%
MFI vs. RAHI	3	277	−0.32(−0.57,−0.06)	0.00%
MFI vs. VI	2	203	−0.06(−1.09,0.96)	87.40%
RAHI vs. VI	1	91	−0.08(−0.50,0.33)	0.00%
Drainage volume				
MBI vs. MFI	3	559	0.16(−0.01,0.33)	0.00%
MBI vs. RAHI	0	0		
MBI vs. VI	3	160	0.02(−0.29,0.34)	0.00%
MFI vs. RAHI	2	220	−0.23(−0.87,0.41)	73.20%
MFI vs. VI	2	203	−0.20(−0.75,0.36)	60.20%
RAHI vs. VI	1	91	−0.01(−0.41,0.42)	0.00%
Tumor size				
MBI vs. MFI	4	691	−0.18(−0.33,−0.03)	0.00%
MBI vs. RAHI	1	64	0.22(−0.27,0.72)	0.00%
MBI vs. VI	2	120	−0.44(−0.80,−0.07)	0.00%
MFI vs. RAHI	2	220	−0.16(−0.44,0.13)	0.00%
MFI vs. VI	1	163	−0.91(−1.28,−0.55)	0.00%
RAHI vs. VI	1	91	−0.98(−1.42,−0.55)	100.00%

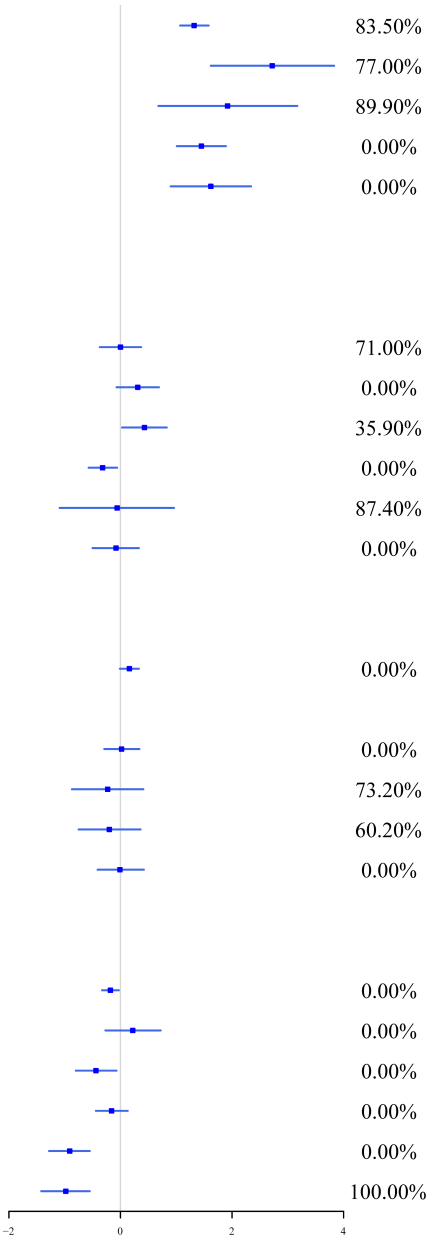

FIGURE 3
A direct comparison forest map of continuous outcomes.

0.59, 6.56; OR 0.86, 95% CrI 0.37, 2.57; OR 1.11, 95% CrI 0.42, 4.62; OR 0.59, 95% CrI 0.25, 1.85; OR 0.39, 95% CrI 0.12, 1.99, respectively) (Frey syndrome: OR 1.41, 95% CrI 0.77, 2.63; OR 1.57, 95% CrI 0.66, 5.17; OR 3.11, 95% CrI 0.80, 62.03; OR 1.06, 95% CrI 0.45, 3.55; OR 2.08, 95% CrI 0.53, 42.44; OR 1.57, 95% CrI 0.37, 38.00, respectively). The SUCRA rankings of the former were 26% MBI, 66% MFI, 79% RAHI, and 28% VI, while that of the latter were 9%, 46%, 57%, and 89%, respectively. The overall heterogeneity of the four complications was zero (I^2 = 0%). Similarly, pooled network meta-analysis did not

TABLE 3 Risk of bias of one RCT with Cochrane Collaboration tools.

Risk of bias	Li et al., 2020, China
Random sequence generation (selection bias)	Quote: "Patients meeting the inclusion criteria were randomly divided into three incision groups by lottery" Method of random sequence generation can produce comparison groups.
Allocation concealment (selection bias)	Impossible due to nature of surgery and peroperative consent.
Blinding of participants and personnel (performance bias)	Impossible due to nature of surgery and peroperative consent.
Blinding of outcome assessme (detection bias)	Impossible due to nature of surgery and peroperative consent.
Incomplete outcome data (attrition bias)	There was no incomplete or missing data.
Selective reporting (reporting bias)	Consistency between outcome measure in methods and results.
Other bias	There were no other sources of bias

Red, yellow and green correspond to a high risk, unknown risk and low risk of bias, respectively.

demonstrate statistically significant ORs comparing MBI vs. RAHI, MBI vs. VI, MFI vs. RAHI, MFI vs. VI, and RAHI vs. VI in terms of transient facial palsy (OR 1.37, 95% CrI 0.60, 4.00; OR 1.23, 95% CrI 0.50, 4.17; OR 0.69, 95% CrI 0.30, 1.96; OR 0.62, 95% CrI 0.25, 2.13; OR 0.75, 95% CrI 0.26, 3.45, respectively). In contrast, MFI was associated with a statistically significant lower facial palsy compared to MBI (OR, 1.92; 95% CrI, 1.22, 2.94). The SUCRA rankings were 15% for MBI, 82% for MFI, 55% for RAHI, and 49% for VI. Overall heterogeneity was low (I^2 = 0). Finally, meta-analysis of pooled networks showed similar MDs in terms of tumor size when comparing MBI vs. MFI (MD -0.01; 95% CrI -3.44, 3.39), MBI vs. RAHI (MD -0.26; 95% CrI -5.04, 4.71), MFI vs. RAHI (MD -0.24; 95% CrI -4.90, 4.61) and RAHI vs. VI (MD 5.41; 95% CrI -0.28, 10.73). However, MBI vs. VI (MD 5.15; 95% CrI 0.76, 9.38), and MFI vs. VI (MD 5.16; 95% CrI 0.34, 9.86) were significant. The SUCRA rankings were 36% for MBI, 35% for MFI, 31% for RAHI, and 98% for VI. Overall heterogeneity was low (I^2 = 4).

3.4 Validation and evaluation of models and results

The model fit using the diagnostic approach described in the methodology was good, and there was no evidence that any results were non-MCMC convergent. Furthermore, the node-splitting method did not exhibit any local inconsistencies. By comparing the adjusted funnel plots, no publication bias was observed in operation time, transient facial palsy, permanent facial palsy, or salivary gland complications; however, publication bias was found regarding the incision satisfaction score and Frey syndrome. Funnel plots were not drawn for the other outcomes because fewer than 10 studies were included. The GRADE rating results are listed in Table 7. The quality of evidence was rated as very low in most comparisons.

4 Discussion

This is the first systematic review and network meta-analysis to compare the surgical outcomes and complications of four major parotidectomy incisions. There were no significant differences in operation time, drainage volume, or permanent facial palsy. Similarly, no differences were found in salivary complications, wound infection, hematoma, or Frey syndrome. The incision satisfaction score was statistically significant in the comparison between the VI and MBI. Moreover, the VI had a smaller tumor size than MBI and MFI, and MFI had a significantly lower risk of transient facial palsy than MBI.

Generally, the following considerations govern the surgical incision design: full surgical field exposure and operability of lesion resection. Based on the above principles, the traditional Blair incision was gradually established as the most common parotidectomy method after modification. Unfortunately, these S-shaped incisions may leave a visible scar on the face and cause psychological distress (33). People are paying more attention to the requirements of beauty as their quality of life improves, and medical research has begun to investigate the potential for a good aesthetic effect while maintaining safety (5). The outcomes of primary incisions have been widely discussed; however, there has been a lack of convincing evidence on which procedure is optimal. Relevant RCTs and pairwise meta-analyses are few and far between, and previously published observational studies have had inconsistent results, which may be related to heterogeneity in the population and surgical technique. We performed a comprehensive Bayesian network meta-analysis to compare the outcomes of major surgical incisions in parotidectomy.

Scarring after parotidectomy is estimated to be between 54% and 60% based on prior research (34, 35). Traditional MBI incisions inevitably leave scarring on the face and neck, and numerous studies have noted significant patient dissatisfaction with scarring, which affects long-term quality of life (36). Although some techniques, such as skin flap and fascia

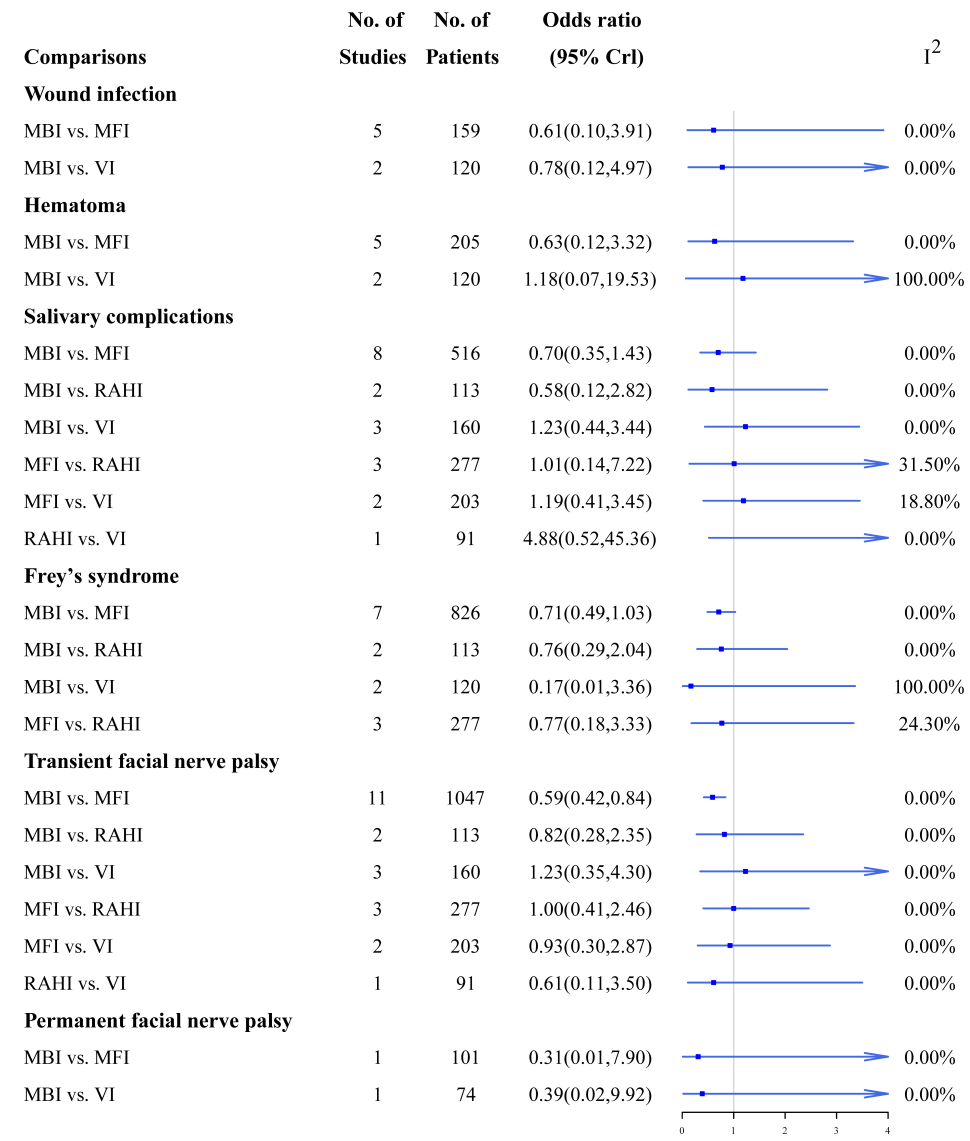

FIGURE 4
A direct comparison forest map of dichotomous outcomes.

reconstruction, can help prevent this issue, locating a better concealed incision can also help lessen the cosmetic negative impacts of scars (37). The novel VI, consisting of only anterior and posterior auricular incisions, has shown good cosmetic results in some previous studies (27, 31, 38). Similarly, based on the results of the SUCRA, our study rated VI as an approach with a higher incision satisfaction score and found it significantly superior to MBI. Furthermore, VI was significantly associated with tumor size when compared with MBI and MFI, indicating that tumor size is one of the parameters used by surgeons to choose surgical incisions. However, SUCRA data revealed that VI required the most operation time and MBI the least, despite no statistically significant difference between the four incisions. This might be attributed to a higher level of mastery of classical procedures; therefore, as proficiency increases, the surgical times for emerging incisions can be expected to decrease.

Owing to the substantial blood supply in the parotid gland region, much of the leaking blood, as well as saliva released by the remaining gland, would be collected in the cavity generated following parotidectomy (39). The presence of these fluids can cause complications such as seroma, and head and neck wounds should be drained with a drainage tube, according to the national consensus (39). Excessive drainage flow is likely to cause complications, such as infection and salivary fistula,

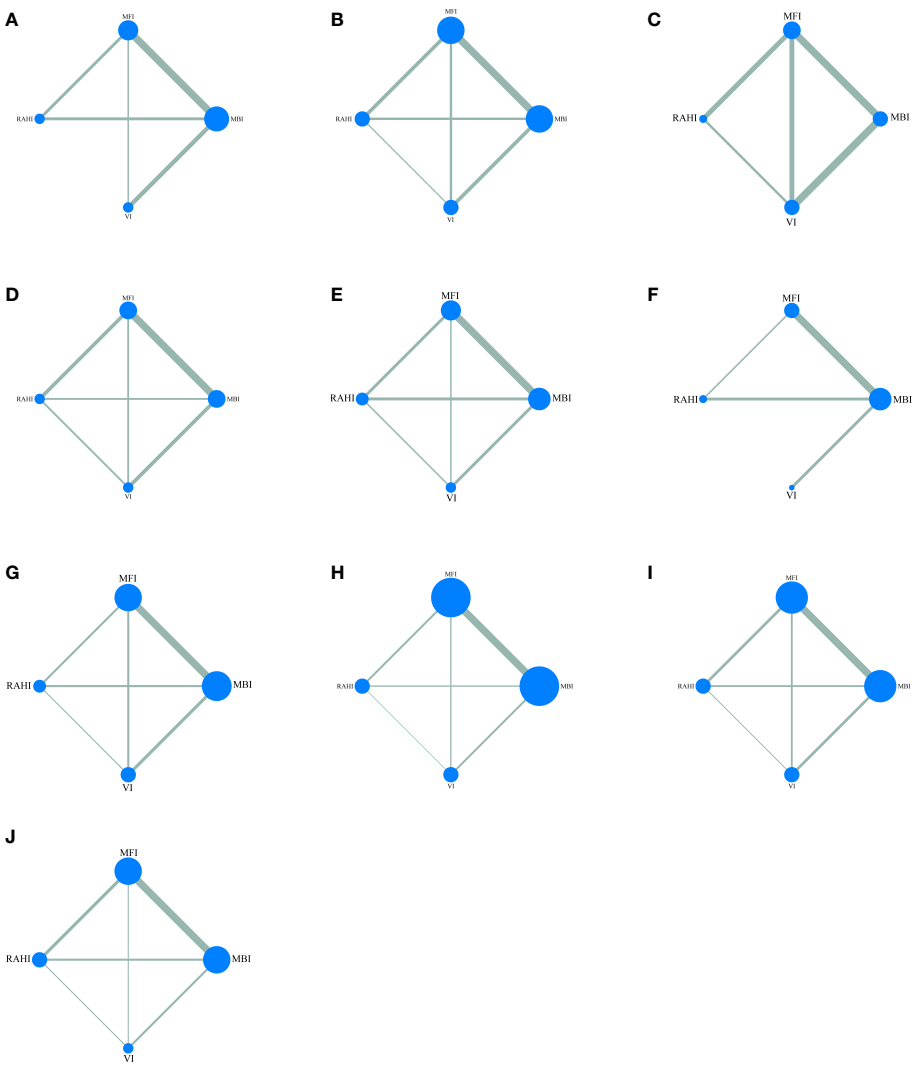

FIGURE 5
Network maps of all outcomes: **(A)** incision satisfaction score, **(B)** operation time, **(C)** drainage volume, **(D)** tumor size, **(E)** hematoma, **(F)** wound infection, **(G)** permanent facial palsy, **(H)** transient facial palsy, **(I)** salivary complications, **(J)** Frey syndrome.

resulting in prolonged hospital stays and increased medical costs (40). Notably, although there was no statistically significant difference in drainage volume between the four types of incisions, the RAHI was classified in the SUCRA ranking as the incisions with the least drainage.

Transient facial palsy is the most frequent early complication of parotidectomy (41). Permanent facial palsy after parotidectomy is the most serious complication that affects patients' quality of life. According to previous studies, the incidences of early transient facial palsy and long-term permanent facial palsy are 42-45% and 0-3.9%, respectively (34, 35). With the gradual standardization of parotid surgery for the dissection and protection of facial nerves, and the wide application of intraoperative facial nerve monitoring, the incidence of facial paralysis has been greatly reduced; this in turn reduces the difference in the incidence of facial paralysis caused by different incisions (42, 43). In this review, the SUCRA results showed that conventional MBI had the highest risk of facial palsy. Furthermore, MBI's SUCRA ranking in complications such as hematoma, wound infection, and salivary gland damage remained low, although the difference was not statistically significant in the pooled comparison results.

Frey syndrome occurs in 4-62% of patients 6 to 18 months after parotidectomy and is characterized by gustatory sweating and flushing (44). The incidence of Frey syndrome was documented in 12 of the included studies; however, none of these studies described the use of objective methods for diagnosis, which may result in the reported incidence being lower than the true value (45). A number of surgical techniques have been described to prevent this complication, and studies

10.3389/fonc.2022.972498

TABLE 4 League table of primary outcomes.

MBI				**A**
-0.76 (-2.19,0.66)	**MFI**			
-1.95 (-4.08,0.17)	-1.18 (-3.30,0.93)	**RAHI**		
-2.47 (-4.51,-0.43)	-1.70 (-4.04,0.62)	-0.52 (-3.39,2.35)	**VI**	
MBI				B
-1.67 (-11.49,10.39)	**MFI**			
-0.40 (-13.52,14.08)	1.30 (-12.60,14.16)	**RAHI**		
-3.53 (-17.91,9.81)	-1.86 (-18.42,11.48)	-3.12 (-21.20,12.57)	**VI**	
MBI				C
-3.22 (-15.16,5.55)	**MFI**			
7.54 (-13.56,22.30)	10.99 (-6.35,24.47)	**RAHI**		
0.36 (-10.68,11.63)	3.67 (-7.12,17.53)	-7.15 (-22.19,14.14)	**VI**	
MBI				D
1.04 (0.30,7.49)	**MFI**			
0.56 (0.11,25.13)	0.37 (0.07,18.85)	**RAHI**		
0.60 (0.13,11.98)	0.36 (0.07.10.17)	0.15 (0.03,20.62)	**VI**	

Values of A, B, and C are expressed as mean difference (MD) and 95% credible intervals (95% CrI).
Values of D is expressed as odds ratio (OR) and 95% credible intervals (95% CrI).
A incision satisfaction score, B operation time, C drainage volume, D permanent facial palsy.
The bold values indicate that the comparison between the two is statistically significant.

TABLE 5 League table of secondary outcomes.

MBI				**Tumor size**
-0.01(-3.44,3.39)	**MFI**			
-0.26 (-5.04,4.71)	-0.24(-4.90,4.61)	**RAHI**		
5.15(0.76,9.38)	**5.16(0.34,9.86)**	5.41(-0.28,10.73)	**VI**	
MBI				**Hematoma**
1.22(0.35,9.09)	**MFI**			
0.52(0.10,33.33)	0.28(0.05,16.67)	**RAHI**		
0.33(0.07,12.50)	0.15(0.03,9.09)	0.08(0.02,16.67)	**VI**	
MBI				**Wound infection**
0.84(0.21,10.13)	**MFI**			
0.26(0.07,98.14)	0.10(0.04,80.26)	**RAHI**		
0.12(0.09,17,69)	0.03(0.04,22.54)	0.001(0.01,49.00)	**VI**	
MBI				**Transient facial palsy**
1.92(1.22,2.94)	**MFI**			
1.37(0.60,4.00)	0.69(0.30,1.96)	**RAHI**		
1.23(0.50,4.17)	0.62(0.25,2.13)	0.75(0.26,3.45)	**VI**	
MBI				**Salivary complications**
1.36(0.73,2.83)	**MFI**			
1.60(0.59,6.56)	1.11(0.42,4.62)	**RAHI**		
0.86(0.37,2.57)	0.59(0.25,1.85)	0.39(0.12,1.99)	**VI**	
MBI				**Frey syndrome**
1.41(0.77,2.63)	**MFI**			
1.57(0.66,5.17)	1.06(0.45,3.55)	**RAHI**		
3.11(0.80,62.03)	2.08(0.53,42.44)	1.57(0.37,38.00)	**VI**	

The bold values indicate that the comparison between the two is statistically significant.

TABLE 6 SUCRA of secondary outcomes.

Outcomes (%)Incisions	MBI	MFI	RAHI	VI
tumor size	36	35	31	98
hematoma	40	67	56	37
wound infection	37	54	60	49
transient facial palsy	15	82	55	49
salivary complications	26	66	79	28
Frey syndrome	9	46	57	89

The smaller the tumor size, the greater the SUCRA value.
The lower the incidence of adverse outcomes, the higher the SUCRA value.

TABLE 7 Quality of evidence for outcomes based on the GRADE method.

Outcomes	Comparison	Study limitations	Imprecision	Inconsistency	Indirectness	Quality of evidence
incision satisfaction score	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	No downgraded	No downgraded	No downgraded	Low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	Downgraded	Very low
operation time	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
drainage volume	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	Downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
permanent facial nerve palsy	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
tumor size	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	No downgraded	No downgraded	No downgraded	Low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	No downgraded	No downgraded	No downgraded	Low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
hematoma	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low

(Continued)

TABLE 7 Continued

Outcomes	Comparison	Study limitations	Imprecision	Inconsistency	Indirectness	Quality of evidence
wound infection	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	Downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	Downgraded	Very low
transient facial palsy	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
salivary complications	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
Frey syndrome	MBI vs. MFI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MBI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. RAHI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	MFI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low
	RAHI vs. VI	Downgraded	Downgraded	No downgraded	No downgraded	Very low

Based on all the above information, we GRADEd each network estimate according to the following criteria.
(1) Study limitations: We downgraded by evidence at high risk of bias.
(2) Imprecision: We considered a clinically meaningful threshold for OR to be 0.80 or 1.25 and downgraded the estimate if the OR point estimate is 1 or more and the lower limit of its CrI is below 0.80; or if the OR point estimate is less than 1 and the upper limit of its CrI is above 1.25. We downgraded when the CrI of MD included zero between the upper and lower CrI limits.
(3) Inconsistency: We looked at the results of node-splitting and we downgraded the comparisons with important inconsistency ($p<0.05$), where we have not downgraded for imprecision.
(4) Indirectness: We downgraded singly-connected nodes for indirectness because evaluation of transitivity for such nodes is unclear.
(5) Publication bias: Publication bias could not be assessed as there were <10 trials available for each of the comparisons.

have attempted to determine the best way to reduce its incidence (46). Studies have shown that the size of the parotid gland tumor affects the incidence of Frey syndrome, which is explained by the fact that the less parotid tissue that needs to be dissected, the lower the likelihood of parasympathetic supply disruption (18, 47, 48). This view is seemingly supported by our findings, which shows that the SUCRA ranking of Frey syndrome and tumor size are consistent among the four incisions.

Although our meta-analysis yielded several novel results, it had certain limitations. First, this study contained only one RCT, with the remainder being single-center observational studies with potential selection and reporting bias. Second, two-thirds of the studies were conducted in East Asia, limiting the worldwide generalizability of our findings. Third, there was significant heterogeneity between MBI and the other three incisions in the pairwise meta-analyses. Fourth, some of the primary outcomes were rated as low or very low in evidential strength, based on the GRADE evaluation. Therefore, this may undermine the strength of the current findings. However, it is important to understand that high-quality evidence might be difficult to obtain because grade judgments can be overly cautious (49).

Conclusion

Based on published studies, our network meta-analysis provides updated evidence for the multiple outcomes of MBI, MFI, RAHI, and VI. The most important advantages of VI are good incision satisfaction and better performance in the management of complications. Further randomized controlled trials and complementary outcome data are needed to test the credibility of our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

All the authors worked together to complete the paper. YJ, SY, and CS did the literature search; YJ, SY, and YL formed the study design; Data collection was done by SY, YL, YH, and ZF. SY, ZF, and YL analyzed the data; BC, SS, JW and XW interpreted the data; YJ, SY, and CS wrote the manuscript; YJ, SY, and BC critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This project was supported by applied medicine research project of Hefei Health Committee (hwk2019zc004).

Acknowledgments

We thank the original studies included for providing data for our study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.972498/full#supplementary-material

References

1. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: Results from a population-based study. *Otolaryngol–head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg* (1999) 120(6):834–40. doi: 10.1016/s0194-5998(99)70323-2

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

3. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: A 23-year retrospective study of 6982 cases in an Eastern Chinese population. *Int J Oral Maxillofac Surg* (2010) 39(3):235–42. doi: 10.1016/j.ijom.2009.10.016

4. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined uk population. *Br J Oral Maxillofac Surg* (2013) 51(5):399–403. doi: 10.1016/j.bjoms.2012.10.002

5. Aggarwal V. Incisions for parotidectomy: A narrative review. *Ann Plast Surg* (2021) 87(4):e71–e8. doi: 10.1097/sap.0000000000002757

6. Nouraei SA, Al-Yaghchi C, Ahmed J, Kirkpatrick N, Mansuri S, Singh A, et al. An anatomical comparison of Blair and facelift incisions for parotid surgery. *Clin Otolaryngol Off J ENT-UK ; Off J Netherlands Soc Oto-Rhino-Laryngol Cervico-Facial Surg* (2006) 31(6):531–4. doi: 10.1111/j.1365-2273.2006.01334.x

7. Fiacchini G, Cerchiai N, Tricò D, Sellari-Franceschini S, Casani AP, Dallan I, et al. Frey Syndrome, first bite syndrome, great auricular nerve morbidity, and quality of life following parotidectomy. *Eur Arch oto-rhino-laryngol Off J Eur Fed Oto-Rhino-Laryngol Societies (EUFOS) affiliated German Soc Oto-Rhino-Laryngol - Head Neck Surg* (2018) 275(7):1893–902. doi: 10.1007/s00405-018-5014-4

8. Lee YC, Liao WC, Yang SW, Luo CM, Tsai YT, Tsai MS, et al. Systematic review and meta-analysis of modified facelift incision versus modified Blair incision in parotidectomy. *Sci Rep* (2021) 11(1):24106. doi: 10.1038/s41598-021-03483-6

9. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Res ed)* (2011) 343:d5928. doi: 10.1136/bmj.d5928

10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ (Clinical Res ed)* (2009) 339:b2700. doi: 10.1136/bmj.b2700

11. Brignardello-Petersen R, Murad MH, Walter SD, McLeod S, Carrasco-Labra A, Rochwerg B, et al. Grade approach to rate the certainty from a network meta-analysis: Avoiding spurious judgments of imprecision in sparse networks. *J Clin Epidemiol* (2019) 105:60–7. doi: 10.1016/j.jclinepi.2018.08.022

12. Dias S, Welton NJ, Sutton AJ, Ades AE. Nice decision support unit technical support documents. nice dsu technical support document 2. In: *A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials*. London: National Institute for Health and Care Excellence (NICE (2014).

13. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Nice decision support unit technical support documents. nice dsu technical support document 4. In: *Inconsistency in networks of evidence based on randomised controlled trials*. London: National Institute for Health and Care Excellence (NICE (2014).

14. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J Clin Epidemiol* (2011) 64(2):163–71. doi: 10.1016/j.jclinepi.2010.03.016

15. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A grade working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Res ed)* (2014) 349:g5630. doi: 10.1136/bmj.g5630

16. Terris DJ, Tuffo KM, Fee WEJr. Modified facelift incision for parotidectomy. *J laryngol otol* (1994) 108(7):574–8. doi: 10.1017/s002221510012746x

17. Roh JL. Retroauricular hairline incision for removal of upper neck masses. *Laryngoscope* (2005) 115(12):2161–6. doi: 10.1097/01.Mlg.0000181496.22493.5a

18. Wasson J, Karim H, Yeo J, Panesar J. Cervicomastoidfacial versus modified facelift incision for parotid surgery: A patient feedback comparison. *Ann R Coll Surgeons Engl* (2010) 92(1):40–3. doi: 10.1308/003588410x12518836440009

19. Bianchi B, Ferri A, Ferrari S, Copelli C, Sesenna E. Improving esthetic results in benign parotid surgery: Statistical evaluation of facelift approach, sternocleidomastoid flap, and superficial musculoaponeurotic system flap application. *J Oral Maxillofac Surg* (2011) 69(4):1235–41. doi: 10.1016/j.joms.2010.03.005

20. Lee SY, Koh YW, Kim BG, Hong HJ, Jeong JH, Choi EC. The extended indication of parotidectomy using the modified facelift incision in benign lesions: Retrospective analysis of a single institution. *World J Surg* (2011) 35(10):2228–37. doi: 10.1007/s00268-011-1209-1

21. Zhi KQ, Ren WH, Gao L, Zhao L, Huang S, Li JW, et al. Face-lift incision combined with sternomastoid muscular flap in parotidectomy. *Aesthetic Plast Surg* (2011) 35(4):558–62. doi: 10.1007/s00266-011-9663-6

22. Graciano AJ, Chone CT, Fischer CA. Cervicomastoidfacial versus modified rhytidectomy incision for benign parotid tumors. *Braz J otorhinolaryngol* (2013) 79 (2):168–72. doi: 10.5935/1808-8694.20130030

23. Kim DY, Park GC, Cho YW, Choi SH. Partial superficial parotidectomy *Via* retroauricular hairline incision. *Clin Exp otorhinolaryngol* (2014) 7(2):119–22. doi: 10.3342/ceo.2014.7.2.119

24. Bulut OC, Plinkert P, Federspil PA. Modified facelift incision for partial parotidectomy versus bayonet-shaped incision: A comparison using visual analog scale. *Eur Arch Oto-Rhino-Laryngol* (2016) 273(10):3269–75. doi: 10.1007/s00405-015-3878-0

25. Wu PA, Lu ZQ, Guan YF, Zhu HL, Liang XN, Liang WY, et al. [Application of functional parotidectomy *Via* retroauricular hairline incision in the excising superficial parotid tumor]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* (2017) 52(12):905–8. doi: 10.3760/cma.j.issn.1673-0860.2017.12.006

26. Xu ZJ, Chen LS, Zhan JD, Xu MM, Zhang B, Huang SL, et al. [Modified rhytidectomy incision and modified Blair incision contrast research in superficial parotid gland tumor resection]. *Lin chuang er bi yan hou tou jing wai ke za zhi = J Clin otorhinolaryngol head Neck Surg* (2017) 31(21):1684–7. doi: 10.13201/j.issn.1001-1781.2017.21.015

27. Zheng ZW, Li J, Wang JB, Sun J. Hidden scar dissection of benign parotid gland tumors *Via* a V-shaped minimal facelift incision. *J Craniofacial Surg* (2018) 29(8):2299–303. doi: 10.1097/scs.0000000000004670

28. Ahn DB, Lee GJ, Sohn JH. Individualized use of facelift, retroauricular hairline, and V-shaped incisions for parotidectomy. *J Oral Maxillofac Surg* (2020) 78(12):1–7. doi: 10.1016/j.joms.2020.08.021

29. Li MM, Li SS, Tang QL, Yang XM, He XB. Feasibility and efficacy of partial superficial parotidectomy with V-shaped incision. *Zhonghua er bi yan hou tou jing wai ke za zhi [Chinese J otorhinolaryngol Head Neck surgery]* (2020) 55(7):658–63. doi: 10.3760cma.j.cn115330-20191109-00678

30. Chen F, Li Y, Ke X, Wu PF, Guo LY, Lei ZG, et al. Application analysis of a modified retroauricular hairline incision in the resection of a benign parotid gland tumor. *Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi = West China J stomatol* (2021) 39(3):293–9. doi: 10.7518/hxkq.2021.03.008

31. Jo MG, Lee DJ, Cha W. A modified V-shaped incision combined with superficial musculo-aponeurotic system flap for parotidectomy. *Acta oto-laryngol* (2019) 139(2):178–83. doi: 10.1080/00016489.2018.1562216

32. Matsumoto F, Ohba S, Fujimaki M, Kojima T, Sakyo A, Kojima M, et al. Efficacy of modified face lift incision for the resection of benign parotid gland tumor located anteriorly or superiorly. *Auris nasus larynx* (2021) 48(5):978–82. doi: 10.1016/j.anl.2021.01.014

33. Kaya BV, Kılıç C, Özlügedik S, Tuncel Ü, Cömert E. Long-term effects of parotidectomy. *Eur Arch oto-rhino-laryngol Off J Eur Fed Oto-Rhino-Laryngol Societies (EUFOS) affiliated German Soc Oto-Rhino-Laryngol - Head Neck Surg* (2016) 273(12):4579–83. doi: 10.1007/s00405-016-4173-4

34. Gaillard C, Périé S, Susini B, St Guily JL. Facial nerve dysfunction after parotidectomy: The role of local factors. *Laryngoscope* (2005) 115(2):287–91. doi: 10.1097/01.mlg.0000154735.61775.cd

35. Mehle ME, Kraus DH, Wood BG, Benninger MS, Eliachar I, Levine HL, et al. Facial nerve morbidity following parotid surgery for benign disease: The Cleveland clinic foundation experience. *Laryngoscope* (1993) 103(4 Pt 1):386–8. doi: 10.1002/lary.5541030404

36. Lambiel S, Dulguerov N, Courvoisier DS, Dulguerov P. Minor parotidectomy complications: A systematic review. *Laryngoscope* (2021) 131 (3):571–9. doi: 10.1002/lary.28912

37. Dell'aversana Orabona G, Salzano G, Petrocelli M, Iaconetta G, Califano L. Reconstructive techniques of the parotid region. *J craniofacial Surg* (2014) 25 (3):998–1002. doi: 10.1097/scs.0000000000000664

38. Ahn D, Sohn JH, Lee GJ. Feasibility of a new V-shaped incision for parotidectomy: A preliminary report. *Br J Oral Maxillofac Surg* (2018) 56 (5):406–10. doi: 10.1016/j.bjoms.2018.03.014

39. Chen WC, Chuang HC, Su YY, Chien CY. Predictive factors for post-operative drainage after partial superficial parotidectomy: A case-control study. *J laryngol otol* (2015) 129(10):1020–4. doi: 10.1017/s002221511500211x

40. Woods RS, Woods JF, Duignan ES, Timon C. Systematic review and meta-analysis of wound drains after thyroid surgery. *Br J Surg* (2014) 101(5):446–56. doi: 10.1002/bjs.9448

41. Venkatesh S, Srinivas T, Hariprasad S. Parotid gland tumors: 2-year prospective clinicopathological study. *Ann Maxillofac Surg* (2019) 9(1):103–9. doi: 10.4103/ams.ams_179_18

42. Brennan J, Moore EJ, Shuler KJ. Prospective analysis of the efficacy of continuous intraoperative nerve monitoring during thyroidectomy, parathyroidectomy, and parotidectomy. *Otolaryngol–head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg* (2001) 124(5):537–43. doi: 10.1067/mhn.2001.115402

43. Sood AJ, Houlton JJ, Nguyen SA, Gillespie MB. Facial nerve monitoring during parotidectomy: A systematic review and meta-analysis. *Otolaryngol–head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg* (2015) 152(4):631–7. doi: 10.1177/0194599814568779

44. Motz KM, Kim YJ. Auriculotemporal syndrome (Frey syndrome). *Otolaryngol Clinics North America* (2016) 49(2):501–9. doi: 10.1016/j.otc.2015.10.010

45. Neumann A, Rosenberger D, Vorsprach O, Dazert S. [the incidence of Frey syndrome following parotidectomy: Results of a survey and follow-up]. *Hno* (2011) 59(2):173–8. doi: 10.1007/s00106-010-2223-6

46. De Virgilio A, Costantino A, Russo E, Ferreli F, Pellini R, Petruzzi G, et al. Different surgical strategies in the prevention of Frey syndrome: A systematic review and meta-analysis. *Laryngoscope* (2021) 131(8):1761–8. doi: 10.1002/lary.29414

47. Myssiorek D. Removal of the inferior half of the superficial lobe is sufficient to treat pleomorphic adenoma in the tail of the parotid gland. *Arch otolaryngol–head Neck Surg* (1999) 125(10):1164–5. doi: 10.1001/archotol.125.10.1164

48. Gordon AB, Fiddian RV. Frey's syndrome after parotid surgery. *Am J Surg* (1976) 132(1):54–8. doi: 10.1016/0002-9610(76)90290-7

49. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PloS One* (2014) 9:1–7. doi: 10.1371/journal.pone.0099682

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 08 August 2022
DOI 10.3389/fonc.2022.915020

OPEN ACCESS

EDITED BY
Giuseppe Cardillo,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Mingran XIE,
USTC Life Sciences and Medicine, China
Hyun Koo Kim,
Korea University Guro Hospital, South Korea

*CORRESPONDENCE
Hui Tian
tianhuiql@email.sdu.edu.cn

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 07 April 2022
ACCEPTED 30 June 2022
PUBLISHED 08 August 2022

CITATION
Li R, Qiu J, Qu C, Ma Z, Wang K, Zhang Y, Yue W and Tian H (2022) Comparison of perioperative outcomes with or without routine chest tube drainage after video-assisted thoracoscopic pulmonary resection: A systematic review and meta-analysis.
Front. Oncol. 12:915020.
doi: 10.3389/fonc.2022.915020

Comparison of perioperative outcomes with or without routine chest tube drainage after video-assisted thoracoscopic pulmonary resection: A systematic review and meta-analysis

Rongyang Li†, Jianhao Qiu†, Chenghao Qu, Zheng Ma, Kun Wang, Yu Zhang, Weiming Yue and Hui Tian*

Department of Thoracic Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, China

Background: In recent years, an increasing number of thoracic surgeons have attempted to apply no routine chest tube drainage (NT) strategy after thoracoscopic lung resection. However, the safety and feasibility of not routinely placing a chest tube after lung resection remain controversial. This study aimed to investigate the effect of NT strategy after thoracoscopic pulmonary resection on perioperative outcomes.

Methods: A comprehensive literature search of PubMed, Embase, and the Cochrane Library databases until 3 January 2022 was performed to identify the studies that implemented NT strategy after thoracoscopic pulmonary resection. Perioperative outcomes were extracted by 2 reviewers independently and then synthesized using a random-effects model. Risk ratio (RR) and standardized mean difference (SMD) with 95% confidence interval (CI) served as the summary statistics for meta-analysis. Subgroup analysis and sensitivity analysis were subsequently performed.

Results: A total of 12 studies with 1,381 patients were included. The meta-analysis indicated that patients in the NT group had a significantly reduced postoperative length of stay (LOS) (SMD = -0.91; 95% CI: -1.20 to -0.61; P < 0.001) and pain score on postoperative day (POD) 1 (SMD = -0.95; 95% CI: -1.54 to -0.36; P = 0.002), POD 2 (SMD = -0.37; 95% CI: -0.63 to -0.11; P = 0.005), and POD 3 (SMD = -0.39; 95% CI: -0.71 to -0.06; P = 0.02). Further subgroup analysis showed that the difference of postoperative LOS became statistically insignificant in the lobectomy or segmentectomy subgroup (SMD = -0.30; 95% CI: -0.91 to 0.32; P = 0.34). Although the risk of pneumothorax was significantly higher in the NT group (RR = 1.75; 95% CI: 1.14–2.68; P = 0.01), the reintervention rates were comparable between groups (RR = 1.04; 95% CI: 0.48–2.25; P = 0.92). No significant difference was found in pleural effusion,

subcutaneous emphysema, operation time, pain score on POD 7, and wound healing satisfactory (all P > 0.05). The sensitivity analysis suggested that the results of the meta-analysis were stabilized.

Conclusions: This meta-analysis suggested that NT strategy is safe and feasible for selected patients scheduled for video-assisted thoracoscopic pulmonary resection.

Systematic Review Registration: https://inplasy.com/inplasy-2022-4-0026, identifier INPLASY202240026.

KEYWORDS

no routine chest tube drainage strategy, traditional chest tube drainage, video-assisted thoracoscopic lung resection, perioperative outcomes, systematic review, meta-analysis

Introduction

Lung cancer is the fastest-growing malignancy worldwide in morbidity and mortality, the most common cause of cancer death in men and the second leading cause of cancer death in women (1). Due to the popularization of low-dose computed tomography (CT) screening, the rate of detection of small pulmonary nodules (especially ground-glass nodules) has significantly increased in recent years, which makes early diagnosis and treatment of lung cancer more challenging (2, 3). With the rapid development of minimally invasive techniques, traditional thoracotomy has been transformed into video-assisted thoracoscopic surgery (VATS) with less risk to patients (4, 5). In general, a chest tube is routinely placed in the pleural cavity to mitigate against possible air leaks, hemorrhage, and chylothorax after VATS (6). However, some side effects of chest tube insertion are still difficult to avoid, such as increased postoperative pain and hindrance to postoperative activity, which could impede patient functional rehabilitation and significantly prolong postoperative length of stay (LOS) (7, 8).

Enhanced recovery after surgery (ERAS) is a multimodal perioperative management strategy first proposed by Dr. Engelman in 1994 in order to reduce postoperative pain, promote patients' recovery, reduce the cost of hospitalization, and shorten the length of hospital stay (9). In recent years, this multidisciplinary perioperative rehabilitation concept has been widely applied in thoracic surgery with satisfactory results (10). An increasing number of thoracic surgeons, in order to promote the idea of ERAS, have attempted to apply no routine chest tube drainage (NT) strategy after thoracoscopic lung resection (11, 12). However, the increased incidence of postoperative pneumothorax and poor recruitment of the lungs are the main issues caused by the NT strategy (13).

Although several centers have conducted studies to explore the effect of NT strategy for thoracoscopic pulmonary resection in recent years, the safety and feasibility of not routinely placing a chest tube after lung resection remain controversial. A meta-analysis performed by Li et al. (14), including 6 retrospective and 3 prospective cohort studies, demonstrated that it was feasible and safe to omit chest tube after VATS for carefully selected patients. However, inappropriate inclusion criteria and relatively small sample sizes may introduce considerable bias, thereby reducing the reliability of the results. In addition, the perioperative outcomes that they reported were not comprehensive enough. To arrive at a more substantial conclusion, we aimed to conduct a systematic review and meta-analysis to determine the effect of NT strategy after thoracoscopic pulmonary resection on perioperative outcomes.

Materials and methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and statement (15, 16). The protocol of this systematic review and meta-analysis has been registered on the INPLASY website (https://inplasy.com/inplasy-2022-4-0026); the registration number is INPLASY202240026.

Databases and search strategy

The literature review was performed by relying on 3 online databases: PubMed, Embase, and the Cochrane Library until 3

January 2022. The Medical Subject Headings (MeSH) considered in the search strategy were "pulmonary neoplasms," "thoracoscopic," and "chest tube," free of charge terms accessed in PubMed. Keywords and free words are used in each valid combination of the 2 Boolean operators ("AND" and "OR"). Search strategies for all databases are detailed in Table S1. Articles were individually evaluated and cross-checked by 2 authors (RL and JQ). In addition, we manually scanned the reference list of excluded publications to indicate any additional viable non-duplicate studies. Any differences between the reviewers are resolved through discussion.

Study selection and criteria

The selection criteria were as follows: 1) involved adult patients who underwent selective thoracoscopic pulmonary resection (wedge resection, segmentectomy, and lobectomy); 2) involved a group that implemented NT strategy, including prophylactic air-extraction catheter insertion procedure (PC) or complete omission of chest tube drainage (OT); 3) involved a routine chest tube drainage (RT) group as control; 4) reported at least one of the relevant outcomes of interests (see below); 5) written in English.

The criteria for exclusion were as follows: 1) ineligible article types such as case reports, reviews, conference abstracts, non-comparative studies; 2) no results of interest existed; 3) non-human participants were included; 4) written in languages other than English.

Endpoints and outcome measures

The primary outcome was postoperative LOS, which was defined as the time from surgery to recovery and discharge. Other related outcomes included operation duration, postoperative complications (including pneumothorax, pleural effusion, and subcutaneous emphysema), reintervention rates, postoperative pain scores, and wound healing satisfaction. Reintervention was defined as chest tube reinsertion or thoracentesis.

Data collection

The 2 reviewers (RL and JQ) independently browsed eligible studies and extracted the corresponding data to fill in predefined forms. Any differences could be resolved by consensus. The following data were extracted from each study: 1) publication data: authors, published year, and country; 2) experimental data: study design and period, surgical procedure, and NT strategy; 3) demographic data: sample size, age, and gender; 4) outcome data: postoperative LOS, operation duration, postoperative complications in detail, postoperative pain score, postoperative reintervention rate, and wound healing satisfaction. We did not contact the authors for any unpublished data.

Quality assessment

The quality of cohort studies was evaluated using the Newcastle–Ottawa Quality Assessment Scale (NOS) (17). We determined that studies with a score comparable to or higher than 6 were applicable to further meta-analysis. The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials (RCTs) (18). Due to the nature of the interventions associated with the NT strategy, it is often not feasible to blind patients and staff. Therefore, if a study does not address blinding, a high risk of performance bias is assumed. The quality of each study was independently appraised by two investigators (RL and JQ). Any disagreement on quality assessment should be resolved by consensus.

Statistical analysis

We calculated the risk ratio (RR) with 95% confidence interval (CI) to summarize the effects of NT strategy on dichotomous data. The standardized mean difference (SMD) with 95% CI appeared as the suitable statistics to summarize the mean values with standard deviations (SDs) for continuous variables. If the SDs were not provided, we would not incorporate the data in the quantitative synthesis because the extrapolation of SDs was only applicable for studies with a large sample size and normal distribution of outcomes due to the guidelines of the Cochrane Collaboration (18).

The Cochrane Q test and I^2 statistics were used to quantify the heterogeneity level. An I^2 greater than 50% is considered to have considerable heterogeneity (19). A 2-sided P value <0.05 was defined as statistical significance. In our study, random-effects models were applied to calculate pooled effect sizes in order to decrease possible bias. Egger's test was used to detect any probable publication bias (20), and a significant publication bias was identified if Egger's $P < 0.05$.

A sensitivity analysis was performed to further examine the stability of pooled estimates, in which the impact of each study on the overall estimates could be detected by omitting individual studies sequentially. In order to evaluate the effect of NT strategy on postoperative recovery for different surgical methods, a meta-analysis of postoperative LOS was then performed on 2 subgroups: wedge resection and segmentectomy or lobectomy.

All statistical analyses were conducted using the Review Manager software (RevMan version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Stata software (version 14.2; StataCorp LLC, College Station, TX, USA).

Results

Literature search

A flowchart outlining the search process was presented in Figure 1. A total of 2,283 potential articles were identified, including 732 PubMed citations, 1,333 Embase citations, and 218 Cochrane Library citations. In addition, manual searches of the literature in the reference list also yielded 5 relevant studies. After checking for duplicates and screening titles, abstracts, and full text, a total of 12 articles were finally included in our meta-analysis (21–32).

Characteristics of the included studies

Baseline characteristics of each eligible study were summarized in Table 1, and the perioperative outcomes were presented in Tables 2–4. This meta-analysis involved 9 retrospective cohort studies (22–26, 28–30, 32), 1 prospective cohort study (27), and 2 RCTs (21, 31). The studies were conducted in 3 different countries during the period from 1998 to 2020, and the sample size varied from 50 to 333. A total of 1,381 patients eventually entered the meta-analysis, of which 764 patients were finally assigned to the NT group and 615 patients to the RT group. Approximately half of the participants were from China (n = 701; 50.8%), followed by 621 patients from Japan (45.0%) and 59 patients from the United States (4.3%). In terms of surgical methods, 1,169 cases underwent wedge pulmonary resection; the other 212 patients received segmentectomy or lobectomy.

Quality assessment

The quality assessment of the included RCTs and cohort studies was presented in Figure S1 and Table S2, respectively. The NOS scores of the 10 included cohort studies were all greater than 6, suggesting that they were all of acceptable quality. As for the other 2 included RCTs, all of them presented a high risk of performance and detection bias due to the nature of the interventions associated with the NT strategy. No other risk of bias was found.

Postoperative length of stay

All of the 12 eligible studies investigated the effect of NT strategy on the length of postoperative hospital stay. The meta-analysis

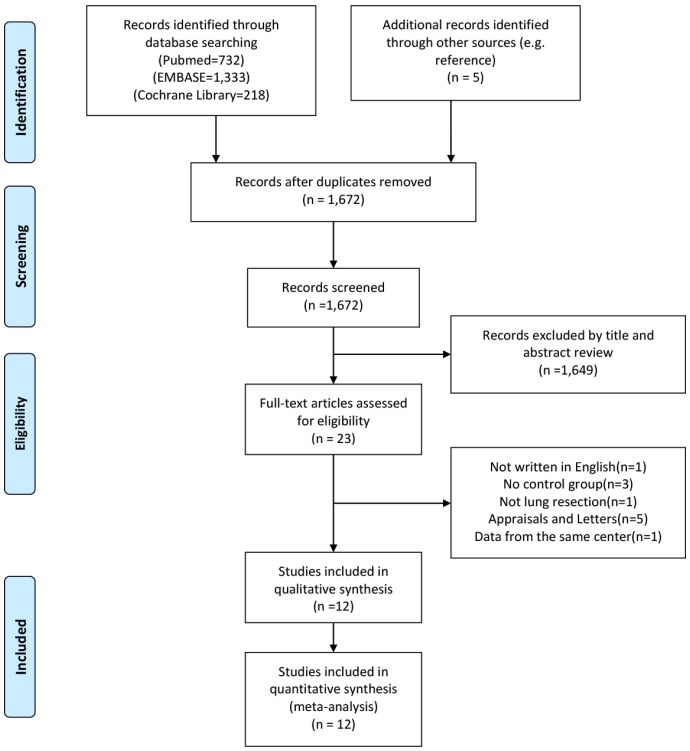

FIGURE 1
PRISMA flow diagram of literature retrieval. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1 Baseline characteristics of the included studies.

Study (year)	Country	Study Period	Study type	No. of Patients			Age (years)		Gender (male ratio)		Surgical Procedure	NT Strategy
				Total	NT	RT	NT	RT	NT	RT		
Zhang et al., 2020 (31)	China	2017-2018	RCT	84	40	44	53.7 ± 11.5	54.4 ± 11.7	15 (37.5)	16 (36.4)	Wedge resection	PC
Liu Z et al., 2020 (23)	China	2018-2019	RCS	110	55	55	44.8 ± 11.1	45.1 ± 10.5	23 (41.8)	24 (43.6)	Wedge resection	OT
Liu C et al., 2020 (22)	China	2016-2019	RCS	135	122	13	47.8 ± 20.1	46.3 ± 19.1	65 (55.3)	12 (92.3)	Wedge resection	OT
Liao et al., 2019 (21)	China	2016-2017	RCT	100	50	50	52.4 ± 10.9	54.9 ± 10.1	6 (12.0)	7 (14.0)	Wedge resection	OT
Zhang et al., 2018 (32)	China	2015-2017	RCS	123	87	36	54 (28–81)	52 (16–82)	40 (46.0)	12 (33.3)	Wedge resection	PC/OT
Murakami et al., 2017 (25)	Japan	2012-2014	RCS	162	102	60	69.4 ± 10.6	71.3 ± 9.9	49 (47.1)	39 (65.0)	Lobectomy; Segmentectomy	OT
Lu et al., 2017 (24)	China	2013-2015	RCS	89	44	45	54.1 ± 12.9	57.0 ± 16.3	21 (47.7)	21 (46.7)	Wedge resection	OT
Yang et al., 2016 (30)	China	2015-2016	RCS	60	30	30	55.5 ± 8.4	59.4 ± 12.3	23 (76.7)	23 (76.7)	Wedge resection	OT
Ueda et al., 2013 (28)	Japan	2011-2012	RCS	50	29	21	71.7 ± 9.6	72.4 ± 11.2	13 (44.8)	16 (76.2)	Lobectomy; segmentectomy	OT
Nakashima et al., 2011 (26)	Japan	2000-2009	RCS	333	132	201	56 ± 15	55 ± 19	67 (50.8)	137 (68.2)	Wedge resection	OT
Watanabe et al., 2004 (29)	Japan	1998-2002	RCS	76	42	34	55 ± 15	53 ± 17	20 (47.6)	21 (61.8)	Wedge resection	OT
Russo et al., 1998 (27)	USA	1995-1997	PCS	59	31	26	61 (24–82)	62 (26–76)	16 (48.5)	13 (50.0)	Wedge resection	OT

NT, no routine chest tube drainage; RT, routine chest tube drainage; PC, prophylactic air-extraction catheter insertion procedure; OT, complete omission of chest tube drainage; USA, The United States of America; RCT, randomized controlled trial; RCS, retrospective cohort study; PCS, prospective cohort study; NR, not reported.

indicated that postoperative LOS was shorter in the NT group (SMD = -0.91; 95% CI: -1.20 to -0.61; P < 0.001) with a considerable heterogeneity (I^2 = 83%; P < 0.001), as shown in Figure 2A. No publication bias was found using Egger's test (P = 0.196).

Further subgroup analysis were performed to evaluate the effect of NT strategy on postoperative recovery for different surgical methods. According to the different surgical procedures, the patients were divided into two subgroups: wedge resection

TABLE 2 Perioperative outcomes of the included studies.

Study (year)	Postoperative LOS (d)		Operation duration (min)		Reintervention (%)		Overall postoperative complications (%)		Wound healing satisfaction (%)	
	NT	RT	NT	RT	NT	RT	NT	RT	NT	RT
Zhang et al., 2020 (31)	2.5 ± 1.5	3.2 ± 2.1	60 (50–80)	60 (50–88)	0	1 (2.3)	NR	NR	38 (95.0)	38 (86.4)
Liu Z et al., 2020 (23)	1.5 ± 0.5	2.5 ± 0.8	59.3 ± 10.6	52.8 ± 11.4	1 (1.8)	1 (1.8)	NR	NR	54 (98.2)	51 (92.7)
Liu C et al., 2020 (22)	2.2 ± 0.9	4.1 ± 2.7	54.2 ± 19.5	53.8 ± 19.1	3 (2.5)	0	NR	NR	NR	NR
Liao et al., 2019 (21)	1.2 ± 0.5	2.6 ± 0.9	59.0 ± 15.8	73.7 ± 26.6	2 (4.0)	0	NR	NR	42 (84.0)	48 (96.0)
Zhang et al., 2018 (32)	3.1 ± 1.5	4.8 ± 2.9	74.6 ± 23.9	66.5 ± 27.5	4 (4.6)	1 (2.8)	NR	NR	NR	NR
Murakami et al., 2017 (25)	9.7 ± 3.8	12.9 ± 7.8	NR	NR	1 (1.0)	2 (3.3)	8 (7.8)	16 (26.7)	NR	NR
Lu et al., 2017 (24)	3.1 ± 1.0	4.1 ± 0.9	NR	NR	NR	NR	15 (34.1)	24 (53.3)	NR	NR
Yang et al., 2016 (30)	3.1 ± 0.7	4.4 ± 1.3	72.0 ± 21.3	79.1 ± 32.2	0	0	NR	NR	27 (90.0)	22 (73.3)
Ueda et al., 2013 (28)	13.3 ± 15.5	12.5 ± 6.6	152.0 ± 53.0	198.0 ± 78.0	0	1 (4.8)	NR	NR	NR	NR
Nakashima et al., 2011 (26)	4.6 ± 2.2	6.7 ± 4.4	NR	NR	4 (3.0)	3 (1.5)	11 (8.3)	10 (5.0)	NR	NR
Watanabe et al., 2004 (29)	3.2 ± 1.0	3.6 ± 1.5	NR	NR	2 (4.8)	2 (5.9)	4 (9.5)	2 (5.9)	NR	NR
Russo et al., 1998 (27)	2.0 ± 1.0	3.9 ± 2.1	NR	NR	0	0	NR	NR	NR	NR

NT, no routine chest tube drainage; RT, routine chest tube drainage; LOS, length of stay; NR, not reported.

TABLE 3 Detailed postoperative complications of the included studies.

Study (year)	Pneumothorax (%)		Pleural effusion (%)		Subcutaneous emphysema (%)		Pneumonia (%)		Arrhythmia (%)	
	NT	RT	NT	RT	NT	RT	NT	RT	NT	RT
Zhang et al., 2020 (31)	4 (10.0)	4 (9.1)	2 (5.0)	2 (4.5)	8 (20.0)	8 (18.2)	0	1 (2.3)	NR	NR
Liu Z et al., 2020 (23)	15 (27.3)	12 (21.8)	1 (1.8)	1 (1.8)	9 (16.4)	8 (14.6)	NR	NR	0	0
Liu C et al., 2020 (22)	35 (28.7)	0	16 (13.1)	0	17 (13.9)	0	NR	NR	NR	NR
Liao et al., 2019 (21)	18 (36.0)	5 (10.0)	4 (8.0)	3 (6.0)	11 (22.0)	6 (12.0)	NR	NR	NR	NR
Zhang et al., 2018 (32)	12 (13.8)	2 (5.6)	1 (1.1)	0	NR	NR	0	1 (2.8)	NR	NR
Murakami et al., 2017 (25)	NR	NR	NR	NR	NR	NR	3 (2.9)	5 (8.3)	5 (4.9)	4 (6.7)
Lu et al., 2017 (24)	0	0	NR	NR	15 (34.1)	24 (53.3)	NR	NR	NR	NR
Yang et al., 2016 (30)	12 (40.0)	4 (13.3)	1 (3.3)	0	2 (6.6)	0	NR	NR	NR	NR
Ueda et al., 2013 (28)	NR	NR	NR	NR	0	1 (4.8)	NR	NR	NR	NR
Nakashima et al., 2011 (26)	10 (7.6%)	8 (4.0)	1 (0.8)	1 (0.5)	NR	NR	NR	NR	NR	NR
Watanabe et al., 2004 (29)	4 (9.5)	2 (5.9)	0	0	NR	NR	NR	NR	NR	NR
Russo et al., 1998 (27)	5 (16.1)	7 (26.9)	0	0	NR	NR	NR	NR	NR	NR

NT, no routine chest tube drainage; RT, routine chest tube drainage; NR, not reported.

group and segmentectomy or lobectomy group. As shown in Figure 2B, the postoperative LOS of the NT group was shorter than that of the RT group (SMD = -1.03; 95% CI: -1.36 to -0.71; P < 0.001) in the subgroup of wedge resection, while the postoperative LOS became comparable between the two groups in the segmentectomy or lobectomy subgroup (SMD = -0.30; 95% CI: -0.91 to 0.32; P = 0.34).

Postoperative complications

The detailed data on postoperative complications of the 12 eligible literatures were presented in Table 3. The meta-analysis indicated that the risk of postoperative pneumothorax was significantly higher in the NT group than that in the RT group (RR = 1.75; 95% CI: 1.14–2.68; P = 0.01) with a relatively low heterogeneity (I^2 = 27%; P = 0.21), as shown in Figure 3A. No publication bias was found using Egger's test (P = 0.450).

In contrast, there was no statistically significant difference in terms of the risks of postoperative pleural effusion (RR = 1.48; 95% CI: 0.62–3.50; P = 0.37; I^2 = 0%) and subcutaneous emphysema (RR = 1.04; 95% CI: 0.65–1.65; P = 0.88; I^2 = 25%) between the NT and RT groups with a slight heterogeneity, as shown in Figures 3B, C, respectively. No publication bias was found using Egger's test (P = 0.335 for pleural effusion; P = 0.215 for subcutaneous emphysema).

TABLE 4 Postoperative pain score of the included studies.

Study (year)	POD 1		POD 2		POD 3		POD 7		Pain scale
	NT	RT	NT	RT	NT	RT	NT	RT	
Zhang et al., 2020 (31)	1.6 ± 0.7	2.4 ± 1.2	NR	NR	NR	NR	NR	NR	NRS
Liu Z et al., 2020 (23)	1.0 ± 0.7	3.0 ± 0.9	NR	NR	0.5 ± 0.5	1.1 ± 1.5	0.4 ± 0.4	0.7 ± 0.4	VAS
Liu C et al., 2020 (22)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liao et al., 2019 (21)	0.9 ± 0.7	1.3 ± 0.9	0.5 ± 0.6	0.9 ± 1.6	NR	NR	NR	NR	VAS
Zhang et al., 2018 (32)	2.3 ± 0.9	3.4 ± 1.1	NR	NR	NR	NR	NR	NR	NRS
Murakami et al., 2017 (25)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lu et al., 2017 (24)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yang et al., 2016 (30)	1.0 ± 0.8	1.5 ± 1.1	0.6 ± 0.5	0.9 ± 0.5	NR	NR	NR	NR	VAS
Ueda et al., 2013 (28)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nakashima et al., 2011 (26)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Watanabe et al., 2004 (29)	1.56 ± 0.42	1.71 ± 0.53	1.40 ± 0.40	1.51 ± 0.43	1.17 ± 0.43	1.25 ± 0.37	0.56 ± 0.31	0.60 ± 0.37	VAS
Russo et al., 1998 (27)	NR	NR	NR	NR	NR	NR	NR	NR	NR

NT, no routine chest tube drainage; RT, routine chest tube drainage; POD, postoperative day; VAS, visual analog scale; NRS, Numeric Rating Scale; NR, not reported.

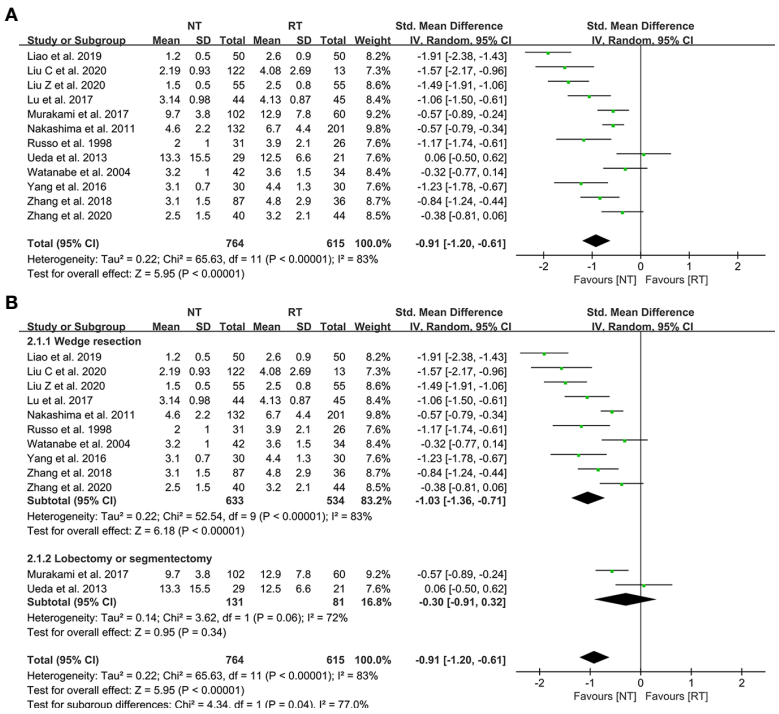

FIGURE 2
Meta-analysis and subgroup analysis of postoperative length of stay (LOS) between the NT and RT groups. **(A)** Meta-analysis of postoperative LOS; **(B)** Subgroup analysis of postoperative LOS. NT, no routine chest tube drainage; RT, routine chest tube drainage; CI, confidence interval.

Reintervention

A total of 11 included studies reported the incidence of postoperative reintervention for patients (21–23, 25–32). The results of the meta-analysis indicated that there was no significant difference in the postoperative reintervention rate between the NT group and the RT group (RR = 1.04; 95% CI: 0.48–2.25; *P* = 0.92) without heterogeneity (I^2 = 0%; P = 0.82) (Figure 4). No publication bias was found using Egger's test (P = 0.241).

Postoperative pain score

The detailed data on postoperative pain score were presented in Table 4. As shown in Figures 5A–C, patients in the NT group experienced a lower pain score on POD 1 (SMD = -0.95; 95% CI: -1.54 to -0.36; P = 0.002), POD 2 (SMD = -0.37; 95% CI: -0.63 to -0.11; P = 0.005), and POD 3 (SMD = -0.39; 95% CI: -0.71 to -0.06; P = 0.02) compared with the RT group. However, the meta-analysis indicated that the pain scores of patients on POD 7 became comparable between the two groups (SMD = -0.44; 95% CI, -1.06 to 0.17; P = 0.16) (Figure 5D).

Operation duration

As shown in Table 2, seven studies mentioned the duration of surgery, of which 6 studies present the data as mean ± SD (21–23, 28, 30–32). The results suggested that there was no statistical difference between the NT group and the RT group in terms of operative duration (SMD = -0.10; 95% CI: -0.55 to 0.35; P = 0.66) with a considerable heterogeneity (I^2 = 83%; P < 0.01) (Figure 6). No publication bias was found using Egger's test (P = 0.351).

Wound healing satisfaction

As demonstrated in Figure 7, there was no statistically significant difference in the wound healing satisfaction between the NT and RT groups (RR = 1.04; 95% CI: 0.92–1.17; P = 0.52) with high heterogeneity (I^2 = 67%; P = 0.03).

Sensitivity analysis

We performed the sensitivity analysis by omitting individual studies sequentially. None of the summary RRs based on the

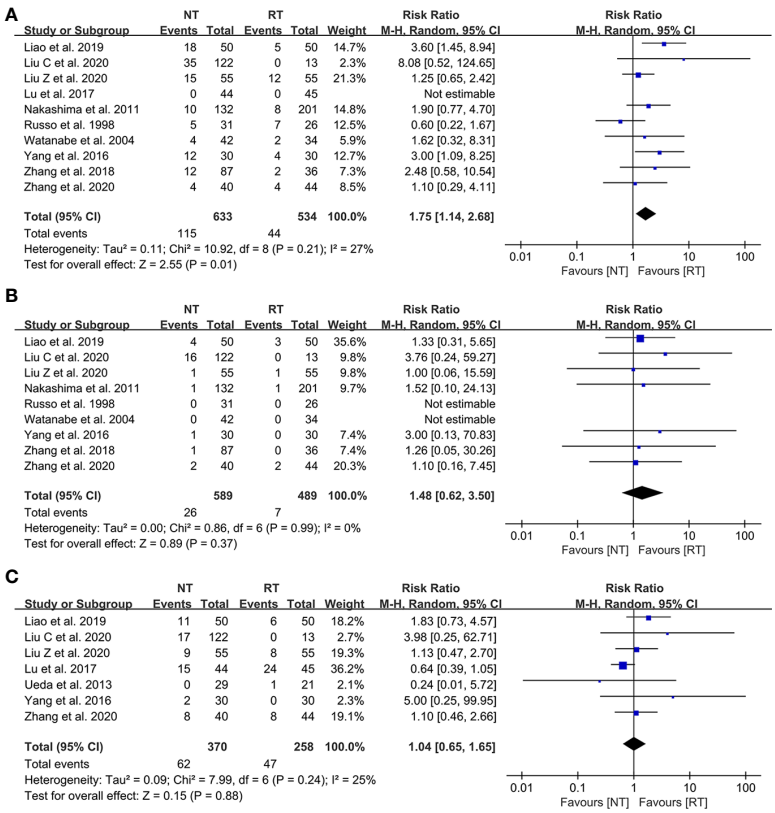

FIGURE 3
Meta-analysis of postoperative complications between the NT and RT groups. **(A)** Pneumothorax; **(B)** Pleural effusion; **(C)** Subcutaneous emphysema. NT, no routine chest tube drainage; RT, routine chest tube drainage; CI, confidence interval.

remaining studies in each component analysis exceeded the estimated range, as shown in Figure S2. Nor was there any substantial change between the adjusted pooled estimates and the major aggregate estimates. The robustness of our meta-analysis was thus confirmed.

Discussion

The placement of routine chest tube drainage after thoracoscopic pulmonary resection has already been the gold standard approach to prevent postoperative pneumothorax and

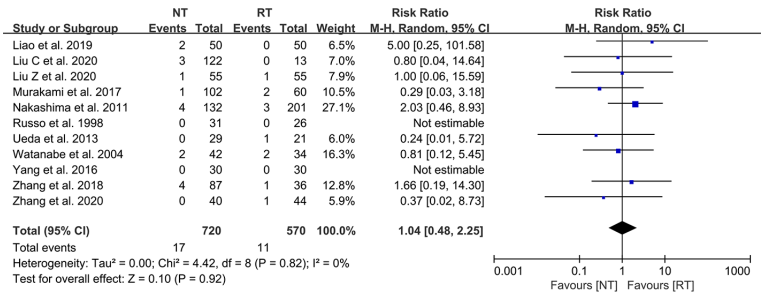

FIGURE 4
Meta-analysis of reintervention rate between the NT and RT groups. NT, no routine chest tube drainage; RT, routine chest tube drainage; CI, confidence interval.

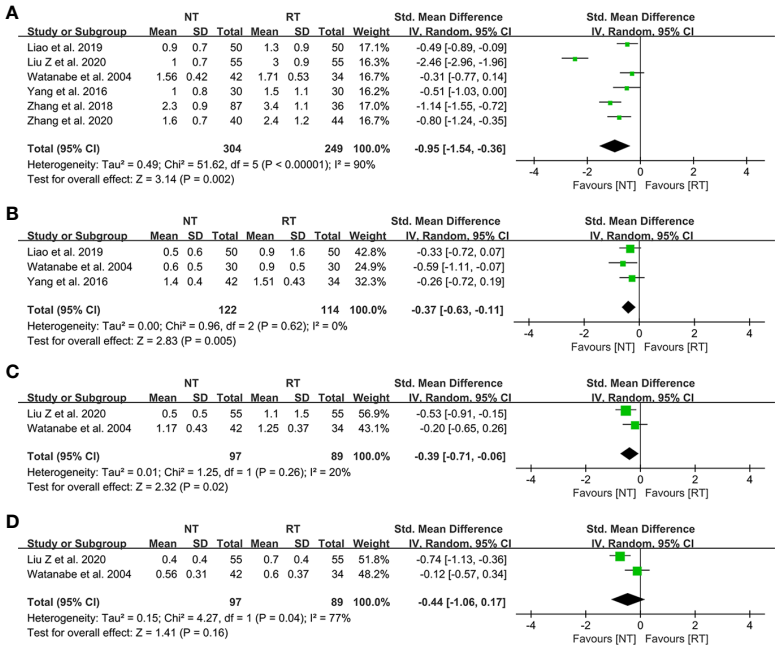

FIGURE 5
Meta-analysis of postoperative pain score between the NT and RT groups. **(A)** POD 1; **(B)** POD 2; **(C)** POD 3; **(D)** POD 7. NT, no routine chest tube drainage; RT, routine chest tube drainage; POD, postoperative day; CI, confidence interval.

pleural effusion (33). In recent years, an increasing number of thoracic surgeons, in order to realize the concept of ERAS, have attempted to not routinely place chest tube drainage and instead use the method of prophylactic air-extraction catheter insertion procedure or complete omission of chest tube drainage (21, 32). However, the safety and feasibility of not routinely placing a chest tube after lung resection remain controversial. To date, no meta-analysis has been conducted to comprehensively compare the perioperative outcomes between with and without routine chest tube drainage after video-assisted thoracoscopic pulmonary resection. Therefore, we performed a systematic review and meta-analysis including 12 comparative studies on this subject to further identify the safety and feasibility of the NT strategy.

In this study, we found that the no routine placement of chest tube drainage after thoracoscopic lung resection can significantly shorten the postoperative hospital stay (SMD = -0.91; 95% CI: -1.20 to -0.61; P < 0.001). However, the meta-analysis of postoperative LOS showed a relatively high heterogeneity (I^2 = 83%; P < 0.001), which might derive from the different surgical approaches (wedge resection, segmentectomy, and lobectomy) and medical insurance of regions and countries. For example, the healthcare system in Japan allows patients to stay in the hospital for a relatively long

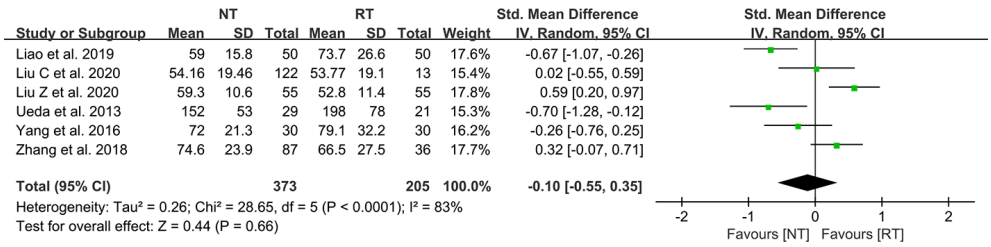

FIGURE 6
Meta-analysis of operation duration between the NT and RT groups. NT, no routine chest tube drainage; RT, routine chest tube drainage; CI, confidence interval.

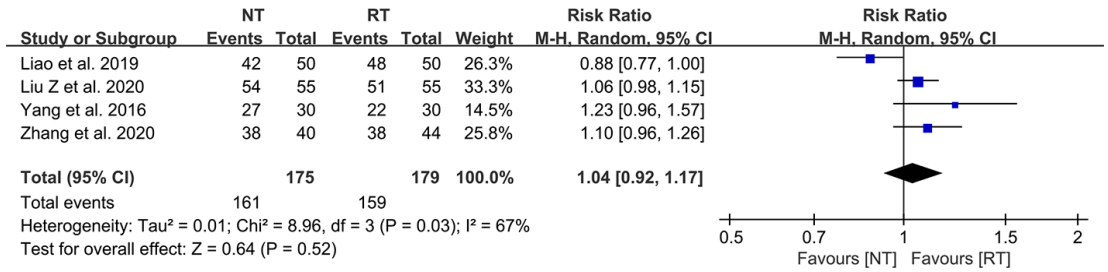

FIGURE 7
Meta-analysis of wound healing satisfaction between the NT and RT groups. NT, no routine chest tube drainage; RT, routine chest tube drainage; CI, confidence interval.

period of time, even if they have already met discharge criteria (34). It is worth mentioning that the difference of postoperative LOS became statistically insignificant in the lobectomy or segmentectomy subgroup (SMD = -0.30; 95% CI: -0.91 to 0.32; P = 0.34). However, this might be caused by too few (only two) studies in this subgroup, and the effectiveness of NT strategy for lobectomy or segmentectomy warrants further exploration in future studies.

The main concerns caused by omitting routine placement of chest tube drainage after pulmonary resection are the risks of pneumothorax, bleeding, pleural effusion, and subcutaneous emphysema (8, 35). In terms of postoperative complications, we did not perform a pooled analysis of the overall incidence of complications because of the small number of studies reporting it. Instead, we performed a meta-analysis of more detailed complications. The results of the meta-analysis indicated that the incidence of pneumothorax was significantly increased in the NT group (RR = 1.75; 95% CI: 1.14–2.68; P = 0.01). However, there was no significant difference between the two groups in the incidence of pleural effusion (RR = 1.48; 95% CI: 0.62–3.50; P = 0.37) and subcutaneous emphysema (RR = 1.04; 95% CI: 0.65–1.65; P = 0.88). Notably, the reintervention rates of the NT group did not significantly increase (RR = 1.04; 95% CI: 0.48–2.25; P = 0.92), suggesting that the vast majority of pneumothorax could be self-absorbed safely without chest tube reinsertion or thoracocentesis.

The traditional drainage tube is often reported as one of the main reasons of postoperative pain and might interfere with postoperative activity, which could prevent patients from functional rehabilitation and thus prolong the duration of hospitalization (21, 36). In this study, we found that the pain scores on POD 1 (SMD = -0.95; 95% CI: -1.54 to -0.36; P = 0.002), POD 2 (SMD = -0.37; 95% CI: -0.63 to -0.11; P = 0.005), and POD 3 (SMD = -0.39; 95% CI: -0.71 to -0.06; P = 0.02) were significantly decreased without routine chest tube placement. However, the pain scores became comparable between the two groups on POD 7 (SMD = -0.44; 95% CI: -1.06 to 0.17; P = 0.16), indicating that the chest tube is one of the major sources of postoperative pain. Enhanced postoperative pain would prevent patients from effective coughing and thus deteriorate the ventilation capacity. A study performed by Ueda et al. (37) in 2019 showed that the omission of chest tube drainage could reduce the pain and preserve the ventilatory capacity and exercise capacity in the early postoperative period for patients undergoing thoracoscopic pulmonary resection. In addition, there was no significant different in wound healing satisfaction postoperatively between the two groups (RR = 1.04; 95% CI: 0.92–1.17; P = 0.52), which might be attributed to the benefits of minimally invasive technology such as video-assisted thoracoscopic surgery.

To ensure the security of the NT strategy, patients should undergo rigorous air tightness tests before being assigned to the NT group. Water-seal air tightness test and suction-induced air leakage test are relatively common methods to test air leaks during the operation and were applied in majority of the studies. If no air leaks were observed in the air tightness tests, then the patients would be assigned to the NT group. Liu Z et al. (23) have reported a modified air leak test in 2020. The water-seal test was first used at the end of the operation, and then patients were changed to reverse Trendelenburg position with 30° with a chest tube placed at the posterior one-third position of the incision to further test for existence of air leaks. They suggested that complete air drainage is more easily achieved by a chest tube in this position (23). In recent years, a digital drainage system (DDS) has also been used for air tightness tests. A single chest tube was placed through the incision into the pleural cavity before closing the incision and was connected to a DDS. If the DDS indicated 0 ml/min airflow before completion of the wound closure, the chest tube would be removed immediately (22, 38). A study performed by Russo et al. (27) in 1998 used an early removal of chest tube approach. Patients assigned to the NT group had their chest tubes removed within 90 min postoperatively in the recovery room (27). Although this approach was not a strict NT strategy, we still included this study in our analysis because traditional chest tube management tends to keep the chest tube inserted for at least 24 h. Some

argued that the operation duration may be extended due to the implementation of the air tightness tests (23, 32). However, our meta-analysis suggested that the operation duration was comparable between the two groups (SMD = -0.10; 95% CI: -0.55 to 0.35; P = 0.66).

At present, the NT strategy mainly includes two methods: prophylactic air-extraction catheter insertion procedure and complete omission of chest tube drainage. Prophylactic air-extraction catheter insertion procedure was first reported by Zhang et al. (32) in 2018. In this procedure, a two-lumen central venous catheter (20 cm, 7 Fr) was inserted into the second intercostal space before directly closing the incision. The air extraction was performed using an injector through the preset catheter if the chest roentgenogram revealed a pneumothorax on POD 1. A recent randomized clinical trial performed by Zhang et al. (31) in 2020 has demonstrated that the prophylactic air-extraction catheter insertion was a safe procedure that could reduce pain and facilitate patients' recovery after pulmonary wedge resection. However, which of the two methods is better has not been discussed. We originally intended to conduct a subgroup analysis to explore this issue, but due to the insufficient data on prophylactic air-extraction catheter procedure, our idea was not implemented, which could be considered in a future meta-analysis.

It is noteworthy that the selection criteria for patients who do not routinely place chest tubes after video-assisted thoracoscopic pulmonary resection are relatively strict. Important factors that should be considered when selecting patients are the following: 1) absence of air leaks during the intraoperative air tightness tests, 2) absence of dense pleural adhesion, 3) absence of a history of previous ipsilateral thoracic surgery, 4) absence of moderate-to-severe obstructive or restrictive pulmonary diseases.

This study has several limitations that should be considered. First, the majority of the included studies were single-center retrospective cohort studies, and only 2 RCTs were included. Some biases common to cohort studies are unavoidable, such as cohort selection bias, which might have reduced the reliability of the results. Second, different surgical approaches and different pain rating scales were included in this meta-analysis, which inevitably increase the clinical heterogeneity. In addition, prophylactic air-extraction catheter insertion procedure and complete omission of chest tube drainage were both included in the NT group, possibly leading to heterogeneity of the results. Third, although 12 studies were included for analysis, not all studies reported the outcomes we were interested in and we just used the available data to analyze in each comparison. In addition, we did not perform subgroup analyses for outcomes other than postoperative LOS due to the limited data reported. Fourth, all of the studies included had their own criteria to select patients into the NT groups; this might lead to different baseline characteristics of the two groups and a high clinical heterogeneity. Finally, a certain language-based bias might have arisen due to the requirement of full-text English language literature.

Conclusion

This systematic review and meta-analysis is the most up-to-date and comprehensive review of the literature on the NT strategy after video-assisted thoracoscopic pulmonary resection. The NT strategy could not only significantly shorten the postoperative LOS but also reduce short-term postoperative pain for patients without increasing the reintervention rate, suggesting that it is safe and feasible for selected patients scheduled for video-assisted thoracoscopic pulmonary resection.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

Conception and design: RL and HT. Administrative support: HT, WY and ZM. Provision of study materials or patients: RL and JQ. Collection and assembly of data: RL, JQ, KW and YZ. Data analysis and interpretation: RL, JQ and CQ. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by National Key Research and Development Program (2021YFC2500904, and 2021YFC2500905), Natural Science Foundation of Shandong Province (ZR2021LSW006) and the Taishan Scholar Program of Shandong Province (no. ts201712087).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.915020/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Detailed quality assessment of included RCTs. **(A)** Risk of bias summary; **(B)** Risk of bias graph.

SUPPLEMENTARY FIGURE 2
Sensitivity analyses of outcomes. **(A)** Postoperative LOS; **(B)** Pneumothorax; **(C)** Pleural effusion; **(D)** Subcutaneous emphysema; **(E)** Reintervention rate; **(F)** Pain score on POD 1; **(G)** Operation duration; **(H)** Wound healing satisfaction. CI, confidence interval.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol* (2021) 18(3):135–51. doi: 10.1038/s41571-020-00432-6

3. Potter AL, Rosenstein AL, Kiang MV, Shah SA, Gaissert HA, Chang DC, et al. Association of computed tomography screening with lung cancer stage shift and survival in the United States: Quasi-experimental study. *BMJ (Clinical Res ed)* (2022) 376:e069008. doi: 10.1136/bmj-2021-069008

4. Cheng AM, Wood DE. VATS versus open surgery for lung cancer resection: Moving beyond the incision. *J Natl Compr Canc Netw* (2015) 13(2):166–70. doi: 10.6004/jnccn.2015.0024

5. Demmy TL, Yendamuri S, D'Amico TA, Burfeind WR. Oncologic equivalence of minimally invasive lobectomy: The scientific and practical arguments. *Ann Thorac Surg* (2018) 106(2):609–17. doi: 10.1016/j.athoracsur.2018.02.089

6. Miller KS, Sahn SA. Chest tubes. *Indic techniq Manage complic Chest* (1987) 91(2):258–64. doi: 10.1378/chest.91.2.258

7. Deng B, Qian K, Zhou JH, Tan QY, Wang RW. Optimization of chest tube management to expedite rehabilitation of lung cancer patients after video-assisted thoracic surgery: A meta-analysis and systematic review. *World J Surg* (2017) 41(8):2039–45. doi: 10.1007/s00268-017-3975-x

8. Satherley LK, Luckraz H, Rammohan KS, Phillips M, Kulatilake NE, O'Keefe PA. Routine placement of an intercostal chest drain during video-assisted thoracoscopic surgical lung biopsy unnecessarily prolongs in-hospital length of stay in selected patients. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2009) 36(4):737–40. doi: 10.1016/j.ejcts.2009.04.067

9. Engelman RM, Rousou JA, Flack JE3rd, Deaton DW, Humphrey CB, Ellison LH, et al. Fast-track recovery of the coronary bypass patient. *Ann Thorac Surg* (1994) 58(6):1742–6. doi: 10.1016/0003-4975(94)91674-8

10. Li R, Wang K, Qu C, Qi W, Fang T, Yue W, et al. The effect of the enhanced recovery after surgery program on lung cancer surgery: A systematic review and meta-analysis. *J Thorac Dis* (2021) 13(6):3566–86. doi: 10.21037/jtd-21-433

11. Holbek BL, Hansen HJ, Kehlet H, Petersen RH. Thoracoscopic pulmonary wedge resection without post-operative chest drain: An observational study. *Gen Thorac Cardiovasc Surg* (2016) 64(10):612–7. doi: 10.1007/s11748-016-0692-6

12. Li S, Jiang L, Ang KL, Chen H, Dong Q, Yang H, et al. New tubeless video-assisted thoracoscopic surgery for small pulmonary nodules. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2017) 51(4):689–93. doi: 10.1093/ejcts/ezw364

13. Cui F, Liu J, Li S, Yin W, Xin X, Shao W, et al. Tubeless video-assisted thoracoscopic surgery (VATS) under non-intubated, intravenous anesthesia with spontaneous ventilation and no placement of chest tube postoperatively. *J Thorac Dis* (2016) 8(8):2226–32. doi: 10.21037/jtd.2016.08.02

14. Li P, Shen C, Wu Y, Lai Y, Zhou K, Che G. It is safe and feasible to omit the chest tube postoperatively for selected patients receiving thoracoscopic pulmonary resection: A meta-analysis. *J Thorac Dis* (2018) 10(5):2712–21. doi: 10.21037/jtd.2018.04.75

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ (Clinical Res ed)* (2009) 339:b2700. doi: 10.1136/bmj.b2700

16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *Jama* (2000) 283(15):2008–12. doi: 10.1001/jama.283.15.2008

17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z

18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.3 (Updated February 2022). In: *Cochrane* (2022).

19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* (2002) 21(11):1539–58. doi: 10.1002/sim.1186

20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* (1994) 50(4):1088–101. doi: 10.2307/2533446

21. Liao HC, Yang SM, Hung MH, Cheng YJ, Hsu HH, Chen JS. Thoracoscopic surgery without drainage tube placement for peripheral lung nodules. *Ann Thorac Surg* (2019) 109(3):887–93. doi: 10.1016/j.athoracsur.2019.10.048

22. Liu CY, Hsu PK, Leong KI, Ting CK, Tsou MY. Is tubeless uniportal video-assisted thoracic surgery for pulmonary wedge resection a safe procedure? *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2020) 58(Suppl_1):i70–i6. doi: 10.1093/ejcts/ezaa061

23. Liu Z, Yang R, Sun Y. Tubeless uniportal thoracoscopic wedge resection with modified air leak test and chest tube drainage. *BMC Surg* (2020) 20(1):301. doi: 10.1186/s12893-020-00910-9

24. Lu TY, Chen JX, Chen PR, Lin YS, Chen CK, Kao PY, et al. Evaluation of the necessity for chest drain placement following thoracoscopic wedge resection. *Surg Today* (2017) 47(5):606–10. doi: 10.1007/s00595-016-1414-5

25. Murakami J, Ueda K, Tanaka T, Kobayashi T, Kunihiro Y, Hamano K. The validation of a no-drain policy after thoracoscopic major lung resection. *Ann Thorac Surg* (2017) 104(3):1005–11. doi: 10.1016/j.athoracsur.2017.03.030

26. Nakashima S, Watanabe A, Mishina T, Obama T, Mawatari T, Higami T. Feasibility and safety of postoperative management without chest tube placement after thoracoscopic wedge resection of the lung. *Surg Today* (2011) 41(6):774–9. doi: 10.1007/s00595-010-4346-5

27. Russo L, Wiechmann RJ, Magovern JA, Szydlowski GW, Mack MJ, Naunheim KS, et al. Early chest tube removal after video-assisted thoracoscopic wedge resection of the lung. *Ann Thorac Surg* (1998) 66(5):1751–4. doi: 10.1016/S0003-4975(98)00946-1

28. Ueda K, Hayashi M, Tanaka T, Hamano K. Omitting chest tube drainage after thoracoscopic major lung resection. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2013) 44(2):225–9; discussion 9. doi: 10.1093/ejcts/ezs679

29. Watanabe A, Watanabe T, Ohsawa H, Mawatari T, Ichimiya Y, Takahashi N, et al. Avoiding chest tube placement after video-assisted thoracoscopic wedge resection of the lung. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2004) 25(5):872–6. doi: 10.1016/j.ejcts.2004.01.041

30. Yang SM, Wang ML, Hung MH, Hsu HH, Cheng YJ, Chen JS. Tubeless uniportal thoracoscopic wedge resection for peripheral lung nodules. *Ann Thorac Surg* (2016) 103(2):462–8. doi: 10.1016/j.athoracsur.2016.09.006

31. Zhang JT, Dong S, Chu XP, Lin SM, Yu RY, Jiang BY, et al. Randomized trial of an improved drainage strategy versus routine chest tube after lung wedge resection. *Ann Thorac Surg* (2020) 109(4):1040–6. doi: 10.1016/j.athoracsur.2019.11.029

32. Zhang JT, Tang YC, Lin JT, Dong S, Nie Q, Jiang BY, et al. Prophylactic air-extraction strategy after thoracoscopic wedge resection. *Thorac Canc* (2018) 9(11):1406–12. doi: 10.1111/1759-7714.12850

33. Coughlin SM, Emmerton-Coughlin HM, Malthaner R. Management of chest tubes after pulmonary resection: A systematic review and meta-analysis. *Can J Surg J Canadien Chirurgie* (2012) 55(4):264–70. doi: 10.1503/cjs.001411

34. Yamauchi T. Healthcare system in Japan. *Nurs Health Sci* (1999) 1(1):45–8. doi: 10.1046/j.1442-2018.1999.00007.x

35. Fibla JJ, Molins L, Pérez J, Vidal G. Early removal of chest drainage and outpatient program after videothoracoscopic lung biopsy. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg* (2006) 29(4):639–40; author reply 40-1. doi: 10.1016/j.ejcts.2006.01.021

36. Wildgaard K, Ringsted TK, Aasvang EK, Ravn J, Werner MU, Kehlet H. Neurophysiological characterization of persistent postthoracotomy pain. *Clin J Pain* (2012) 28(2):136–42. doi: 10.1097/AJP.0b013e3182261650

37. Ueda K, Haruki T, Murakami J, Tanaka T, Hayashi M, Hamano K. No drain after thoracoscopic major lung resection for cancer helps preserve the physical function. *Ann Thorac Surg* (2019) 108(2):399–404. doi: 10.1016/j.athoracsur.2019.03.018

38. Liu CY, Hsu PK, Chien HC, Hsieh CC, Ting CK, Tsou MY. Tubeless single-port thoracoscopic sublobar resection: Indication and safety. *J f Thorac Dis* (2018) 10(6):3729–37. doi: 10.21037/jtd.2018.05.119

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 09 August 2022
DOI 10.3389/fsurg.2022.985654

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Luigi Della Corte,
University of Naples Federico II, Italy
Diana Butera,
University Hospital of Parma, Italy

*CORRESPONDENCE
Zhimin Hao
fyhaozhimin@nbu.edu.cn
Sufen Yang
yangsufenedu@sina.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 04 July 2022
ACCEPTED 25 July 2022
PUBLISHED 09 August 2022

CITATION
Hao ZM and Yang SF (2022) The role of postoperative radiotherapy in patients with uterine sarcomas: A PSM-IPTW analysis based on SEER database.
Front. Surg. 9:985654.
doi: 10.3389/fsurg.2022.985654

The role of postoperative radiotherapy in patients with uterine sarcomas: A PSM-IPTW analysis based on SEER database

Zhimin Hao[1,2]* and Sufen Yang[1]*

[1]Department of Gynecology, The Affiliated Hospital of Medical School of Ningbo University, Ningbo, China, [2]School of Medicine, Ningbo University, Ningbo, China

Objective: The optimal adjuvant therapy for uterine sarcomas remains poorly determined due to its rarity and histological diversity. The purpose of the study is to explore and characterize the association between utilization of radiotherapy and survival outcome in patients with surgically resected uterine sarcomas.

Methods: We collected data regarding uterine sarcomas which were confirmed after total hysterectomy between 2010 and 2018 period from the latest version of the Surveillance, Epidemiology, and End Results (SEER) database. Initially, 1-, 3- and 5-year survival rate were calculated to predict potential risk factors and possible role of adjuvant chemotherapy and radiotherapy. Propensity score matching (PSM) and inverse probability treatment weighting (IPTW) technique were employed to balance confounding factors in the utilization of additional therapy. Multivariate and exploratory subgroup analyses were respectively conducted to evaluate the impact of adjuvant therapy on overall survival (OS) and cause-specific survival (CSS).

Results: A total of 2897 patients were enrolled in the analysis. Survival benefit at 1-, 3-and 5-year after initial treatment was observed in the group of radiotherapy given, however, poorer prognosis in the group of chemotherapy administration. Accordingly, chemotherapy was enrolled as a confounding factor when stratifying and matching patients by receipt of radiotherapy. Prior to and after PSM-IPTW adjustment, radiotherapy both demonstrated beneficial effect on OS and CSS based on multivariate analysis. Further subgroup analysis indicated radiotherapy improved OS and CSS among a subset of patients in stage II-IV, particularly with uterine leiomyosarcoma, tumor grade IV, bigger tumor size than 100 mm and even with chemotherapy administration.

Conclusions: Adjuvant radiotherapy in uterine sarcomas after hysterectomy might be underutilized, and proper use of adjuvant radiotherapy combined with chemotherapy after surgery in advanced-stage and high-risk patients might improve survival.

KEYWORDS

uterine sarcomas, PSM, IPTW, leiomyosarcoma, radiotherapy, chemotherapy methods study population

Introduction

Uterine sarcomas (US) are a heterogeneous and rare group of neoplasms, accounting for approximately 1% of female genital tract malignancies and 3%–7% of all uterine neoplasms (1). The most represented histological subtype of uterine sarcomas is leiomyosarcoma (LMS), followed subsequently by endometrial stromal sarcoma (ESS), adenosarcoma and undifferentiated uterine sarcoma (USS) (2). Low-grade ESS and high-grade ESS represents approximately 86% and 14%, respectively, of all endometrial stromal sarcomas as described in a relatively large study regarding uterine mesenchymal tumors (3). Uterine carcinosarcoma has been excluded from US division, instead, as a subtype of high-grade endometrial carcinoma (4).

Total hysterectomy remains the standard surgery mode for newly diagnosed early-stage uterine sarcomas, often in combination with bilateral salpingo- oophorectomy, and generous tumor debulking if present outside the uterus (5). Although lymphadenectomy may confer more accurate staging, it was not related to a clear survival benefit in patients with uterine sarcomas (6). It's worth noting that the uncontained power morcellation during laparoscopic hysterectomy or myomectomy has become as a popular surgical modality for tissue extraction within past decades. In recent years, where several cases of abdominopelvic dispersion developing from electrical morcellation of unexpected uterine sarcomas were reported in term of severely negative repercussions (7), clinicians paid more attention to its impact on US patients' outcomes and survival. It was commonly recognized that women whose malignant tumor tissue was unintended morcellated at time of hysterectomy or myomectomy posed a higher risk of distant recurrence as compared to local recurrence presumed to be attributed to intra-abdominal seeding or lymphvascular spread of small volume specimen at time of *en bloc* hysterectomy (8). Even in the setting of localized disease, the 5-year survival rate for US is 50%–75%. Prognosis of those in advanced stage disease is poorer, with the 5-year survival probability of approximately 30%–45% (9). The high rate of recurrence and poor prognosis, particularly for LMS (10) and high grade ESS (3, 11), provides the rationale for evaluation of adjuvant therapy to improve prognosis. Given its rarity and histological diversity, it is difficult to reach consensus concerning the best route of adjuvant radiotherapy or chemotherapy through prospective clinical trials (12). Hence, large-database retrospective analysis utilizing the tools currently available, such as SEER, can still help tailor clinical practice and inform investigation of future treatments.

Moreover, individual differences in patients' response to adjuvant therapy are of key interest in clinical practice. In light of this, some important clinical parameters, such as age, race, tumor grade and size, are usually considered when predicting survival outcomes. For instance, black women experienced a higher risk of uterine sarcoma than those white females, as well as women aged over 50 years posed a higher risk of sarcoma (13). Accordingly, balancing the potential confounding factors is necessary to improve the accuracy of survival prediction among women with uterine sarcomas.

The purpose of the current study is to comprehensively explore and characterize the association between utilization of radiotherapy and survival outcome in patients with surgically resected uterine sarcomas. Besides, we evaluate other variables for their prognostic significance in uterine sarcomas.

Methods

Study population

We conducted a retrospective analysis for patients with uterine sarcomas between 2010 and 2018. The Surveillance, Epidemiology and End Results (SEER) database (SEER*Stat 8.3.9.2), which contains data of cancer patients from 18 regional registries (https://seer.cancer.gov/seerstat/), was employed for the analysis. Uterine sarcomas were confirmed by histology of hysterectomy specimen and based on the WHO International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes as follows: Leiomyosarcoma: 8890-leiomyosarcoma, NOS, 8891-epithelioid leiomyosarcoma, 8896-myxoid leiomyosarcoma; Endometrial stromal sarcoma: 8930-endometrial stromal sarcoma, 8931-endometrial stromal sarcoma, low-grade; 8935-Stromal sarcoma, NOS; Undifferentiated uterine sarcoma: 8805; Adenosarcoma: 8933. Based on site-specific surgery codes, women who underwent total hysterectomy with or without bilateral salpingoopherectomy were selected, including those with modified or radical hysterectomy. We excluded those cases with the surgery code "local tumor excision or destruction; subtotal hysterectomy; surgery NOS" given the fact that we could not identify the scope of the surgical procedure performed. Since all data included in the SEER database is publicly available online, this study does not require Institutional Review Board approval, or informed consent by the study subjects. While, we obtained permission to access the SEER program data from the US National Cancer Institute (reference number: 22756-Nov2020).

Those cases with more than one malignancy or secondary tumor, missing information on age, stage, unknown survival period or not hysterectomy performed were excluded from the analysis. A landmark survival time of 3 months was applied in order to account for immortal time bias. These procedures were demonstrated as detailed in the diagram **Figure 1**.

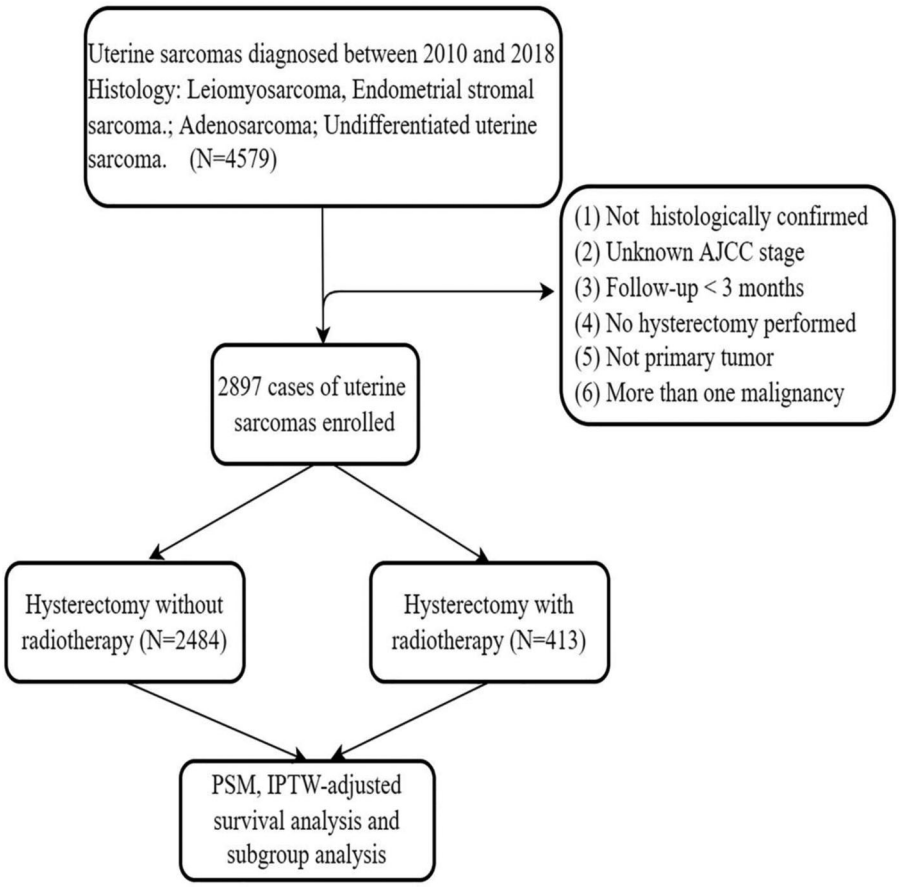

FIGURE 1
Eligibility, inclusion, and exclusion criteria of the study population.

Variable record and cohort definition

Demographic information of the patients encompassed age (<50, 50–60, >60), year of diagnosis (2010–2012, 2013–2015, 2016–2018), marital status (married, single, divorced, widowed), race (white, black, others), urban or rural area patients lived and median household income. Tumor characteristics included stage (I, II, III and IV), grade (grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; grade IV, undifferentiated; unknown grade), tumor size (<50 mm, 50–100 mm, >100 mm, unknown), peritoneal cytology (negative, positive or unknown). Treatment data involved lymphadenectomy (yes, none or unknown), months from diagnosis to treatment, radiotherapy (external beam, brachytherapy, combined of both or none) and chemotherapy (yes, none or unknown).

The primary endpoints were 1-, 3-and 5-year overall survival (OS), as well as the corresponding cause specific survival (CSS). The definition of OS was the time from confirmed diagnosis to death for any cause or to date of last follow-up, and CSS was defined as the interval from final diagnosis to death due to uterine sarcomas. Data from patients alive at the last visit were censored.

Statistical analysis

Categorical variables are shown as frequency and continuous variables are described as median (interquartile range [IQR]). Baseline patient characteristics were compared both pre- and post-matching with Chi-square test analysis, where the statistical significance in proportions' differences with P value <0.05 was identified unbalanced. To investigate impact of radiotherapy on survival in US patients, multiple imputations by chained equations were conducted to reduce potential bias resulted from missing data. First, we used a propensity score adjustment by inverse probability of treatment-weighting (IPTW) to maximally reduce the differences between radiotherapy and no radiotherapy

TABLE 1 The 1-, 3- and 5-year cause-specific survival and overall survival in terms of uterine sarcoma patients.

Characteristics	Num	Cause-specific survival (%)			Overall survival(%)		
		1-year	3-year	5-year	1-year	3-year	5-year
Total	2897	56.89	39.63	24.54	55.02	38.69	24.23
Age (years)							
<50	1003	69.19	49.05	31.31	68.10	48.55	31.11
50–60	1026	65.52	45.81	28.57	63.79	45.20	28.33
>60	868	48.62	32.72	19.01	45.28	30.76	18.43
Race							
Black	501	49.70	32.93	21.36	47.70	32.33	21.16
Others	327	62.69	42.51	25.38	61.16	42.51	25.38
White	2069	57.71	42.73	25.18	55.82	39.63	24.79
Marital status							
Married	1515	59.41	40.79	25.48	57.69	40.01	25.35
Divorced/separated	320	60.63	42.81	25.63	57.81	41.25	25.00
Single/unmarried	712	51.97	36.24	22.47	50.70	35.53	22.19
Unknown	151	56.95	42.38	28.48	55.63	42.38	28.48
Widowed	199	49.25	35.68	20.10	45.23	32.66	18.59
Median income							
<$50,000	339	56.64	39.82	26.84	53.39	38.05	25.66
$50,000–$65,000	998	54.61	43.29	29.16	52.71	42.28	28.76
>$65,000	1560	58.40	37.24	21.09	56.86	36.54	21.03
Year of diagnosis							
2010–2012	915	50.16	48.42	46.33	47.43	46.67	45.57
2013–2015	980	55.82	52.04	29.29	53.37	51.02	29.08
2016–2018	1002	64.07	19.36	N/A	63.57	19.36	N/A
Tumor grade							
I	544	88.05	62.87	39.55	86.58	61.76	38.97
II	223	79.37	65.47	43.95	78.03	65.02	43.50
III	389	40.87	22.62	13.37	37.79	21.33	13.11
IV	696	37.36	28.30	17.39	35.49	27.87	17.39
Unknown	1045	54.83	35.89	21.53	53.11	34.74	21.15
Histology							
Adenosarcoma	404	73.02	51.24	30.94	70.30	49.51	30.45
ESS	862	70.42	51.28	32.48	68.91	50.46	32.13
LMS	1582	45.76	30.66	18.77	44.06	29.9	18.52
UUS	49	44.90	28.57	18.37	38.78	24.49	18.37
AJCC stage							
I	1841	70.45	49.43	30.58	68.39	48.18	30.15
II	274	52.55	40.51	26.28	51.09	39.78	25.91
III	243	36.21	20.99	14.81	32.92	20.99	14.81
IV	539	23.01	14.10	7.42	21.33	13.73	7.42
Distant metastasis							
Lung	310	19.35	10.97	5.48	17.74	10.65	5.48
Liver	56	21.43	14.29	3.57	17.86	14.29	3.57
Bone	49	14.29	8.16	2.04	14.29	8.16	2.04
Brain	7	0	0	0	0	0	0
Lymphadenectomy							
Yes	1000	58.10	42.70	28.80	56.20	41.90	28.60
None/unknown	1897	56.25	38.01	22.30	54.40	37.01	21.93

(*continued*)

TABLE 1 Continued

Characteristics	Num	Cause-specific survival (%)			Overall survival(%)		
		1-year	3-year	5-year	1-year	3-year	5-year
Peritoneal cytology							
Negative	1095	59.54	42.37	27.12	57.17	41.19	26.76
Positive	114	27.19	21.05	13.16	23.68	18.42	13.16
Unknown	1688	57.17	39.10	23.64	55.75	38.45	23.34
Tumor size(mm)							
<50	475	78.53	56.00	34.95	76.00	54.74	34.32
50–100	1018	61.59	42.34	25.05	59.73	41.26	24.75
>100	1054	39.56	26.28	15.37	37.76	25.62	15.18
Unknown	350	66.00	49.71	36.57	64.86	48.86	36.29
Chemotherapy							
Yes	1166	35.93	23.41	12.86	33.88	22.56	12.78
None/unknown	1731	71.00	50.51	32.41	69.27	49.57	31.95
Radiotherapy							
None/unknown	2484	57.76	39.39	24.00	55.95	38.50	23.71
Beam	301	47.18	37.54	24.58	45.52	36.54	24.58
Brachytherapy	45	60.00	44.44	28.89	55.56	42.22	26.67
Combination	67	66.67	55.56	42.86	63.49	53.97	41.27

EES, endometrial stromal sarcoma; LMS, leiomyosarcoma; UUS, undifferentiated uterine sarcoma.

administration, as previously described (14, 15). Specifically, the propensity score was calculated using a logistic regression model based on the abovementioned characteristics. Stratified by radiotherapy administrated or not, propensity score matching (PSM) method (16) was employed through the nearest neighbor-matching with caliper value 0.4 for 1:4 matching. Afterwards, IPTW was calculated as 1/PS in the group of radiotherapy given, whereas 1/(1-PS) in the cohort without radiotherapy administered (17). Stabilization of the IPTW was performed by multiplying the standard IPTW by the probability of undergoing treatment that each patient received (18). Prior to and after IPTW-adjustment, univariate analysis (UVA) of patient characteristics effect on CSS and OS was conducted using the Kaplan-Meier (KM) method, with the log-rank method for evaluation for significance. Multivariable analysis (MVA) was performed through Cox proportional hazards regression model. Covariates enrolled in the MVA model were selected if they were significant in the UVA model. Next, we conducted exploratory subgroup analyses and evaluated heterogeneity as the subgroups are presumed to have been subjected to similar conditions (19). Quantification of heterogeneity was evaluated with the I^2 statistic and the Cochran Q test (20). Random-effects models were used when study heterogeneity was high ($I^2 > 50\%$) and fixed-effects models were employed whereas heterogeneity was low ($I^2 \leq 50\%$) (21). Finally, IPTW-adjusted Kaplan-Meier plots illustrated CSS rates based on radiotherapy administration or not in some selected subgroups. Statistical analyses were executed with SPSS (version 22.0, SPSS, Chicago, IL, USA), R software (version 3.6.3; http://www.r-project.org/) and STATA-MP (version 17.0, College Station, TX, USA), with two-sided $P < 0.05$ considered statistically significant.

Results

Descriptive characteristics of the study population and survival outcome among all subgroups

According to the set criteria, a total of 2897 patients, who were diagnosed as uterine sarcomas as the primary malignancy and underwent total hysterectomy, were extracted during 2010 and 2018 period. The cohort comprised 1582 leiomyosarcomas, 862 endometrial stromal sarcomas, 404 adenosarcomas and 49 undifferentiated uterine sarcomas. 63.55% (1841/2897) of cases were present in stage I, of note, nearly 87% of uterine adenosarcoma presented with stage I disease. The median age at initial diagnosis in the whole cohort was 54 year old [interquartile range (IQR): 47-62 years old]. The median follow-up period was 33 months [interquartile range (IQR): 15-63 months]. The 1-, 3-year and 5-year CSS rates were 56.89%, 39.63% and 24.54% for the whole cohort, respectively. Meanwhile, the corresponding OS rates were 55.02%, and 38.69% and 24.23%, respectively. However, for patients diagnosed between 2016 and 2018, 5-year CSS and rates were

TABLE 2 Baseline characteristics in uterine sarcomas before and after IPTW-adjustment according to RT.

Characteristics	Unadjusted (n = 2897)			IPTW-adjusted (n = 2886)		
	Surgery-RT(n, %)	Surgery + RT(n, %)	P-value	Surgery-RT	Surgry + RT	P-value
Age (years)			0.004*			0.417
<50	886(35.67)	117(28.33)		34.52%	31.29%	
50–60	878(35.35)	148(35.84)		35.47%	36.58%	
>60	720(28.99)	148(35.84)		30.01%	32.13%	
Year of diagnosis			0.000*			0.543
2010–2012	748(30.11)	167(40.44)		31.66%	32.55%	
2013–2015	841(33.86)	139(33.66)		33.82%	35.66%	
2016–2018	895(36.03)	107(25.91)		34.52%	31.80%	
Marital status			0.080			0.945
Married	1297(52.21)	218(52.78)		52.33%	52.68%	
Single/unmarried	622(25.04)	90(21.79)		24.55%	24.30%	
Divorced/separated	270(10.87)	50(12.11)		11.01%	11.54%	
Unknown	135(5.43)	16(3.87)		5.20%	4.21%	
Widowed	160(6.44)	39(9.44)		6.91%	7.26%	
Race			0.519			0.716
Black	428(17.23)	73(17.68)		17.30%	17.07%	
Others	274(11.03)	53(12.83)		11.35%	12.76%	
White	1782(71.74)	287(69.49)		71.35%	70.17%	
Tumor differentiation			0.000*			0.915
I	508(20.45)	36(8.72)		18.74%	16.93%	
II	197(7.93)	26(6.30)		7.70%	7.79%	
III	323(13.00)	66(15.98)		13.39%	12.98%	
IV	538(21.66)	158(38.26)		24.11%	25.42%	
Unknown	918(36.96)	127(30.75)		36.06%	36.88%	
Histology			0.032			0.648
Adenosarcoma	344(13.85)	60(14.53)		13.81%	12.14%	
ESS	746(30.03)	116(28.09)		29.79%	27.98%	
LMS	1359(54.71)	223(54.00)		54.69%	58.02%	
UUS	35(1.41)	14(3.39)		1.72%	1.86%	
AJCC Stage			0.000*			0.129
I	1632(65.70)	209(50.61)		63.35%	57.24%	
II	201(8.09)	73(17.68)		9.60%	10.42%	
III	205(8.25)	38(9.20)		8.36%	10.05%	
IV	446(17.95)	93(22.52)		18.69%	22.29%	
Lymphadenectomy			0.000*			0.767
Yes	819(32.97)	181(43.83)		34.61%	35.42%	
None/unknown	1665(67.03)	232(56.17)		65.39%	64.58%	
Peritoneal Cytology			0.004*			0.913
Negative	911(36.67)	184(44.55)		37.74%	38.05%	
Positive	95(3.82)	19(4.60)		3.94%	3.55%	
Unknown	1478(59.50)	210(50.85)		58.32%	58.40%	
Tumor size (mm)			0.069			0.378
50–100	862(34.70)	156(37.77)		35.21%	35.85%	
<50	420(16.91)	55(13.32)		16.34%	13.45%	
>100	892(35.91)	162(39.23)		36.42%	39.63%	

(*continued*)

TABLE 2 Continued

Characteristics	Unadjusted ($n = 2897$)			IPTW-adjusted ($n = 2886$)		
	Surgery-RT(n, %)	Surgery + RT(n, %)	P-value	Surgery-RT	Surgry + RT	P-value
Unknown	310(12.48)	40(9.69)		12.03%	11.06%	
Chemotherapy			0.000*			0.170
Yes	937(37.72)	229(55.45)		40.46%	44.28%	
No	1547(62.28)	184(44.55)		59.54%	55.72%	
Radiotherapy						
Yes						
No						
Median income			0.178			0.910
$50,000–$65,000	847(34.10)	151(36.56)		34.47%	34.97%	
<$50,000	283(11.39)	56(13.56)		11.72%	12.21%	
>$60,000	1354(54.51)	206(49.88)		53.81%	52.82%	
Rural-urban			0.393			0.643
Rural	209(8.41)	40(9.69)		8.64%	9.48%	
Urabn	2275(91.59)	373(90.31)		91.36%	90.52%	
Months from DX to treatment			0.003*			0.979
<1	1886(75.93)	285(69.01)		74.93%	75.00%	
≥1	598(24.07)	128(30.99)		25.07%	25.00%	

Others *American Indian/Alaskan Native, Asian/Pacific Islander; P value with two asterisks indicates significantly statistical difference. DX, diagnosis; ESS, endometrial stromal sarcoma; LMS, leiomyosarcoma; UUS, undifferentiated uterine sarcoma.

not calculated due to the short follow period. Also, some information about surgeon who performed the surgery was not specified, as well as mode of surgery, open or minimal invasive. For patients with LMS and UUS, shorter survival period was observed compared to those with EES and adenosarcoma. Positive peritoneal cytology posed a significant poorer survival in every specific study period compared to those negative cases. Patients with lymphadenectomy showed similar survival outcomes to those without the procedure. In stage IVB patients, lung was the commonest metastatic site, while all of those with brain metastasis were dead within 1 year after initial diagnosis. Although adjuvant chemotherapy was administered in 40.25% (1166/2897) of cases, no improved survival was shown, conversely, detrimental effect on CSS and OS. Whereas radiotherapy was just administered in 14.26% (413/2897) of patients, beneficial effect was observed on CSS and OS, particularly the combination of external beam and brachytherapy. The demographic and clinical characteristics of these US patients and survival outcome in those subgroups were summarized in Table 1.

Exploration of adjuvant radiotherapy utilization among subgroups

To further investigate the association of radiotherapy among various uterine sarcomas and clinicopathologic parameters, we stratified the cohort by receipt of adjuvant radiotherapy or not. Before PSM and IPTW-adjustment, most baseline characteristics were significantly unbalanced. Patients who received additional radiotherapy tended to be older than 60 years of age, diagnosed between 2010 and 2012, with tumor grade III-IV and tumor size bigger than 50 mm, in groups of AJCC stage II-IV and chemotherapy administration. After PSM and IPTW-adjustment by RT, all baseline characteristics were well balanced with P value >0.05. The results were demonstrated in Table 2.

Univariate and multivariate analysis for cause-specific survival and overall survival

Prior to PSM and IPTW-adjustment, receipt of RT was associated with detrimental CSS (HR 1.17, 95% CI 1.00–1.36) and OS (HR 1.15, 95% CI 0.99–1.33) effect on univariate analysis (UVA), however, improved CSS (HR 0.80, 95% CI 0.68–0.94) and OS (HR 0.79, 95% CI 0.67–0.92) outcome on multivariate analysis (MVA), both with statistical significance. Based on UVA and MVA, chemotherapy showed detrimental effect on CSS and OS ($HR > 1$, $P < 0.001$). Factors associated with worse CSS and OS were patients older than 60 years, black race, single or unmarried status, higher tumor stage and grade, positive peritoneal cytology, tumor size bigger than

TABLE 3 Univariate and multivariate analysis of predicting CSS and OS after IPTW-adjusted in stage I-IV US patients.

Characteristics	Cause-specific survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*
Age (years)								
50–60	Reference		Reference		Reference		Reference	
<50	0.54(0.47–0.63)	<0.001*	0.70(0.60–0.82)	<0.001*	0.55(0.47–0.63)	<0.001*	0.70(0.60–0.81)	<0.001*
>60	1.12(0.98–1.28)	0.091	1.08(0.94–1.24)	0.302	1.21(1.07–1.38)	0.003	1.15(1.00–1.31)	0.049
Year of diagnosis								
2010–2012	Reference				Reference			
2013–2015	0.94 (0.82–1.08)	0.398			0.97 (0.85–1.11)	0.622		
2016–2018	0.97 (0.83–1.13)	0.672			0.99 (0.85–1.15)	0.871		
Marital status								
Divorced/separated	Reference		Reference		Reference		Reference	
Married	1.04(0.85–1.27)	0.689	0.99(0.82–1.22)	0.992	1.02(0.84–1.23)	0.858	0.98(0.80–1.19)	0.806
Single/unmarried	1.33(1.07–1.64)	0.011	1.27(1.02–1.58)	0.031	1.27(1.04–1.57)	0.022	1.23(1.00–1.52)	0.049
Unknown	1.10(0.81–1.51)	0.538	1.15(0.84–1.58)	0.397	1.07(0.79–1.45)	0.647	1.12(0.83–1.53)	0.454
Widowed	1.41(1.07–1.86)	0.015	1.23(0.93–1.63)	0.153	1.51(1.17–1.96)	0.002	1.29(0.99–1.68)	0.063
Race								
Black	Reference		Reference		Reference		Reference	
White	0.72(0.62–0.83)	<0.001*	0.80(0.69–0.93)	0.004	0.71(0.62–0.82)	<0.001*	0.80(0.70–0.92)	0.002
Others	0.58(0.46–0.73)	<0.001*	0.71(0.56–0.90)	0.005	0.60(0.48–0.74)	<0.001*	0.73(0.58–0.91)	0.006
Tumor grade								
I	Reference		Reference		Reference		Reference	
II	2.451(1.58–3.79)	<0.001*	2.28(1.46–3.56)	<0.001*	2.05(1.38–3.05)	<0.001*	1.90(1.26–2.87))	0.002
III	12.20(8.67–11.17)	<0.001*	7.60(5.23–11.03)	<0.001*	10.21(7.53–13.83)	<0.001*	6.52(4.66–9.11)	<0.001*
IV	11.77(8.48–16.35)	<0.001*	6.96(4.88–9.93)	<0.001*	9.54(7.14–12.75)	<0.001*	5.76(4.9–7.91)	<0.001*
Unknown	7.02(5.06–9.75)	<0.001*	5.02(3.50–7.19)	<0.001*	5.76(4.316–7.69)	<0.001*	4.17(3.02–5.75)	<0.001*
Histology								
Adenosarcoma	Reference		Reference		Reference		Reference	
ESS	1.21(0.94–1.55)	0.134	1.31(1.01–1.72))	0.042	1.11(0.88–1.40)	0.36	1.22(0.96–1.57)	0.106
LMS	2.68(2.15–3.34)	<0.001*	1.24(0.97–1.57)	0.085	2.41(1.96–2.95)	<0.001*	1.16(0.93–1.45)	0.186
UUS	3.19(2.07–4.92)	<0.001*	1.21(0.77–1.90)	0.403	3.00(2.00–4.51)	<0.001*	1.18(0.77–1.80)	0.442
AJCC Stage								
I	Reference		Reference		Reference		Reference	
II	1.85 (1.51–2.27)	<0.001*	1.65(1.33–2.04)	<0.001*	1.82 (1.50–2.22)	<0.001*	1.65(1.34–2.02)	<0.001*
III	3.67(3.04–4.39)	<0.001*	2.38(1.95–2.89)	<0.001*	3.44(2.88–4.12)	<0.001*	2.30(1.90–2.78)	<0.001*
IV	4.94 (4.31–5.66)	<0.001*	2.99(2.56–3.50)	<0.001*	4.72 (4.14–5.38)	<0.001*	2.98(2.56–3.47)	<0.001*
Lymphadenectomy								
None/unknown	Reference				Reference			
Yes	0.93 (0.82–1.05)	0.264			0.93 (0.83–1.05)	0.221		
Peritoneal Cytology								
Negative	Reference		Reference		Reference		Reference	
Unknown	1.10 (0.97–1.25)	0.132	1.01(0.89–1.14)	0.921	1.07 (0.95–1.21)	0.239	0.9 (0.88–1.12)	0.926
Positive	2.99 (2.34–3.82)	<0.001*	1.62(1.26–2.09)	<0.001*	2.99 (2.37–3.79)	<0.001*	1.64(1.29–2.09)	<0.001*
Tumor size (mm)								
50–100	Reference		Reference		Reference		Reference	
<50	0.43 (0.33–0.54)	<0.001*	0.68(0.53–0.87)	0.002	0.48 (0.39–0.60)	<0.001*	0.75(0.60–0.94)	0.013

(*continued*)

TABLE 3 Continued

Characteristics	Cause-specific survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*	HR (95% CI) *P*	*P*
>100	1.96 (1.72–2.23)	<0.001*	1.32(1.15–1.52)	<0.001*	1.92 (1.69–2.18)	<0.001*	1.31(1.15–1.50)	<0.001*
Unknown	0.78 (0.63–0.97)	0.022	0.92(0.73–1.14)	0.436	0.76 (0.62–0.94)	0.011	0.90(0.73–1.11)	0.326
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	3.31 (2.93–3.73)	<0.001*	1.30(1.13–1.50)	<0.001*	3.11 (2.77–3.49)	<0.001*	1.27(1.11–1.46)	0.001
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	1.14 (0.98–1.34)	0.093	0.83(0.96–1.25)	0.029	1.13 (0.97–1.33)	0.126	0.81(069–0.95)	0.011
Median income								
$50,000–$65,000	Reference				Reference			
<$50,000	0.98(0.81–1.19)	0.815			1.01(0.83–1.21)	0.958		
>$65,000	0.94(0.83–1.07)	0.340			0.95(0.84–1.08)	0.443		
Rural-urban area								
Rural	Reference				Reference			
Urabn	1.13(0.91–1.40)	0.266			1.12(0.91–1.37)	0.294		
Months from DX to treatment								
<1	Reference		Reference		Reference		Reference	
≥1	1.33(1.17–1.51)	<0.001*	1.09(0.96–1.25)	0.195	1.32(1.17–1.50)	<0.001*	1.07(0.94–1.22)	0.299

Inverse probability of treatment weighting (IPTW)-adjusted univariate and multivariable analysis. UVA included all variables and MVA included those with $P < 0.1$ on UVA.
*A hazard ratio (HR) of <1 favors surgery followed by RT and HR > 1 favors hysterectomy without RT given.

50 mm. Worse CSS and OS were also seen in patients administered with chemotherapy. Similar results were obtained following PSM and IPTW-adjustment by RT. CSS and OS improvements in patients who underwent RT persisted, as did the CSS and OS detriments associated with all other significant factors pre-adjustment. Adjusted and unadjusted UVA and MVA were shown in Table 3 and Supplementary Table S1, respectively.

Exploratory subgroup analysis in stage I-IV patients

Based on the above analysis, radiotherapy showed beneficial effect of survival outcome, which promoted us to further explore who will finally benefit from radiotherapy administration. An exploratory subgroup analysis was conducted as shown in the forest plot (Figure 2). Before matching, heterogeneity was high ($I^2 > 50\%$) on fixed-effects model, interestingly, after matching by RT, heterogeneity was evidently decreased in both CSS and OS analysis ($I^2 < 50\%$). Therefore, we explored the fixed-effects model to illustrate the result. Prior to IPTW- adjustment, there were several subgroups with possible improved CSS (Figure 2A) and OS (Figure 2B) after RT administration, including patients older than 60 years of age, tumor grade III-IV, AJCC stage II-IV, LMS and UUS histology, positive peritoneal cytology, tumor size bigger than 100 mm, and those given with adjuvant chemotherapy. After IPTW-adjustment, improved CSS (Figure 2C) and OC (Figure 2D) were persistently observed in patients with LMS and UUS, tumor grade IV, AJCC stage III-IV, tumor size bigger than 100 mm, and with chemotherapy administration, although only patients in stage III showed statistical significance ($P < 0.05$).

Cause-specific survival analysis for stage II-IV US patients in selected subgroups

As demonstrated above, patients in stage II-IV possibly benefit from RT administration, interestingly, similar effect in CSS and OS. Therefore, we further explored RT impact on CSS in specific subgroups. A total of 1056 patients were identified within the stage II-IV cohort, of whom, 664 patients were diagnosed with LMS, 346 cases presented with tumor grade IV, 570 cases had bigger tumor size (>100 mm) and 694 patients received chemotherapy as part of their partial treatment. After IPTW-adjustment, patients in stage II-IV, particularly with LMS histology, tumor grade IV, tumor size bigger than 100 mm had improved CSS (Figures 3A–C,

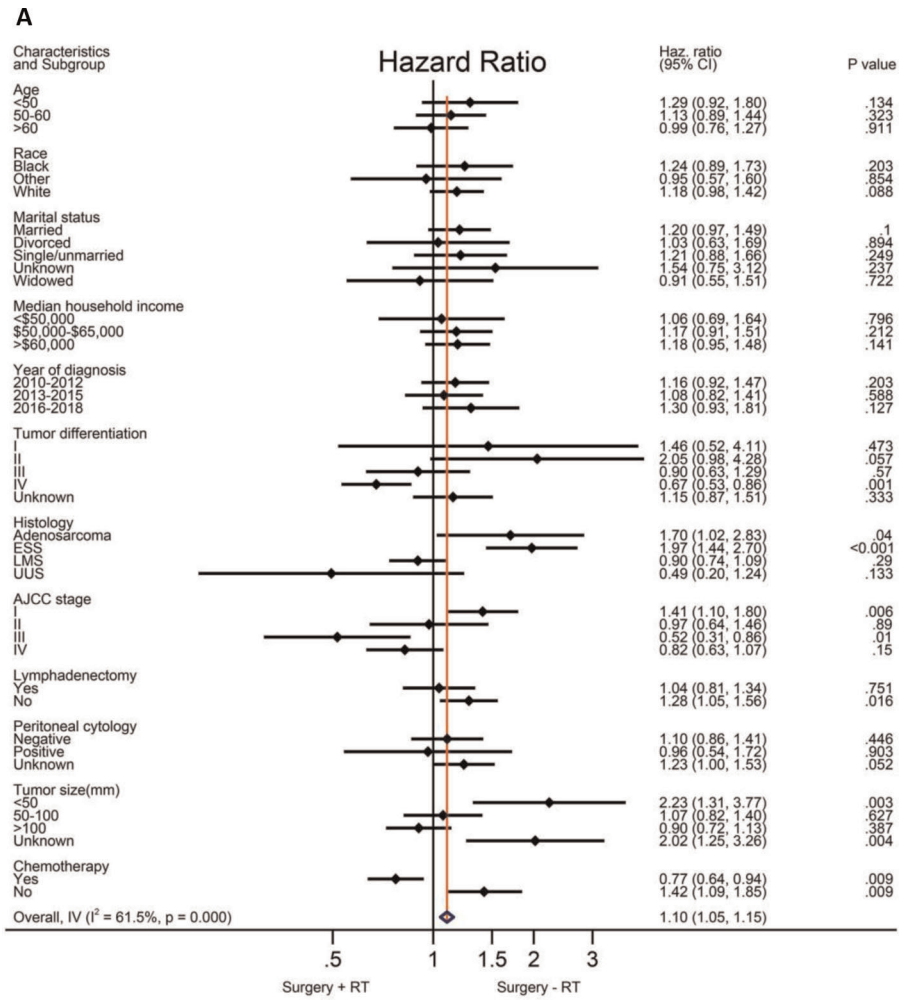

FIGURE 2
Exploratory subgroup analysis concerning radiotherapy impact on survival outcome in the whole cohort. (A) Cause-specific survival before IPTW-adjustment. (B) Overall survival before IPTW-adjustment. (C) Cause-specific survival after IPTW-adjustment. (D) Overall survival after IPTW-adjustment. CI: confidence interval; HR: hazard ratio; LMS: leiomyosarcoma; ESS: endometrial stromal sarcoma; USS: undifferentiated uterine sarcoma; IPTW: inverse probability of treatment weighting. The vertical solid-line refers to a hazard ratio of 1.0. HR < 1 favors surgery followed by radiotherapy and HR > 1 favors surgery without radiotherapy administered. $P < 0.05$ indicates statistical significance. (continued)

HR < 1, $P < 0.05$), however, no improvement in ESS patients (Figure 3D) across all tumor grades. Moreover, we performed survival analysis for USS in combination with HG-ESS (grade III/IV) at stage II-IV given the limited number of USS, and observed RT use could improve survival outcome. Among those cases who received chemotherapy, there was also improvement in CSS (Figure 3E). In contrast, no survival improvement was observed after RT given alone without CHT (Figure 3F).

Discussion

Using the population-based, cancer registry SEER database and restricting the analysis to more recent period between 2010 and 2018, we gradually demonstrated a substantial survival improvement for high-risk patients with uterine sarcomas, when incorporating radiotherapy as an integral part following total hysterectomy. Most importantly, this benefit remained significant after stabilized IPTW adjustment to control for confounding factors and conditional landmark analysis, reducing the possibility that this conclusion suffered from selection bias and immortality bias, respectively. To our known, our analysis was the most up-to date, the first attempt to account for comprehensive confounding factors, and also encompassed a relatively wide spectrum of histological subtypes of uterine sarcomas.

Although chemotherapy was given in nearly 40% of patients in the present study, detrimental effect was observed at each specific follow-up period. The result promoted us to account

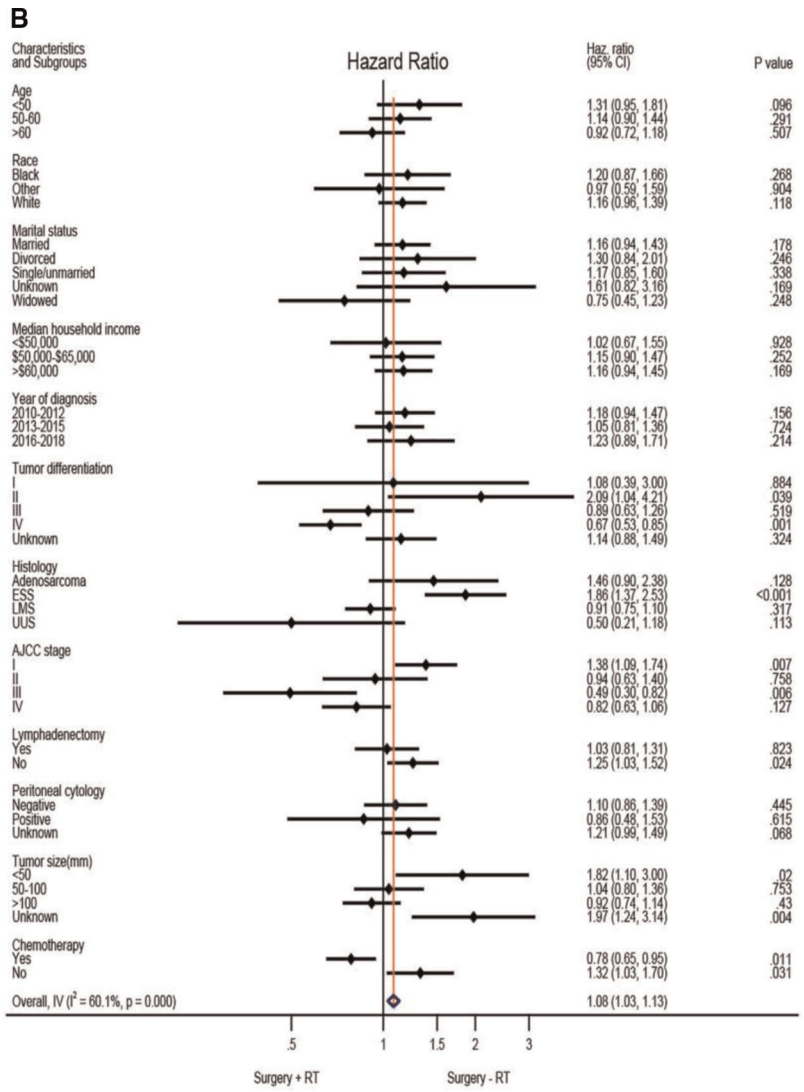

FIGURE 2
Continued.

for chemotherapy as a confounding factor and then focused radiotherapy impact on survival improvement, thus the corresponding results representing better balance between patients with or without adjuvant radiotherapy administration. Furthermore, exploratory subgroup analysis suggested the benefit of radiotherapy trended towards significance among the subgroup of patients receiving chemotherapy, although chemotherapy was found to be related to detrimental effect compared to no chemotherapy administration. This controversy might be explained by that chemotherapy was usually given in high-risk patients with poor prognosis. The subgroup analysis also indicated adjuvant radiotherapy was of detrimental for women with stage I disease in comparison to those who were treated with surgery alone, consistent with one previous largest SEER report regarding RT impact on uterine sarcomas patients (13). It is worth mentioning that RT was suggestive of potential benefit for patients with poor prognostic factors such as stage II-IV, grade IV, bigger tumor, in particular, patients with uLMS may benefit most from radiotherapy.

In cases of uterine LMS, due to its high recurrence rates (45%–75%) and extremely low 5-year survival rate (10%–15%) in metastatic disease (22), there has been great interest in exploring adjuvant therapy following surgery to reduce the risk of recurrence and improve survival. Yet, the utility of adjuvant RT has long been debated, given the majority of literature addressing the problem limited to retrospective reviews. The highest level of evidence from one prospective trial, the European Organization for Research and Treatment of Cancer (EORTC) protocol 55874, evaluated the impact of

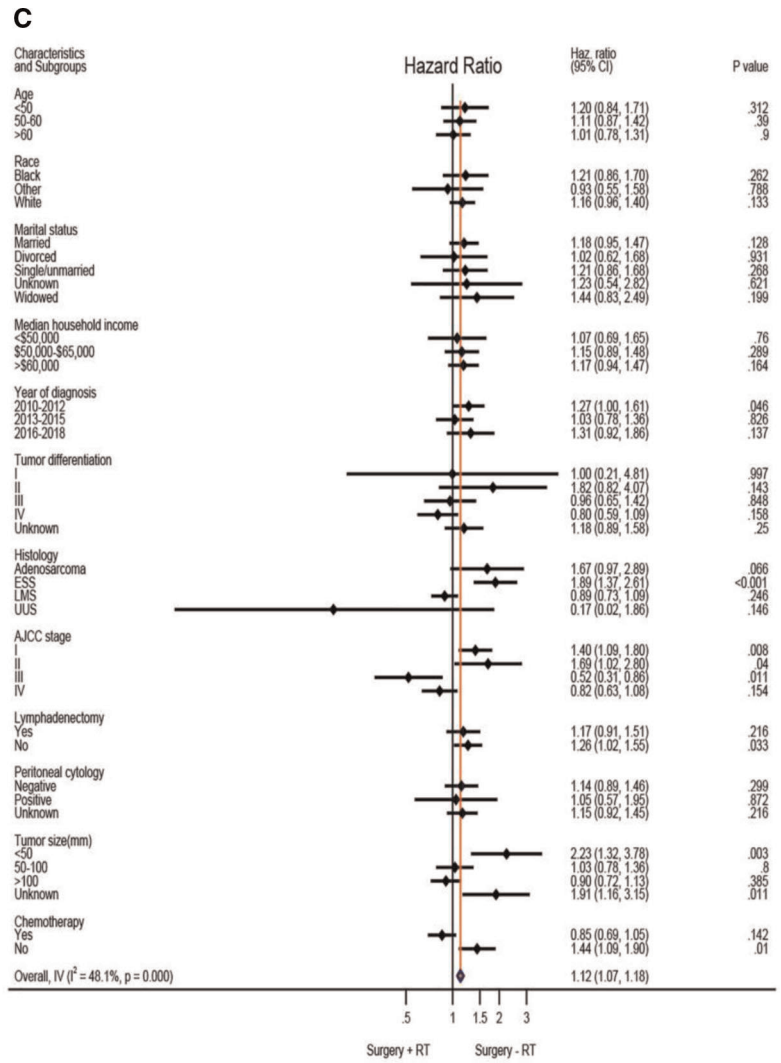

FIGURE 2
Continued.

adjuvant RT on patients with stage I or II uterine sarcomas. As expected, the subgroup analysis of patients with uterine LMS indicated no benefit from RT in achieving either overall survival or local control, conversely a trend towards shorter OS period in the RT arm (23). Mahdavi et al. (24) investigated 147 patients with uterine LMS reported from 11 regional medical centers from 1985 to 2005 and then found the 5-year survival of patients who undertook radiotherapy was significantly higher than those who did not (70% vs. 35%); however, the survival advantage was no longer evident at 7.5 years. In addition, the local recurrence rate was lower in the radiotherapy group. The French Sarcoma Group compared adjuvant chemotherapy followed by RT with RT alone in surgically removed stage I-III uterine sarcomas including LMS. The 3-year DFS was 55% for adjuvant chemoradiotherapy vs. 41% for RT alone. Unfortunately, the study was prematurely closed for accrual futility (25). The above three studies either did not balance baseline characteristics to account for the receipt of chemotherapy, or not perform subgroup analysis in a wide perspective. Determining optimal adjuvant therapy is further confused in that stage II patients are often grouped with stage I subjects in clinical trials. Considering a number of unmeasured confounders influenced RT use, our study adjusted the confounding factors, finally, identifying RT use could possibly improve OS and CSS in stage II-IV LMS patients. This conclusion was in accordance with both ESMO and NCCN guidelines, both of which concluded RT is not recommended for stage I uLMS and should be discussed with patients in cases with higher stages considering special risk factors, such as mitotic count, age and tumor necrosis (26, 27). Based on the limited literature, in the advanced stage that is

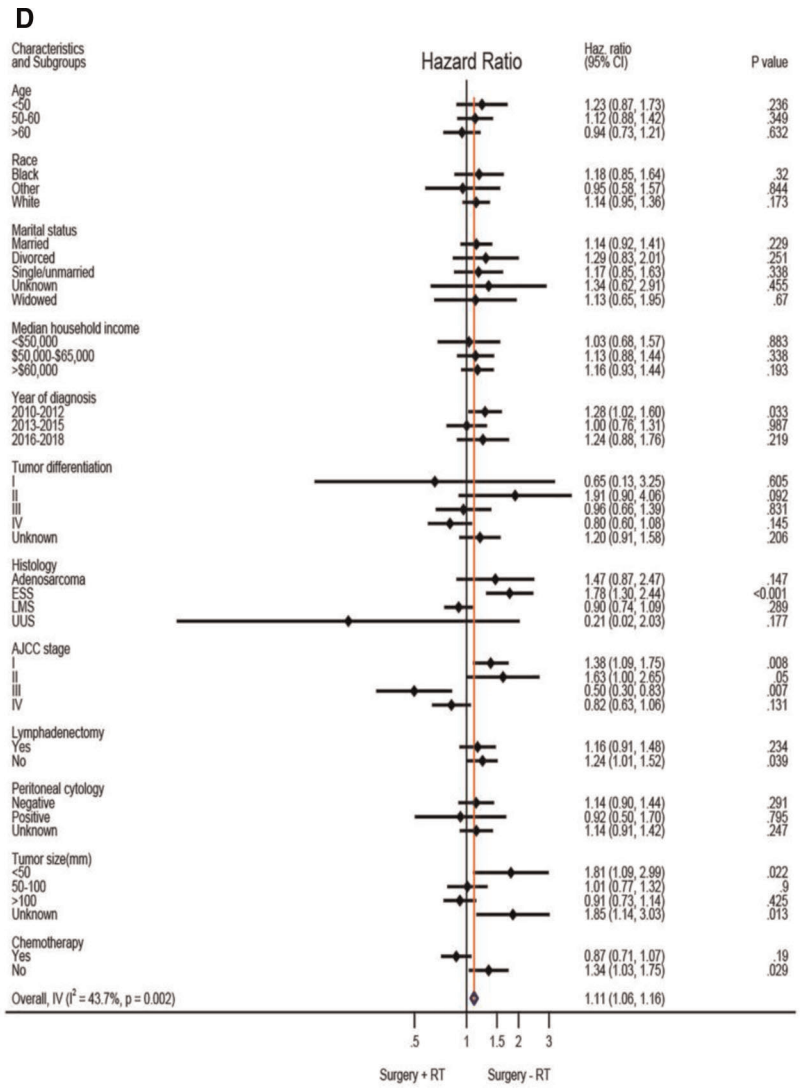

FIGURE 2
Continued.

incompletely removed or metastatic disease, radiotherapy is persistently valuable when used in palliative treatment to distant locations (15), although adjuvant systemic chemotherapy is usually administered for unresectable advanced or recurrent disease (28).

With regard to endometrial stromal sarcoma (ESS), which represents the most common stromal sarcoma after leiomyosarcoma by frequency, several changes have been made in its classification. According to the recent 2020 WHO classification (29), it is currently divided into four main categories: endometrial stromal nodules, low-grade ESS (LG-ESS), high-grade ESS (HG-ESS) and undifferentiated uterine sarcoma (USS). Recurrences develop in 23–59% of all patients with ESS, and 15%–25% of these patients die of recurrent disease (30). In particular, HG-ESS showed a poor prognosis, with the 5-year survival rate of approximately 25%–30%. More than 60% of UUS patients are diagnosed at advanced stage and associated with an extremely poor prognosis (11). Due to the rarity and diversity of histology, there is no consensus or high level of evidence to support RT use in ESS. Some retrospective studies reported external pelvic radiation in patients across various stages of disease with HG-ESS and UUS to decrease local recurrence and improve overall survival (30, 31), although did not affect OS and PFS for low grade histology (32). However, NCCN guideline recommended observation after total hysterectomy with bilateral salpingoopherectomy (TAHBSO) for patients with stage I ESS irrespective of tumor grade, for stage II-IV TAHBSO, anti-estrogen hormone therapy and external beam could be performed for LG-ESS, systematic therapy and/or external beam radiation therapy for HG-ESS.

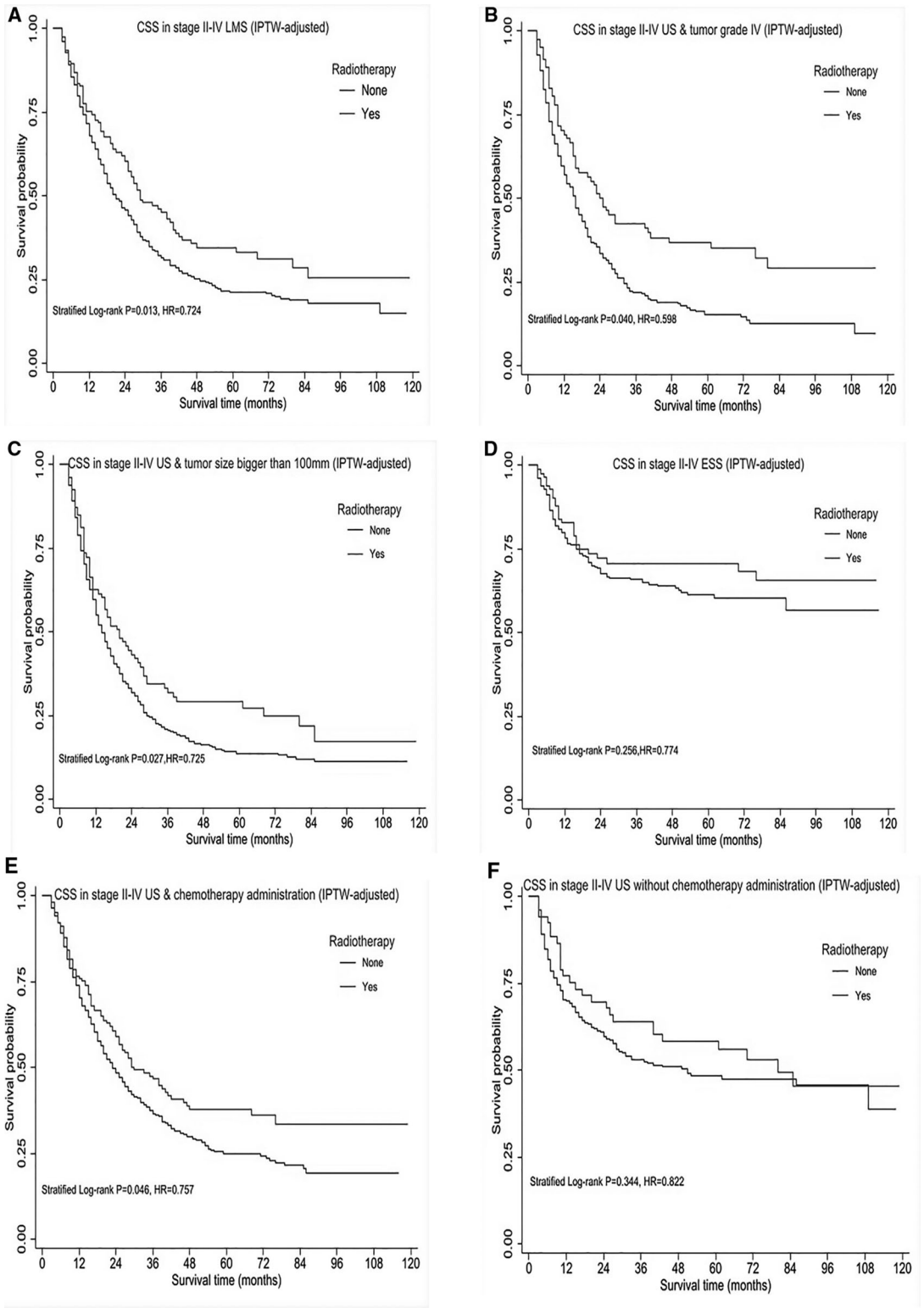

FIGURE 3
Subgroup survival analysis of cause-specific survival (CSS) in stage II-IV uterine sarcomas, after IPTW-adjustment by receipt of postoperative radiotherapy. (**A**) CSS in stage II-IV uterine leiomyosarcoma. (**B**) CSS in stage II-IV uterine sarcomas with tumor grade IV. (**C**) CSS in stage II-IV uterine sarcomas with tumor size bigger than 100mm. (**D**) CSS in stage II- IV ESS across all tumor grades. (**E**) CSS in stage II- IV uterine sarcomas treated by chemotherapy with/without radiotherapy. (**F**) CSS in stage II-IV uterine sarcomas without chemotherapy administration. HR < 1 favors surgery followed by radiotherapy and HR > 1 favors surgery without radiotherapy administered. $P < 0.05$ indicates statistical significance.

Given small sample of USS and similar poor prognosis between USS and HG-ESS, our study performed survival analysis for USS in combination with HG-ESS at stage II-IV, and observed RT use could improve survival outcome, although no statistical significance at stage II-IV ESS across all tumor grades. This discrepancy between our study and NCCN guideline could be explained by HG-ESS reintroduced in 2014 (33) and experienced several alterations before then, yet our study included patients from 2010. Another potential explanation is that UUS is an extremely rare uterine sarcoma and represents the exclusion of diagnosis, thus no clear distinction between HG-ESS and UUS, limiting our analysis for RT impact on UUS and HG-ESS separately.

Similar to other uterine sarcomas, the majority of uterine adenosarcoma present with stage I disease in our study. Previous studies often pooled adenosarcoma with malignant Müllerian mixed tumors or other uterine mesenchymal neoplasms in adjuvant treatment strategies. Consequently, adjuvant treatment regimens did not reach consensus in general, only few studies in the literature referring to adjuvant therapy after complete staging surgery. However, it has been stated that patients at low risk of disease recurrence required observation alone, whereas for high-risk patients chemotherapy may be recommended (1, 34). Notably, in the 2016 National Cancer Data Base study of Müllerian adenosarcomas, adjuvant radiotherapy were reported to associate with a decreased overall survival (35). Both UVA and MVA in our study suggested adenosarcoma of better CSS and OS compared to other histological subtypes, yet small number of stage II-IV adenosarcomas restricted our analysis of adjuvant therapy effect on survival outcome.

Moreover, we also identified other potential prognostic factors, for instance, positive peritoneal cytology and bigger tumor. Survival period of US patients with positive peritoneal cytology was significantly shorter compared with those with negative cytology results, which agreed with the recent SEER analysis that recommended routine cytology testing at surgical treatment (36). Interestingly, the subgroup analysis prior to matching found radiotherapy meaningful in those cases with malignant peritoneal cytology, although the significance was not evident after matching, likely due to underestimate of peritoneal cytology as a prognostic factor in uterine sarcoma. Concerning tumor size, it is well recognized that the cut-off value between stage IA and stage IB is defined as 5 cm, based on 2009 FIGO staging system for LMS and ESS (37). However, only 25% of LMS measure less than 5 cm, typically voluminous tumors with a mean diameter of 10 cm (5). Hence, we divided tumor size with the cut-off point of 50 and 100 mm, consequently, demonstrating tumor size bigger than 100 mm as a possible indicator for radiotherapy utilization.

Although we attempted to account for nonrandom selection of patients, we recognized several inherent methodological limitations in this retrospective database analysis. First, our data lacked detailed information regarding tumor margin status which could have influenced the decision and effect of adjuvant therapy. Second, due to the unavailability of information in the SEER database, specific details on RT dose and technique, the effect of course as well as regimen of chemotherapy, sequencing with respect to adjuvant, neoadjuvant, or coadministration with RT remain unknown. Additionally, the current SEER database did not provide accurate distinction between none versus unknown chemotherapy receipt. Third, the SEER database did not describe specific surgery procedure such as the person who performed the surgery as well as mode of surgery, open or minimal invasive. Fourth and most importantly, our analysis focused primarily on OS and CSS, without details concerning local recurrence and distant metastasis after initial treatment, which could have important implications for the impact of adjuvant therapy in this patient population.

Conclusions

Uterine sarcomas raise many controversies in oncogynecological practice. The results of the present study, in a stepwise process, suggested adjuvant radiotherapy might be underutilized, and proper use of adjuvant radiotherapy combined with chemotherapy after surgery in advanced stage and high-risk patients might improve survival. Prospective trials exploring precision medicine based on molecular profiles are still needed to determine the optimal adjuvant therapy for this rare disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SY was responsible for study planning. ZH was responsible for data collection, statistical analysis and manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Ningbo Natural Science Foundation (grant no. 2018A610331).

Acknowledgments

The authors sincerely thank all the staff of the SEER program for their important work and diligent effort.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.985654/full#supplementary-material.

References

1. Nathenson MJ, Conley AP. Prognostic factors for uterine adenosarcoma: a review. *Expert Rev Anticancer Ther.* (2018) 18:1093–100. doi: 10.1080/14737140.2018.1518136

2. Hensley ML, Chavan SS, Solit DB, Murali R, Soslow R, Chiang S, et al. Genomic landscape of uterine sarcomas defined through prospective clinical sequencing. *Clin Cancer Res.* (2020) 26:3881–8. doi: 10.1158/1078-0432.CCR-19-3959

3. Capozzi VA, Monfardini L, Ceni V, Cianciolo A, Butera D, Gaiano M, et al. Endometrial stromal sarcoma: a review of rare mesenchymal uterine neoplasm. *J Obstet Gynaecol Res.* (2020) 46:2221–36. doi: 10.1111/jog.14436

4. Denschlag D, Ulrich UA. Uterine carcinosarcomas - diagnosis and management. *Oncol Res Treat.* (2018) 41:675–9. doi: 10.1159/000494335

5. Mbatani N, Olawaiye AB, Prat J. Uterine sarcomas. *Int J Gynaecol Obstet.* (2018) 143 Suppl 2:51–8. doi: 10.1002/ijgo.12613

6. Nasioudis D, Mastroyannis SA, Latif NA, Ko EM, Haggerty AF, Kim SH, et al. Role of lymphadenectomy for apparent early stage uterine sarcoma; a comprehensive analysis of the National Cancer Database. *Surg Oncol.* (2021) 38:101589. doi: 10.1016/j.suronc.2021.101589

7. Mercorio A, Della Corte L, Vetrella M, Russo M, Serafino P, Palumbo M, et al. Uterine fibroids morcellation: a puzzle topic. *Minim Invasive Ther Allied Technol.* (2022) 31:1–9. doi: 10.1080/13645706.2022.2095872

8. Raspagliesi F, Maltese G, Bogani G, Fucà G, Lepori S, De Iaco P, et al. Morcellation worsens survival outcomes in patients with undiagnosed uterine leiomyosarcomas: a retrospective MITO group study. *Gynecol Oncol.* (2017) 144:90–5. doi: 10.1016/j.ygyno.2016.11.002

9. Ganjoo KN. Uterine sarcomas. *Curr Probl Cancer.* (2019) 43:283–8. doi: 10.1016/j.currproblcancer.2019.06.001

10. Juhasz-Böss I, Gabriel L, Bohle RM, Horn LC, Solomayer EF, Breitbach GP. Uterine leiomyosarcoma. *Oncol Res Treat.* (2018) 41:680–6. doi: 10.1159/000494299

11. Horng HC, Wen KC, Wang PH, Chen YJ, Yen MS, Ng HT. Uterine sarcoma Part II-Uterine endometrial stromal sarcoma: the TAG systematic review. *Taiwan J Obstet Gynecol.* (2016) 55:472–9. doi: 10.1016/j.tjog.2016.04.034

12. Desar IME, Ottevanger PB, Benson C, van der Graaf WTA. Systemic treatment in adult uterine sarcomas. *Crit Rev Oncol Hematol.* (2018) 122:10–20. doi: 10.1016/j.critrevonc.2017.12.009

13. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. *Int J Gynecol Cancer.* (2016) 26:1098–104. doi: 10.1097/IGC.0000000000000720

14. Squires BS, Quinn TJ, Nandalur SR, Jawad MS. Adjuvant radiotherapy improves overall survival when added to surgery and chemotherapy for uterine carcinosarcoma: a surveillance, epidemiology, and end results analysis. *Int J Clin Oncol.* (2021) 26:2282–94. doi: 10.1007/s10147-021-02007-6

15. Diggs A, Sia TY, Huang Y, Gockley A, Melamed A, Khoury-Collado F, et al. Utilization and outcomes of adjuvant therapy for stage II and III uterine leiomyosarcoma. *Gynecol Oncol.* (2022) 166:308–16. doi: 10.1016/j.ygyno.2022.05.018

16. Kane LT, Fang T, Galetta MS, Goyal DKC, Nicholson KJ, Kepler CK, et al. Propensity score matching: a statistical method. *Clin Spine Surg.* (2020) 33:120–2. doi: 10.1097/BSD.0000000000000932

17. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* (2008) 168:656–64. doi: 10.1093/aje/kwn164

18. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* (2015) 34:3661–79. doi: 10.1002/sim.6607

19. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg.* (2018) 27:317–21. doi: 10.1093/icvts/ivy163

20. Bowden J, Tierney JF, Copas AJ, Burdett S. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med Res Methodol.* (2011) 11:41. doi: 10.1186/1471-2288-11-41

21. Foreman J, Salim AT, Praveen A, Fonseka D, Ting DSW, Guang He M, et al. Association between digital smart device use and myopia: a systematic review and meta-analysis. *Lancet Digit Health.* (2021) 3:e806–e18. doi: 10.1016/S2589-7500(21)00135-7

22. Roberts ME, Aynardi JT, Chu CS. Uterine leiomyosarcoma: a review of the literature and update on management options. *Gynecol Oncol.* (2018) 151:562–72. doi: 10.1016/j.ygyno.2018.09.010

23. Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *Eur J Cancer.* (2008) 44:808–18. doi: 10.1016/j.ejca.2008.01.019

24. Mahdavi A, Monk BJ, Ragazzo J, Hunter MI, Lentz SE, Vasilev SA, et al. Pelvic radiation improves local control after hysterectomy for uterine leiomyosarcoma: a 20-year experience. *Int J Gynecol Cancer.* (2009) 19:1080–4. doi: 10.1111/IGC.0b013e3181acae50

25. Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. *Ann Oncol.* (2013) 24:1099–104. doi: 10.1093/annonc/mds545

26. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* (2018) 29:iv51–67. doi: 10.1093/annonc/mdy096

27. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* (2018) 16:170–99. doi: 10.6004/jnccn.2018.0006

28. Asano H, Isoe T, Ito YM, Nishimoto N, Watanabe Y, Yokoshiki S, et al. Status of the current treatment options and potential future targets in uterine leiomyosarcoma: a review. *Cancers (Basel).* (2022) 14:1180–93. doi: 10.3390/cancers14051180

29. Akaev I, Yeoh CC, Rahimi S. Update on endometrial stromal tumours of the uterus. *Diagnostics (Basel)* (2021) 11:429–48. doi: 10.3390/diagnostics11030429

30. Cabrera S, Bebia V, Acosta U, Franco-Camps S, Mañalich L, García-Jiménez A, et al. Survival outcomes and prognostic factors of endometrial stromal sarcoma and undifferentiated uterine sarcoma. *Clin Transl Oncol*. (2021) 23:1210–9. doi: 10.1007/s12094-020-02512-6

31. Meurer M, Floquet A, Ray-Coquard I, Bertucci F, Auriche M, Cordoba A, et al. Localized high grade endometrial stromal sarcoma and localized undifferentiated uterine sarcoma: a retrospective series of the French Sarcoma Group. *Int J Gynecol Cancer*. (2019) 29:691–8. doi: 10.1136/ijgc-2018-000064

32. Seagle BL, Shilpi A, Buchanan S, Goodman C, Shahabi S. Low-grade and high-grade endometrial stromal sarcoma: a National Cancer Database study. *Gynecol Oncol*. (2017) 146:254–62. doi: 10.1016/j.ygyno.2017.05.036

33. Conklin CM, Longacre TA. Endometrial stromal tumors: the new WHO classification. *Adv Anat Pathol*. (2014) 21:383–93. doi: 10.1097/PAP.0000000000000046

34. Ulrich UA, Denschlag D. Uterine adenosarcoma. *Oncol Res Treat*. (2018) 41:693–6. doi: 10.1159/000494067

35. Nathenson MJ, Ravi V, Fleming N, Wang WL, Conley A. Uterine adenosarcoma: a review. *Curr Oncol Rep*. (2016) 18:68. doi: 10.1007/s11912-016-0552-7

36. Matsuo K, Matsuzaki S, Nusbaum DJ, Ki S, Chang EJ, Klar M, et al. Significance of malignant peritoneal cytology on survival of women with uterine sarcoma. *Ann Surg Oncol*. (2021) 28:1740–8. doi: 10.1245/s10434-020-09202-1

37. Prat J. FIGO Staging for uterine sarcomas. *Int J Gynaecol Obstet*. (2009) 104:177–8. doi: 10.1016/j.ijgo.2008.12.008

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 11 August 2022
DOI 10.3389/fonc.2022.891710

OPEN ACCESS

EDITED BY
Giuseppe Brisinda,
Agostino Gemelli University Polyclinic (IRCCS), Italy

REVIEWED BY
Carolyn Nessim,
Ottawa Hospital, Canada
Sonal Sharma,
University of Delhi, India

*CORRESPONDENCE
Jolene Si Min Wong
jolene.wong.s.m@singhealth.com.sg

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 08 March 2022
ACCEPTED 18 July 2022
PUBLISHED 11 August 2022

CITATION
Paik B, Seo CJ, Tan JW-S, Juan WKD, Soo KC, Ong C-AJ, Chia CS and Wong JSM (2022) A systematic review of margin status in retroperitoneal liposarcomas: Does the R0 margin matter? *Front. Oncol.* 12:891710. doi: 10.3389/fonc.2022.891710

A systematic review of margin status in retroperitoneal liposarcomas: Does the R0 margin matter?

Benjamin Paik[1,2,3], Chin Jin Seo[1,2,4], Joey Wee-Shan Tan[1,2,5], Wen Kai Darryl Juan[1,2], Khee Chee Soo[1,2], Chin-Ann Johnny Ong[1,2,4,5,6,7], Claramae Shulyn Chia[1,2,4,6] and Jolene Si Min Wong[1,2,4,6]*

[1]Department of Sarcoma, Peritoneal and Rare Tumours (SPRinT), Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore, [2]Department of Sarcoma, Peritoneal and Rare Tumours (SPRinT), Division of Surgery and Surgical Oncology, Singapore General Hospital, Singapore, Singapore, [3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, [4]Sing Health Duke-NUS Surgery Academic Clinical Program, Duke-NUS Medical School, Singapore, Singapore, [5]Laboratory of Applied Human GenetiCJS, Division of Medical Sciences, National Cancer Centre Singapore, Singapore, Singapore, [6]Sing Health Duke-NUS Oncology Academic Clinical Program, Duke-NUS Medical School, Singapore, Singapore, [7]Institute of Molecular and Cell Biology, ASTAR Research Entities, Singapore, Singapore

Retroperitoneal liposarcomas (RPLPSs) are a rare tumor group for which current guidelines recommend aggressive *en bloc* resection to attain microscopically negative (R0) margins. To ensure R0 margins, resection of adherent or adjacent organs is often required. However, it is still unclear if R0 margins confer any additional benefit to patients over a grossly negative but microscopically positive (R1) margin. We performed a systematic search of PubMed and Embase databases for studies including patients receiving R0 or R1 resection for RPLPS. Nine retrospective cohort studies, one prospective cohort study, and 49 case reports/case series were included. A total of 552 patients with RPLPS were evaluated: 346 underwent R0 resection and 206 underwent R1 resection. In the R0 group, 5-year overall survival (OS) ranged from 58.3% to 85.7%; local recurrence (LR) ranged from 45.5% to 52.3%. In the R1 group, 5-year OS ranged from 35% to 55.3%; LR ranged from 66.7% to 91.7%. Among cohort studies, OS, disease-free survival (DFS), LR rate, and LR-free survival (LRFS) were significantly associated with R0 resections. Assessment of case series and reports suggested that the R0 margin led to a slightly higher morbidity than that of R1. In conclusion, this review found the R0 margin to be associated with reductions in LR rates and improved OS when compared with the R1 margins, though accompanied by slight increases in morbidity. The roles of tumor histotype and perioperative chemotherapy or radiotherapy were not well-elucidated in this review.

KEYWORDS

liposarcoma, margin, retroperitoneal, sarcoma, R0

1 Introduction

Retroperitoneal soft tissue sarcomas are uncommon and affect less than 0.1% of the population (1). Among them, a multitude of histological subtypes exist, with liposarcomas (LPSs) representing the most common histotype (2). Favorable survival profiles and lower propensity for distant metastases in LPS, especially in the well-differentiated (WDLPS) and low-grade dedifferentiated (DDLPS) patients (3), have generated great interest among sarcoma surgeons. For once, when tumor biology is "favorable," the surgeon is now at the helm to possibly dictate patient outcomes *via* strategies to lower local recurrence (LR) rates.

Up-front extended resection (ER) to achieve microscopically clear (R0) margins was introduced by Gronchi et al. (4) and has been shown to significantly lower rates of LR with acceptable morbidity and mortality profile. While adopted by most of Europe and the Trans-Atlantic group (TARPSWG) (5), differing opinions continue to exist regarding the utility of such an aggressive surgical approach in the management of retroperitoneal sarcomas (RPS). Few would argue for the preservation of involved or encased organs; as such, the debate lies mainly in the *en bloc* removal of adherent or adjacent organs in which the suspicion of histological invasion is low (6, 7).

The addition of perioperative radiation therapy (RT) to the armamentarium of tools aimed at minimizing LR rates further adds complexity to the subject matter (8). It is unknown if a planned R1 (microscopically positive) margin in the context of neoadjuvant RT is of equivalence to the R0 margin. In the subset of patients with LPS, however, exploratory analysis from the STRASS trial appears to suggest a potential benefit of preoperative RT (9).

To date, data on the optimal surgical margins in retroperitoneal LPS (RPLPS) have been limited to retrospective cohort studies or case series/reports. As such, our study aims to provide a summative analysis on patients with RPLPS in an attempt to shed light on the effects of margins status, RT, chemotherapy (CT), and histotype on survival and recurrence outcomes.

2 Materials and methods

A literature search of PubMed, OvidSP, Embase, and Cochrane databases was conducted for studies reporting on the surgical management of RPLPS up to March 2020. The medical search headings (MeSH) "retroperitoneal liposarcoma," "well-differentiated liposarcoma," "de-differentiated liposarcoma," "R0," "R1," "resection," "extended resection," "microscopic," and "margin" were used. Additional relevant studies were identified by screening the references cited in shortlisted articles. This study was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) (10).

2.1 Criteria for inclusion of study

Articles were included if they 1) were original articles published in English in peer-reviewed journals; 2) included patients with RPLPS identified *via* imaging modalities such as computed tomography or magnetic resonance imaging scans; 3) included patients with biopsy-proven RPLPS; 4) unambiguously reported margin status, patient survival, and morbidity outcomes.

Articles were excluded if they 1) did not report the margin status of the resections; 2) included patients presenting with metastatic disease at initial diagnosis; 3) reported all outcomes for R0 and R1 resections collectively. Studies that presented data on RPS patients with other non-LPS histotypes were included only if data of patients with RPLPS could be extracted independently. For example, the retrospective cohort study of RPS patients from the Memorial Sloan-Kettering Cancer Center could not be included because survival and recurrence data for R1 or R0 resections were merged with other non-LPS histotypes (11). Similarly, the TAPRSWG 2020 study evaluating a large cohort of RPS patients was excluded, as outcomes for R1 and R0 resections were reported together (12).

2.2 Data extraction and analysis

Data were extracted using standardized forms, which recorded patient and study characteristiCJS, the radicality of resection performed (R0 or R1), histologic subtype (well-differentiated, dedifferentiated, pleomorphic, or myxoid), tumor grade (FNCLCC), postoperative morbidity and mortality, the use of neoadjuvant and/or adjuvant chemotherapy (CT) or radiotherapy (RT), number of additional organs removed and other perioperative outcomes, by two independent reviewers. Where appropriate, data that were reported for R0 and R1 collectively were extracted but were not considered in further analysis.

All studies were assessed for their level of evidence using the Oxford Centre for Evidence-Based Medicine Levels of Evidence (13). The authors elected to perform a descriptive review of the data as opposed to a meta-analysis due to the heterogeneity of the studies assessed.

2.3 Definitions

In accordance with residual tumor classification (R-classification) guidelines laid out by the American Joint Committee on Cancer (AJCC), an R1 resection was defined as microscopic tumor cells present at the border of the specimen, while an R0 resection was defined as the absence of tumor cells at the inked resection surface (14).

An "R+1" margin was defined as having >1 mm of normal tissue between the tumor and the inked resection margin (15).

3 Results

The search identified 59 relevant articles published between 1996 and 2019 (Tables 1A, B).

3.1 Quality of evidence

3.1.1 R0-margin resection

A total of 52 studies reported on the outcomes of RPLPS patients who received R0 resection (Tables 2A, 3A).

Eight were retrospective cohort studies evaluating the relationship between margin status and recurrence and survival outcomes (16–23). R0-margin patients receiving adjuvant or neoadjuvant CT/RT were included in these studies, but data on their recurrence and survival outcomes were reported together with R1-margin patients and hence could not be extracted. Of note, three studies (16, 20, 21) adopted the stricter R+1 margin classification system that classifies margins as R0 only if the resection margins are surrounded by >1 mm of tumor-negative tissue.

Of the remaining 44 studies, 4 were case series (26–29) and 40 were case reports (30–69), both documenting the recurrence and survival outcomes of RPLPS patients receiving R0-margin resection for RPLPS.

3.1.2 R1-margin resection

A total of 16 studies reported on the outcomes of RPLPS patients who received R1 resection (Tables 2B, 3B). R1-margin patients receiving adjuvant or neoadjuvant CT/RT were included in these studies, but data on their recurrence and survival outcomes were reported together with R0-margin patients and hence could not be extracted.

Ten were retrospective cohort studies evaluating the relationship between margin status (R0/R1) with recurrence and survival outcomes (16–25). One study (19) was a prospective cohort study examining the effect of preoperative irradiation by high-dose helical tomotherapy with a total dose of 54 Gy over 30 fractions.

Of the remaining six studies, one was a retrospective case series (26) and five were case reports (70–74), both documenting

TABLE 1A List of cohort studies reporting on retroperitoneal liposarcomas.

Study	Yr	Design	Study Duration	Level of Evidence	R0	R1	Outcomes reported	Description
Sanchez-Hidalgo et al. (16)	2018	Cohort study	2004-2015	2b	27	8	DFS, OS, early (<12 mo) recurrence, late (>12 mo) recurrence	Analyses influence of tumor size, stage, grade, histology, contiguous resection, BMI, age and adjuvant therapy on OS and DFS.
Nathenson et al. (17)	2018	Cohort study	2000-2013	2b	12	11	PFS, OS	Analyses influence of tumor size, stage, grade and histology and margin on OS and PFS.
Zhao et al. (18)	2015	Cohort study	2000-2007	2b	39	22	OS	Analyses the prognostic factors of postoperative outcomes. Margin status, tumor grade, ascites, postop metastasis and age were significant predictors of OS.
Sargos et al. (19)	2012	Cohort study	2007-2008	2b	4	4	RR, RFS[a], OS[a]	Case series documenting the effect of pre-op tomotherapy on RPLPS patients.
Lee et al. (20)	2011	Cohort study	1990-2005	2b	11	10	OS, DFS, morbidity[a], mortality	Analyses influence of tumor size, grade, histology, margin status, and age on OS and DFS.
Milone et al.(21)	2011	Cohort study	1990-2011	2b	21	6	OS, LRFS, RR	Case series documenting the overall survival and recurrence rate for R0 and R1
Singer et al. (22)	2003	Cohort study	1982-2001	2b	77	66	DSS, LRFS, DRFS	Analyses factors predicting recurrence patterns and OS. De-differentiated histology and the need for contiguous organ resection increases risk for LR; margin is prognostic for survival.
Linehan et al. (23)	2000	Cohort study	1982-1998	2b	105	54	DSS,LR, DR[a]	Analyses influence of anatomic site, margin status, tumor size and grade on LR and DSS.
Wu et al. (24)	2018	Cohort study	2005-2015	2b	0	15	DSS, LR[a]	Assesses the utility of vimentin and Ki-67 as prognostic biomarkers. R1 margins were not a prognostic factor for DSS, while gross margins were.
Rhu et al. (25)	2017	Cohort study	1998-2016	2b	0	6	OS, RFS	Reports the influence of tumor grade and histology, sex, age, margin status, adjuvant therapy on OS and DFS, and compares the postop outcomes of RPLPS and inguinoscrotal LPS

BMI, body mass index; DFS, disease-free survival; DR, distant recurrence; DRFS, distant recurrence-free survival; DSS, disease specific survival; LR, local recurrence; LRFS, local recurrence-free survival; LPS, liposarcoma; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RPLPS, retroperitoneal liposarcoma; RR, recurrence rate.
[a]Outcomes were collectively reported for R0/R1.

10.3389/fonc.2022.891710

TABLE 1B List of case series/case reports reporting on retroperitoneal liposarcomas.

Study	Year	Margin status	Description
Fernandez-Ruiz et al. (26)	2010	4 R0 5 R1	Case series documenting the evolution of RPLPS patients
Han et al. (27)	2010	2 R0	Case series of 1) RPLPS abutting the left kidney and adrenal gland removed *via en bloc* resection with removal of those organs; 2) RPLPS encasing left kidney removed *via en bloc* resection with nephrectomy
Crisan et al. (28)	2015	2 R0	Case report of 2 patients with primary LPS of the kidney. Patient 1 is a 65 y/o man with a giant RPLPS occupying the right hemi-abdomen and compressing various abdominal organs but treated with organ-sparing complete resection of tumor. Patient 2 is a 70 y/o man with LPS in the right perirenal area displacing the right kidney and colon toward the midline, treated by *en bloc* excision together with kidney.
Daldoul et al. (29)	2017	2 R0	Case series of 1) a giant RPLPS with colonic involvement removed by hemicolectomy and nephrectomy; and 2) a giant RPLPS removed by R0 resection with nephrectomy
Yaman (30)	1996	R0	Case report of RPLPS removed *via* complete resection with nephrectomy
Susini et al. (31)	2000	R0	Case report of a 27 y/o pregnant woman with RPLPS extending from the left adnexa to the epigastric region but removed sparing the left ovary, uterus, and right adnexa
Sener et al. (32)	2004	R0	Case report of a 44 y/o woman with 2.0 cm cystic mass abutting the right kidney, treated by radical nephrectomy, adrenalectomy, and *en bloc* resection of the tumor.
Mehrotra et al. (33)	2006	R0	Case report of giant inflammatory RPLPS abutting the left kidney and pushing the IVC, aorta, and the left ureter
Calo et al. (34)	2007	R0	Case report of primary mesenteric LPS removed without intestinal resection or small bowel devascularization
Gaston et al. (35)	2007	R0	Case report of a patient whose kidney was encased by RPLPS and extended into the diaphragm, treated with *en bloc* resection with partial diaphragmatic resection
Gupta and Yadav (36)	2007	R0	Case report of a patient with RPLPS invading the kidney, treated by complete resection of the tumor with wedge resection of the renal parenchyma. (This is a case series of 2 patients but only 1 had margin specified)
Perez-Ponce et al. (37)	2008	R0	Case report of RPLPS with paravertebral involvement removed *via en bloc* resection
Yildirim et al. (38)	2008	R0	Case report of a 61 y/o man with RPLPS filling the pelvic cavity and extending to the epigastric region displacing intestines and pancreas, treated by organ-sparing complete excision.
Benseler et al. (39)	2009	R0	Case report of RPLPS removed *via en bloc* resection including the left kidney and descending colon
Goertz et al. (40)	2009	R0	Case report of RPLPS dimensions 45 cm × 35 cm × 19 cm and weighed 15.5 kg, resected *via en bloc* resection
Salemis et al. (41)	2011	R0	Case report of a 73 y/o man with RPLPS extending into the thigh
Coleblunders et al. (42)	2011	R0	Case report of recurrent RPLPS invading the thoracoabdominal wall but sparing the peritoneum, treated by an *en bloc* wide margin excision caudally down to the iliopsoas muscle and cranially up to the left adrenal.
Makni et al. (43)	2012	R0	Case report of a 60 y/o man with primary RPLPS extending from the epigastrium to the pelvic region, treated with complete but organ-sparing resection. (This paper is actually a case series, but only 1 case had sufficient data suitable for review)
Bansal et al. (44)	2013	R0	Case report of giant RPLPS with adherent ileum and ureter removed by wide excision along with ileum and ureter
Sharma et al. (45)	2013	R0	Case report of inflammatory WD RPLPS removed by wide excision
Nagy et al. (46)	2013	R0	Case report of recurrent RPLPS displacing the left kidney. Although the RPLPS recurred multiple times, only the results from the resection of the primary tumor are presented in this review.
Hoshi et al. (47)	2014	R0	Case report of RPLPS removed *via* complete resection with partial nephrectomy
Caizzone et al. (48)	2015	R0	Case report of a huge RPLPS involving the vena cava and iliac vessels removed *via en bloc* resection with nephrectomy
Kasashima et al. (49)	2015	R0	Case report of a 34 y/o woman with RPLPS after first delivery
Reznichenko (50)	2016	R0	Case report of giant RPLPS involving small bowel and mesentery removed by *en bloc* resection with small intestine
Kobayashi et al. (51)	2016	R0	Case report of recurrent RPLPS managed *via* re-resection
Machado et al. (52)	2016	R0	Case report of DDLPS of the pancreas treated with distal pancreatectomy with splenectomy and regional lymphadenectomy.

(Continued)

TABLE 1B Continued

Study	Year	Margin status	Description
Zeng et al. (53)	2017	R0	Case report of giant RPLPS removed by *en bloc* resection
Tsiao et al. (54)	2017	R0	Case report of a patient with RPLPS who developed right sided femoral nerve neuropraxia after resection
Singal et al. (55)	2018	R0	Case report of a 55 y/o man with RPLPS occupying the abdominal cavity and displacing colon anteriorly abutting the kidney, treated by meticulous dissection to free the mass from its adhesions, hence preserving the bowel.
Ioannidis et al. (56)	2018	R0	Case report of a 55 y/o woman with giant RPLPS extending from the epigastrium into the pelvic region in contact with numerous abdominal and pelvic organs. However, the mass was excised without mention of multiorgan resection.
Agrusa et al. (57)	2019	R0	Case report of a 62 y/o woman with RPLPS removed *via en bloc* laparoscopic resection along with kidney and left adrenal gland
Argadjendra et al. (58)	2019	R0	Case report of a 30 y/0 woman with RPLPS invading the left perirenal fascia and displacing the descending colon, pancreas, and duodenum, removed *via* organ-sparing resection
Huo et al. (59)	2015	R0	Case report of a 27 y/o pregnant woman with a giant left RPLPS extending from the left kidney into the left pelvis, compressing the left kidney and ureter, treated by organ-sparing complete resection; fetus was preserved and successfully delivered subsequently.
Clar et al. (60)	2009	R0	Case report of RPLPS enclosing left kidney, removed *via* marginal resection and left nephrectomy
Hashimoto et al. (61)	2010	R0	Case report of giant RPLPS abutting the kidney and diaphragm removed *via* R0 resection
Akhoondinasab and Omranifard (62)	2011	R0	Case report of WD RPLPS abutting the aorta, kidneys, and ureters, removed *en bloc* while preserving the structures
Bhat et al. (63)	2013	R0	Case report of RPLPS encasing and displacing the left kidney anteriorly, extending cranially onto the diaphragm and inferiorly into the pelvis, treated with wide excision but organ-sparing.
Oh et al. (64)	2016	R0	Case report of RPLPS encasing the kidney and abutting the aorta removed by wide excision and organ-sparing surgery
Tanaka et al. (65)	2017	R0	Case report of huge RPLPS involving the pancreas, kidney, IVC, and aorta, removed *via en bloc* resection with resection of right kidney, duodenum, pancreatic head, IVC, and abdominal aorta
Abufkhaida and Alsalameh (66)	2019	R0	Case report of an RPLPS displacing the bowel, removed *via* gross total resection
Montenegro et al. (67)	2019	R0	Case report of an anemic 65 y/o woman with RPLPS removed *via* laparoscopic resection requiring intraoperative blood transfusion
Herzberg et al. (68)	2019	R0	Case report of a 75 y/o man presenting with anorexia with RPLPS removed *via en bloc* resection with kidney and part of diaphragm
Yang et al. (69)	2016	R0	Case report of a huge RPLPS with renal involvement removed *via en bloc* resection with nephrectomy
McCallum et al. (70)	2006	R1	Case report of a postmenopausal 47 y/o woman with RPLPS involving iliac vessels and ureter managed *via en bloc* resection with total abdominal hysterectomy and bilateral salpingo-oophorectomy
Keil et al. (71)	2008	R1	Case report of a patient with relapse of high-grade RPLPS treated with incomplete (R1) resection and adjuvant RT
Sato et al. (72)	2014	R1	Case report of RPLPS with colonic involvement treated by *en bloc* resection with right colon and right kidney.
Bruce et al. (73)	2018	R1	Case report of a patient with RPLPS vascularized by branches from external iliac artery and inferior epigastric artery, treated by *en bloc* resection removing the external iliac artery and renal fascia.
Ghose et al. (74)	2018	R1	Case report of a patient with dedifferentiated RPLPS involving inter- and infra-renal IVC, treated with *en bloc* resection with right kidney (the paper is a case series, but all other patients reported had non-LPS histology)

DDLPS, dedifferentiated liposarcoma; IVC, inferior vena cava; LPS, liposarcoma; RPLPS, retroperitoneal liposarcoma; RT, radiotherapy; WD, well-differentiated.

the recurrence and survival outcomes of RPLPS patients receiving R1-margin resection for RPLPS.

In total, our systematic review evaluated a total of 552 patients with RPLPS of whom 346 underwent R0-margin resection and 206 underwent R1-margin resection.

3.2 Outcomes of the R0 margin for retroperitoneal liposarcoma (RPLPS)

A total of 346 patients achieved R0 resections, of whom 296 patients came from cohort studies and 50 from case series/case reports.

3.2.1 Cohort studies (R0)

A total of 296 patients from eight cohort studies received R0-margin resection (Table 2A). The rates of LR ranged from 45.5% to 52.3%. The 3-year OS and DFS ranged from 87% to 87.5% and 22.2% to 62.5%, respectively. The 5-year OS ranged from 58.3% to 85.7%. From the study by Sargos et al. (19), the recurrence rate among R0-margin patients who received preoperative RT was 0%.

Due to the heterogeneity of the data, there is little basis for comparison between studies that adopted an "R+1" margin definition (16, 20, 22) vs. studies using the "R" margin

definition. For example, Lee et al. (20) who used the "R+1" definition reported a lower 5-year OS (58.3%) than Milone et al. (21) (85.7%) who used the "R" definition.

3.2.2 Case series and case reports (R0)

A total of 50 patients from 44 case series/case reports received R0-margin resection. The data extracted from the case series and case reports for RPLPS patients receiving R0 resection are shown in Table 3A and are summarized as follows. The median follow-up duration was 22 months. The histological distribution was as follows: 58% WDLPS (n = 29), 20% DDLPS (n = 10), 10% myxoid (n = 5), 6% pleomorphic (n = 3), and 6% mixed or unreported (n = 3). Moreover, 32% (n = 16) of tumors were low-grade (G1), 12% (n = 5) were high-grade (G2/G3), and 56% (n = 28) did not report tumor grade. In addition, 54% of patients (n = 27) received multivisceral resection, of whom 28% (n = 14) of patients had one additional organ resected, 24% (n = 12) had two additional organs resected, and 2% (n = 1) had five additional organs resected. The most common organ removed was the kidney (78%, n = 21) followed by the adrenal gland (15%, n = 4), diaphragm (11%, n = 3), colon (8%, n = 2), and pancreas (8%, n = 2). Regarding adjuvant CT and RT, two patients had adjuvant CT and RT, two patients had adjuvant RT, two patients had adjuvant CT, and 44 patients had neither adjuvant CT nor RT.

The postoperative outcomes are presented as follows. The median follow-up time was 22 (range 1–120 months), and two out of 50 patients demised at the end of follow-up. Cause of the two mortalities were tumor recurrence (40) and septic shock secondary to burst abdomen (26). The recurrence rate ranged from 0% to 100%. No distant metastases were reported during the duration of follow-up. Furthermore, 12% of patients (n = 6) (26, 51, 53, 54, 60, 62) experienced postoperative complications, of which 50% were Clavien–Dindo Grade 3 and above (75).

3.2.2.1 Comparing well-differentiated liposarcoma (WDLPS) vs. dedifferentiated liposarcoma (DDLPS) Patients (R0)

LR among WDLPS patients was 24% (n = 7/29) while that among DDLPS patients was 40% (n = 4/10).

3.2.2.2 Comparing outcomes of adjuvant chemotherapy (CT) radiotherapy (RT) vs. no CT/RT (R0)

LR among patients who received no CT or RT, only adjuvant CT, only adjuvant RT, and adjuvant CT and RT was 31% (n = 14), 50% (n = 1), 50% (n = 1), and 0% (n = 0), respectively.

TABLE 2A Summary of cohort studies which included patients receiving R0-margin resection.

Study	Year	No. cases	CT/RT	Post-op Morbidity	OS	DFS	LRFS	RR	Margin definition in study
Sanchez-Hidalgo et al. (16)	2018	27	Unable to extract	Clavien-Dindo ≥ III: 17.1% [a]	Median: 93 mos (95%CI: 44.9-141) [a]	1-yr: 81% 3-year: 22.2% Median: 22 mos	NR	Early recurrence (<12mo) = 45.5%	R+1
Nathenson et al. (17)	2018	12	Adjuvant CT: n=1 [c] Adjuvant/neoadjuvant RT: n= 10 [c]	NR	2-yr: 100%	2-yr: 62%	NR	LR: 50% [c]	R
Zhao et al. (18)	2015	39	Intraop RT: n=2 [c] adjuvant RT: n=7 [c] adjuvant CT: n=15 [c] adjuvant CT+RT: n=11 [c]	0%	Median: 114 mo	NR	NR	RR: 59/61 [b]	R
Sargos et al. (19)	2012	4	Neoadjuvant RT	Unable to extract	Unable to extract	NR	NR	0%	R
Lee et al. (20)	2011	11	NR	28.6% [a]	3-yr: 87.5% 5-yr: 58.3%	3-yr: 62.5%	NR	52% [a]	R+1
Milone et al. (21)	2011	21	NR	0%	5-yr; 85.7%	NR	NR	52.3%	R
Singer et al. (22)	2003	77	CT 0%	NR	3-yr: 87%	NR	3-yr: 55%	50% [a]	R+1
Linehan et al. (23)	2000	105 (derived)	NR	NR	5-yr: 65%	NR	5-yr: 42%	25% [d]	R

CT, chemotherapy; DFS, disease-free survival; LR, local recurrence; LRFS, local recurrence-free survival; NR, not reported; OS, overall survival; RR, recurrence rate; RT, radiotherapy; CI, confidence interval.
[a] reported collectively for R0/R1.
[b] reported collectively for R1/R2.
[c] reported collectively for R0/R1/R2.
[d] reported collectively with RPLPS of the extremity and trunk.

10.3389/fonc.2022.891710

TABLE 2B Summary of cohort studies that included patients receiving R1-margin resection.

Study	Year	No. cases (R1=)	CT/RT	Post-op Morbidity	OS	DFS	LRFS	RR	Margin definition in study
Sánchez-Hidalgo et al. (16)	2018	8	adjuvant CT 100% RT 100%	Clavien–Dindo ≥III: 17.1% [a]	Median: 93 mo (95% CI: 44.9-141) [a]	1-yr: 25%	NR	Early recurrence rate (<12 mo) = 91.7%	R+1
Nathenson et al. (17)	2018	11	Adjuvant CT: n=1 [c] Adjuvant/ neoadjuvant RT: n= 10 [c]	NR	2-yr: 91%	2-yr: 44 %	NR	LR: 50% [c]	R
Zhao et al. (18)	2015	22	Intraop RT: n=2 [c] adjuvant RT: n=7 [c] adjuvant CT: n=15 [c] adjuvant CT+RT: n=11 [c]	0%	Median: 55 mo	NR	NR	RR: 59/61 [b]	R
Sargos et al. (19)	2012	4	Neoadjuvant RT	Unable to extract	Unable to extract	NR	NR	0%	R
Lee et al. (20)	2011	10	28.6% [a]	Reported collectively	3-yr: 88.9% 5-yr: 44.4%	3-yr: 31.7%	NR	52% [a]	R+1
Milone et al. (21)	2003	6	NR	0%	5-yr: 33.3%	NR	NR	LR = 66.6% DM = 33.3%	R
Singer et al. (22)	2000	66	NR	NR	3-yr: 70%	3-yr probability free of distant recurrence: 87%	3-yr: 50%	50% [a]	R+1
Linehan et al. (23)	2000	54 (derived)	NR	NR	5-yr: 35%	NR	5-yr: 47%	25% [d]	R
Wu et al. (24)	2017	15	Collectively reported for R0/ R1	NR	Median: 36.9	NR	NR	NR	R
Rhu et al. (25)	2017	6	adjuvant 66.7% (CT/RT)	66.70%	Median: 44.3mo 1-yr: 80% 5-yr: 53.3%	Median: 12.5 mo 1-yr: 66.7% 5-yr: 22.2%	NR	66.70%	R

CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; LR, local recurrence; LRFS, local recurrence-free survival; NR, not reported; OS, overall survival; RR, recurrence rate; RT, radiotherapy.
[a]reported collectively for R0/R1.
[b]reported collectively for R1/R2.
[c]reported collectively for R0/R1/R2.
[d]reported collectively with RPLPS of the extremity and trunk.

3.3 Outcomes of the R1 margin for retroperitoneal liposarcoma (RPLPS)

A total of 206 patients in this review received resections leading to an R1 margin, of whom 196 patients came from cohort studies and 10 from case series or case reports.

3.3.1 Cohort studies (R1)

A total of 196 patients from 10 cohort studies received R1-margin resection. The rates of LR ranged from 66.7% to 91.7% (Table 2B). The 3-year OS ranged from 70% to 88.9%. The 5-year OS ranged from 35% to 55.3%. The 3-year LRFS was 50%, and the 5-year LRFS was 47%.

Due to the heterogeneity of the data, there is little basis for comparison between studies that adopted an "R+1" margin definition (16, 20, 22) vs. studies using the "R" margin definition.

3.3.2 Case series and case reports (R1)

A total of 10 patients from six case series/case reports received R1-margin resection. The data extracted from the case series and case reports for RPLPS patients receiving R1 resection are shown in Table 3B and are summarized as follows. The median follow-up duration was 15.5 months. The histological distribution was as follows: 30% WDLPS (n = 3), 50% DDLPS (n = 5), 10% myxoid (n = 1), and 10% unreported (n = 1). In addition, 20% (n = 2) of tumors were low-grade (G1) and 70% (n = 7) were high-grade (G2/G3), with 10% (n = 1) unreported grade. Moreover, 70% of patients (n = 7) received multivisceral organ resection, of whom 20% (n = 2) had one additional organ resected, 30% (n = 3) had two additional organs resected, 10% (n = 1) had four additional organs resected, and 10% (n = 1) had six additional organs resected. Of the patients who received multivisceral resection, the most common organ

TABLE 3A Summary of 4 case series and 40 case reports which included patients receiving R0-margin resection.

First Author	Year	Histology	Grade (FNCLCC)	CT/RT	Post-op Mortality reported	Clavien-Dindo Grade	Additional organs removed	No. of organs removed	Recurrence at last followup (Yes/No)	Follow-up duration	Patient alive at last followup?
Fernandez-Ruiz et al. (26)	2010	WDLPS	1	none given	No	NA	None	0	No	50.4mo	Yes
		WDLPS	1	none given	No	NA	None	0	No	59.1mo	Yes
		pleomorphic	2	none given	Yes (operative-related death 36 days post-op)	Grade V	left hemicolon	1	No	1 mo	No (operative-related death)
		WDLPS	1	adjuvant RT	No	NA	kidney	1	Yes	62.9 mo	Yes
Han et al. (27)	2010	WDLPS	NR	none given	No	NA	kidney, adrenal gland	2	No	1.5y	Yes
		WDLPS	NR	none given	No	NA	kidney	1	No	1.5y	Yes
Crisan et al. (28)	2015	Myxoid	2	Adjuvant CT	No	NA	None	0	Yes	18 mo	Yes
		Myxoid	2	none given	No	NA	kidney	1	Yes	3 y	Yes
Daldoul et al. (29)	2017	DDLPS	NR	none given	No	NA	kidney	1	No	12 mo	Yes
		WDLPS	NR	none given	No	NA	kidney	1	Yes	3 y	Yes
Yaman (30)	1996	WDLPS	NR	none given	No	NA	kidney	1	No	42 mo	Yes
Susini et al. (31)	2000	WDLPS	NR	none given	No	NA	fallopian tube	1	No	2y	Yes
Sener et al. (32)	2004	WDLPS	1	none given	No	NA	kidney, adrenal gland	2	No	12mo	Yes
Mehrotra et al. (33)	2006	WDLPS	NR	none given	No	NA	None	0	No	24 mo	Yes
Calo et al. (34)	2007	WDLPS	NR	Adjuvant CT	No	NA	None	0	No	33 mo	Yes
Gaston et al. (35)	2007	NR	1	none given	No	NA	left hemidiaphragm	1	No	22mo	Yes
Gupta and Yadav (36)	2007	WDLPS	NR	none given	No	NA	None	0	No	6mo	Yes
Perez-Ponce et al. (37)	2008	WDLPS	low	none given	No	NA	kidney, ureter	2	No	7y	Yes

(Continued)

10.3389/fonc.2022.891710

TABLE 3A Continued

First Author	Year	Histology	Grade (FNCLCC)	CT/RT	Post-op Mortality reported	Clavien-Dindo Grade	Additional organs removed	No. of organs removed	Recurrence at last followup (Yes/No)	Follow-up duration	Patient alive at last followup?
Yildirim et al. (38)	2008	WDLPS	NR	none given	No	NA	None	0	No	3mo	Yes
Benseler et al. (39)	2009	WDLPS	1	none given	No	NA	kidney, descending colon	2	Yes	10y	Yes
Goertz et al. (40)	2009	WDLPS	NR	none given	No	NA	None	0	Yes	2y	No (died of disease)
Salemis et al. (41)	2011	WDLPS	NR	none given	No	NA	None	0	No	18mo	Yes
Coleblunders et al. (42)	2011	DDLPS	NR	none given	No	NA	diaphragm, iliopsoas muscle	2	Yes	7mo	Yes
Makni et al. (43)	2012	DDLPS	NR	none given	No	NA	None	0	Yes	1.5y	Yes
Bansal et al. (44)	2013	Mixed	NR	none given	No	NA	ileum, ureter	2	Yes	63 mo	Yes
Sharma et al. (45)	2013	WDLPS	NR	none given	No	NA	None	0	No	6 mo	Yes
Nagy et al. (46)	2013	DDLPS	low	none given	No	NA	kidney	1	Yes	8 mo	Yes
Hoshi et al. (47)	2014	WDLPS	NR	none given	No	NA	kidney	1	No	10 y	Yes
Caizzone et al. (48)	2015	Pleomorphic	NR	none given	No	NA	kidney	1	No	24 mo	Yes
Kasashima et al. (49)	2015	WDLPS	NR	none given	No	NA	kidney, adrenal gland	2	No	3 y	Yes
Reznichenko (50)	2016	Myxoid	NR	none given	No	NA	small intestine, kidney	2	Yes	7 y	Yes
Kobayashi et al. (51)	2016	DDLPS	high	none given	No	Grade III	None	0	Yes	4 y	Yes
Machado et al. (52)	2016	DDLPS	high	adjuvant CT,RT	No	NA	pancreas, spleen	2	No	5 y	Yes
Zeng et al. (53)	2017	WDLPS	1	adjuvant RT	No	Grade IV	None	0	No	8 mo	Yes
Tsiao et al. (54)	2017	NR	low	none given	No	Grade III	none	0	No	6 mo	Yes
Singal et al. (55)	2018	Myxoid	NR	none given	No	NA	none	0	Yes	16 mo	Yes

(Continued)

10.3389/fonc.2022.891710

TABLE 3A Continued

First Author	Year	Histology	Grade (FNCLCC)	CT/RT	Post-op Mortality reported	Clavien-Dindo Grade	Additional organs removed	No. of organs removed	Recurrence at last followup (Yes/No)	Follow-up duration	Patient alive at last followup?
Ioannidis et al. (56)	2018	WDLPS	NR	none given	No	NA	none	0	No	4 y	Yes
Agrusa et al. (57)	2019	DDLPS	NR	none given	No	NA	kidney, adrenal gland	2	No	12 mo	Yes
Argadjendra et al. (58)	2019	WDLPS	NR	none given	No	NA	none	0	No	12 mo	Yes
Huo et al. (59)	2015	Myxoid	low	none given	No	NA	None	0	No	6 mo	Yes
Clar et al. (60)	2009	WDLPS	1	none given	No	Grade I	kidney	1	No	3y	Yes
Hashimoto et al. (61)	2010	DDLPS	2	none given	No	NA	kidney	1	No	12mo	Yes
Akhoondinasab and Omranifard (62)	2011	WDLPS	1	none given	No	Grade I	None	0	Yes	2y	Yes
Bhat et al. (63)	2013	WDLPS	NR	none given	No	NA	None	0	No	8 mo	Yes
Oh et al. (64)	2016	WDLPS	1	none given	No	NA	None	0	Yes	28 mo	Yes
Tanaka et al. (65)	2017	DDLPS	NR	none given	No	NA	kidney, head of pancreas, duodenum, IVC, abdominal aorta	5	No	16 mo	Yes
Abufkhaidaand Alsalameh (66)	2019	WDLPS	low	none given	No	NA	none	0	Yes	22 mo	Yes
Montenegro et al. (67)	2019	Pleomorphic	NR	none given	No	NA	kidney, spleen	2	No	6 mo	Yes
Herzberg et al. (68)	2019	DDLPS	low	none given	No	NA	kidney, part of diaphragm	2	No	2 y	Yes
Yang et al. (69)	2016	WDLPS	NR	adjuvant CT, RT	No	NA	None	0	No	6 mo	Yes

All time-points are taken with respect to the date of initial operation.

CT, chemotherapy; DDLPS, dedifferentiated liposarcoma; DM, distant metastasis; LR, local recurrence; MO, months; NA, not applicable NR, not reported; RT, radiotherapy; WDLPS, well-differentiated liposarcoma; Y, years.

10.3389/fonc.2022.891710

10.3389/fonc.2022.891710

TABLE 3B Summary of 1 case series and 5 case reports that included patients receiving R1-margin resection.

First Author	Year	Histology	Grade (FNCLCC)	CT/RT	Postop Mortality	Clavien–Dindo Grade	Additional organs removed	No. of organs removed	Recurrence at last follow-up (Yes/No)	Follow-up duration	Patient alive at last follow-up?
Fernandez-Ruiz et al. (26)	2010	WDLPS	1	adjuvant CT	None	NA	None	0	No	31.2 mo	Yes
		myxoid	2	none given	None	NA	kidney	1	Yes	7.7 mo	No (died of disease after 7.7 mo)
		WDLPS	1	none given	None	NA	Left ovary and fallopian tube	2	Yes	35 mo	Yes
		DDLPS	2	none given	None	NA	Left kidney and adrenal gland	2	No	50.7 mo	No (death due to unknown cause at 50.7 mo)
		DDLPS	2	none given	None	NA	None	0	Yes	2.6 mo	Yes
McCallum et al. (70)	2006	DDLPS	high	none given	0%	Grade I	Uterus, cervix, both ovaries, both fallopian tubes	6	No	35 mo	Yes
Keil et al. (71)	2008	NR	3	adjuvant RT	NR	NR	None	0	Yes	1 y	Yes
Sato et al. (72)	2014	WDLPS	NR	none	None	NA	Right kidney, right colon	2	No	19 mo	Yes
Bruce et al. (73)	2018	DDLPS	high	no	None	NA	Splenic bed, external iliac vessel, renal fascia, colonic mesentery	4	No	9 mo	Yes
Ghose et al. (74)	2018	DDLPS	high	adjuvant RT	None	NA	Right kidney	1	Yes	8 mo	Yes

All time points are taken with respect to the date of initial operation.
CT, chemotherapy; DDLPS, dedifferentiated liposarcoma; DM, distant metastasis; LR, local recurrence; mo, months; NA, not applicable; NR, not reported; RT, radiotherapy; WDLPS, well-differentiated liposarcoma; y, years.

removed was the kidney (58%, n = 4), followed by the ovary (29%, n = 2). Regarding adjuvant CT/RT, seven patients had neither CT nor RT, one patient had adjuvant CT, and two patients had adjuvant RT.

At a median follow-up of 15.5 months (range 2.6–50.7), two out of 50 patients had demised (26). Only one patient (70) experienced minor Clavien–Dindo Grade 1 postoperative complications.

3.3.2.1 Comparing well-differentiated liposarcoma (WDLPS) vs. dedifferentiated liposarcoma (DDLPS) patients (R1)

LR among WDLPS patients was 33% (n = 1/3) while that among DDLPS patients was 40% (n = 2/5).

3.3.2.2 Comparing outcomes of adjuvant chemotherapy (CT)/radiotherapy (RT) vs. no CT/RT (R1)

LR among patients who received neither CT nor RT was 43% (three out of seven patients), LR among patients who received only CT was 0% (zero out of one patient), and LR among patients who received only RT was 100% (two out of two patients).

3.4 Outcomes of patients who received neoadjuvant or adjuvant radiotherapy (RT) chemotherapy (CT)

In the cohort studies, survival and recurrence outcomes of patients receiving neoadjuvant or adjuvant CT/RT were reported collectively as R0/R1 and could not be extracted independently for aggregation across studies. However, three retrospective cohort studies individually reported on the effects of neoadjuvant or adjuvant CT/RT upon univariate or multivariate analysis, with differing results. Sánchez-Hidalgo et al. (16) reported that administering adjuvant CT or RT to patients with dedifferentiated tumor histology neither improved

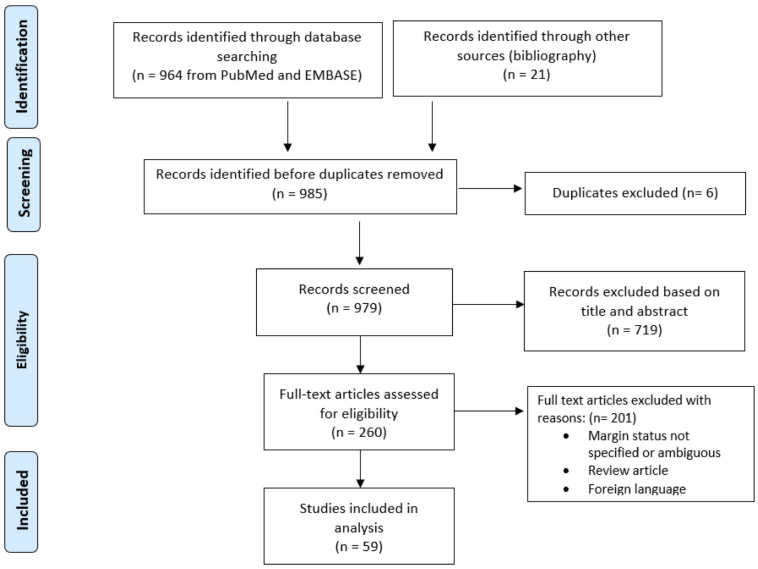

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of selection of eligible studies.

DFS/OS nor reduced LR rates. Similarly, Nathenson et al. (17) reported that none of adjuvant CT, neoadjuvant RT, or adjuvant RT had a significant influence on OS and PFS, regardless of tumor histology and grade. Zhao et al. (18) reported a lower median survival for patients receiving adjuvant therapy (intraoperative/postoperative RT or CT) than those who did not undergo adjuvant therapy ($p = 0.03$) but acknowledged selection bias due to adjuvant therapy being arranged only for patients with high-grade tumors.

4 Discussion

RPS accounts for 15% of all soft tissue sarcomas and represents a rare class of tumors occurring in approximately 5 per 100,000 people in Europe (76). To date, the impact of microscopic margin status (R0 *vs.* R1 margin) has never been validated in RPS. While few would defend the preservation of involved or encased organs, much of the debate lies in whether an *en bloc* approach to remove all adjacent or adherent organs should override intraoperative assessment of suspected histopathologic organ invasion (HOI). To further complicate the matter, it has been shown that up to 26% of patients in whom there was no suspicion of organ involvement actually demonstrate pathologically identified HOI; this underscores the need for a more aggressive and extended resection regardless of intraoperative assessment (7). Hence, while groups like the TARPSWG (77) and EORTC-STBSG (78) recommend *en bloc* resection to maximize the chances of achieving an R0 margin, so far, there is limited evidence to conclude if the elusive R0 margin even makes a difference to patient outcomes. As such, the role of the R0-margin status is controversial in RPS.

The results of our systematic review provide some clarity on this matter. As shown in Tables 2A, B, although the numerical values for OS and DFS vary considerably between cohort studies, the R0 margin demonstrated benefits over the R1 margin with regard to these outcomes in most individual studies. For OS, the R0 margin was prognostic for increased OS in the studies by Nathenson et al. (17), Zhao et al. (18), Milone et al. (21), Singer et al. (22), and Linehan et al. (23), while studies by Sánchez-Hidalgo et al. (16) and Lee et al. (20) did not find a statistically significant correlation between the R0/R1 margin and OS. For DFS, the R0 margin was prognostic for increased DFS in studies by Sánchez-Hidalgo et al. (16) and Nathenson et al. (17), but the study by Lee et al. (20) did not find a statistically significant correlation between the R0/R1 margin and DFS. Among the case series and case reports included in our review, the follow-up duration varied tremendously and follow-up data were limited, hence preventing any formal assessment of the benefits of the R0 margin on survival outcomes.

Additionally, while different studies adopted the R+1 classification system that requires at least 1 mm of healthy tissue around the tumor margin to qualify as R0 (in essence, an R0+1 margin), there was no obvious superiority over the standard R0 margin.

One of the biggest arguments for aggressive surgical approaches, such as frontline extended resection, is the reduction in the LR rate and hence an increase in local control. Gronchi et al. (79) showed that the 5-year LR rate was

lower at 28% with the frontline extended approach compared to 48% with standard less aggressive approaches. The French Sarcoma Group (80) also cited a 3.29-fold reduced LR rate for an aggressive extended approach compared to patients who underwent simple complete resection.

The studies included in our analysis showed that the R0 margin led to a lower LR rate compared to that of the R1 margin. The LR rate for the R0 margin ranged from 45.5% to 52.3%, lower than the LR rate of the R1 margin that ranged from 66.7% to 91.7%. In particular, Sánchez-Hidalgo et al. (16) found that the R1 margin was strongly correlated with early recurrence (<12 months) on univariate analysis, and in the series by Milone et al. (21), the R0-margin LR rate was lower than the R1-margin LR rate, although no statistical significance analysis was done to reinforce these findings. The limited data for LRFS appear to corroborate the above findings. Only the studies by Singer et al. (22) and Linehan et al. (23) presented LRFS data for the R0 and R1 margin separately for comparison between R0 and R1 to be done. While Singer et al. (22) reported that the R0 margin led to longer LRFS and longer distant recurrence-free survival, the benefit over the R1 margin was not statistically significant. On the other hand, Linehan et al. (23) reported that the R1 margin paradoxically led to a longer LRFS (albeit not statistically significant).

From our analysis, there were hardly any extractable data from the cohort studies concerning survival and LR data stratified by RPLPS subtypes (WDLPS/DDLPS), although the case series and reports suggest that the R0 margin benefits LR in WDLPS patients (R0, 24%; R1, 33%) but offers no additional benefit in DDLPS patients (R0, 40%; R1, 40%). At the same time, while a more aggressive multivisceral resection would increase the chance of attaining R0 margins (77, 78), the final margin status attained potentially also depends on underlying tumor biology because more dedifferentiated RPLPS tends to be more locally invasive (6) and hence has a higher inherent tendency to invade the tumor capsule to increase the chance of margins being positive on final histopathology. It is therefore possible that despite a multivisceral resection, the margin status may end up as R1. In our dataset, out of the R0 patients, majority were WDLPS histotype, whereas of the R1 patients, majority were DDLPS histotype. Yet, the more common margin status attained in each of the WDLPS and DDLPS was still R0, suggesting that R1-margin cases are grossly underrepresented in the available literature. Hence, it is challenging to conclude regarding the extent that tumor biology and extent of resection contribute to the margin status attained just based on these limited data from case series and reports. The patients with pleomorphic and myxoid RPLPS were too few to be adequately represented, and no further analysis on their outcomes was done.

That being said, proponents of aggressive resection argue that it offers the best chances of local control that in turn drives oncologic outcomes in WDLPS and <G2 DDLPS. However, aggressive resection does not offer further benefit in high-grade DDLPS patients in whom distant metastases are the main driver of outcomes (3).

Existing large-scale studies on RPS in general are not unanimous on whether aggressive resections increase morbidity and mortality. While studies by Gronchi et al. (79) argue that aggressive resections do not increase morbidity and mortality, this is refuted by groups such as the TARPSWG (81) that argues that the removal of major organs when resecting aggressively puts patients at 1.5 times greater risk of morbidity.

In our analysis, postoperative morbidity/mortality data could only be extracted from case series and case reports; where it was extractable from cohort studies, the morbidity rate for R0 and R1 was equal (Tables 2A, B). Among the case series and reports, although there were more incidences of morbidity among R0 than R1 patients, the percentage morbidity in both patient groups was roughly equal (R0 = 12% *vs*. R1 = 10%) due to the different total numbers of patients. It is however valid to say that R0 has slightly higher morbidity as evidenced by the presence of Clavien–Dindo Grade 3, 4, and 5 complications. Postoperative mortality was low in both R0 and R1 patients, with there being only one case of mortality in R0 and none among R1 patients. On the whole, our analysis suggests that postoperative morbidity and mortality are only slightly higher for the R0 margin than those for the R1 margin in the context of RPLPS.

While the precise role of each of CT and RT in survival and LR outcomes in RPLPS is not well-established due to most studies being conducted on RPS in general, it has been reported elsewhere that standard chemotherapy has a marginal role in WDLPS due to the very low mitotic rate (82), and its use is therefore limited to metastatic and recurrent tumors (83). Furthermore, within the retroperitoneal space, the presence of radiosensitive organs, such as the pancreas, and kidney, in close proximity to the primary tumor limits the effectiveness and delivery of radiotherapy (be it neoadjuvant or adjuvant) (84).

Among the studies included in our review, analysis in studies performed by Sánchez-Hidalgo et al. (16), Nathenson et al. (17), and Zhao et al. (18) failed to find any statistically significant influence of CT/RT on survival and LR outcomes. As these are retrospective studies, there is expected to be some selection bias, since CT/RT would be offered more to patients with high-grade tumors or inherently aggressive tumor biology. Furthermore, the regimen of CT and RT was not standardized among the cohort studies and, in some instances, not specified at all. The limited follow-up data from case series and reports do not show any improvement of CT/RT to survival and LR in both R0 and R1 patients nor is there any definitive proof to address the question of whether R1 with CT/RT is of equivalence to the R0 margin.

The findings of our systematic review support and allude to the latest general consensus management guidelines for RPS published by the TARPSWG in 2021 (85). Our review showed that the R0-margin resection for RPLPS increased OS and reduced LR. Indeed, the TARPSWG recommends an extended approach to resect adherent organs regardless of expected microscopic infiltration, with removal of all ipsilateral

retroperitoneal fat, especially for well-differentiated histotypes that are harder to distinguish from normal adipose tissue. For this reason, obtaining intraoperative frozen sections will not add further value to guide the extent of resection.

Our review showed that WDLPS histotypes could potentially stand to benefit more from the R0 resection than DDLPS in terms of LR. While the TARPSWG suggests that the same aggressive strategy be used for both WDLPS and DDLPS, it acknowledges that more data are required to guide operative strategies for DDLPS (especially the high-grade type); data from the ongoing STRASS2 trial will shed further light on this matter.

While the studies included in our review seems to suggest that perioperative CT/RT has no significant effect on survival and LR, the TARPSWG recommends preoperative CT to downsize the primary tumor in order to facilitate grossly complete resection. Preoperative RT should be considered only for WDLPS and low-grade DDLPS that have high risks of LR, whereas high-grade DDLPS does not benefit from preoperative RT. There is still no proven benefit of postoperative CT or RT after grossly complete resection.

4.1 Limitations of the analysis

Our review highlighted that the majority of available studies on this topic are retrospective in nature. Outcome data for R0 were not always reported separately from those of R1, and if it was reported separately, there was also heterogeneity in the patient populations included under the R0 and R1 groups, and each study had varying proportions of WDLPS and DDLPS patients. The heterogeneity of the data limited the authors' ability to perform a formal meta-analysis; as such, the authors elected to perform a systematic review of the available evidence.

Inconsistencies in the definitions of margin status among the cohort studies also limited the extent to which the results could be analyzed. For example, in the case of resections that had less than 1 mm of healthy tissue around the margin, this would be classified in papers adopting the "R+1" system as R1 but classified in papers adopting the "R" system as R0. Among the case reports and case series, some of the papers used did not categorically specify if the margins were R0 or R1 but described resections as "margin-positive" or "margin-negative."

Although the numbers of R0 and R1 patients from cohort studies are fairly equal, there were much more case series and case reports of R0 patients than those of R1 patients, possibly stemming from publication bias. As such, data for short case series and case reports were simply presented in a descriptive manner. Therefore, it is difficult to make definitive conclusions regarding the effect of CT/RT, tumor histotype, or extent of resection on survival or recurrence outcomes.

5 Conclusion

Among the publications included in our systematic review, there was unanimity that the R0 margin delivered statistically significant improvements to OS, and there was fairly strong evidence that the R0 margin led to increased DFS. Data heterogeneity and collective reporting of R0 and R1 outcomes prevented a direct comparison of the differences in LRFS and RR, but the evidence points toward decreased RR from R0-margin resection. A modest amount of evidence points to a roughly equal postoperative morbidity rate between R0 and R1 resection.

To date, there have been no systematic reviews on the impact of the R0 margin in the treatment of RPLPS or even RPS for that matter. On the whole, our review suggests that the R0 margin benefits survival and LR in RPLPS patients without compromising postoperative morbidity. The role of other factors such as tumor biology and the role of CT/RT, while important, have yet to be delineated. At this juncture, our review emphasizes the need for larger-scale multicenter cohort studies assessing the effect of histotype, CT/RT, and extent of resection on survival and recurrence outcomes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: JSMW. Data curation: BP, JSMW. Formal analysis: BP, CJS, JW-ST, WKDJ, JSMW. Funding acquisition: JSMW. Investigation: BP, CJS, JW-ST, WKDJ, JSMW. Methodology: JSMW. Project administration: CC, CO. Resources: KCS, CC, C-AJO, JSMW. Supervision: KCS, C-AJO, CC, JSMW. Validation: BP, CS JW-ST, WKDJ, JSMW. Visualization: BP, CS. Roles/Writing - original draft: BP, JSMW. Writing - review and editing: BP, CJS, JW-ST, WKDJ, KCS, CC, C-AJO, JSMW. All authors contributed to the article and approved the submitted version.

Funding

This study is supported by the NCCS Cancer Fund (Research) and SingHealth Duke-NUS Academic Medicine Centre, facilitated by Joint Office of Academic Medicine (JOAM). C-AJO is supported by the National Research Council Clinician Scientist-Individual Research Grant

(CIRG21jun-0038). All the funding sources had no role in the study design, data interpretation or writing of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Seinen J, Almquist M, Styring E, Rydholm A, Nilbert M. Delays in the management of retroperitoneal sarcomas. *Sarcoma* (2010) 2010:702573. doi: 10.1155/2010/702573

2. Kirane A, Crago AM. The importance of surgical margins in retroperitoneal sarcoma. *J Surg Oncol* (2016) 113:270–6. doi: 10.1002/jso.24135

3. Dingley B, Fiore M, Gronchi A. Personalizing surgical margins in retroperitoneal sarcomas: An update. *Expert Rev Anticancer Ther* (2019) 19:613–31. doi: 10.1080/14737140.2019.1625774

4. Gronchi A, Miceli R, Colombo C, Stacchiotti S, Collini P, Mariani L, et al. Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. *Ann Oncol* (2011) 23:1067–73. doi: 10.1093/annonc/mdr323

5. van Houdt WKDJ, Raut CP, Bonvalot S, Swallow CJ, Haas R, Gronchi A. New research strategies in retroperitoneal sarcoma. the case of TARPSWG, STRASS and RESAR: making progress through collaboration. . *Curr Opin Oncol* (2019) 31:310–6. doi: 10.1097/CCO.0000000000000535

6. Strauss DC, Renne SL, Gronchi A. Adjacent, adherent, invaded: A spectrum of biologic aggressiveness rather than a rationale for selecting organ resection in surgery of primary retroperitoneal sarcomas. *Ann Surg Oncol* (2018) 25:13–6. doi: 10.1245/s10434-017-6137-3

7. Fairweather M, Wang J, Jo VY, Baldini EH, Bertagnolli MM, Raut CP. Surgical management of primary retroperitoneal sarcomas: Rationale for selective organ resection. *Ann Surg Oncol* (2018) 25:98–106. doi: 10.1245/s10434-017-6136-4

8. Molina G, Hull MA, Chen Y-L, DeLaney TF, De Amorim Bernstein K, Choy E, et al. Preoperative radiation therapy combined with radical surgical resection is associated with a lower rate of local recurrence when treating unifocal, primary retroperitoneal liposarcoma. *J Surg Oncol* (2016) 114:814–20. doi: 10.1002/jso.24427

9. Bonvalot S, Gronchi A, Le Pechoux C, Swallow CJ, Strauss DC, Meeus P, et al. STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. *J Clin Oncol* (2019) 37:11001. doi: 10.1200/JCO.2019.37.15_suppl.11001

10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* (2009) 339:b2700–0. doi: 10.1136/bmj.b2700

11. Tan MCB, Brennan MF, Kuk D, Agaram NP, Antonescu CR, Qin LX, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. *Ann Surgery Lippincott Williams Wilkins* (2016) 263(3):593–600. doi: 10.1097/SLA.0000000000001149

12. Callegaro D, Raut CP, Ng D, Strauss DC, Honoré C, Stoeckle E, et al. Has the outcome for patients who undergo resection of primary retroperitoneal sarcoma changed over time? A study of time trends during the past 15 years. *Ann Surg Oncol* (2021) 28:1700–9. doi: 10.1245/s10434-020-09065-6

13. *OCEBM levels of evidence* (2016). Available at: https://www.cebm.net/2016/05/ocebm-levels-of-evidence/ (Accessed December 26, 2019).

14. Gundle KR, Kafchinski L, Gupta S, Griffin AM, Dickson BC, Chung PW, et al. Analysis of margin classification systems for assessing the risk of local recurrence after soft tissue sarcoma resection. *J Clin Oncol Am Soc Clin Oncol* (2018) 36(7):704–9. doi: 10.1200/JCO.2017.74.6941

15. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer* (2002) 94:2511–6. doi: 10.1002/cncr.10492

16. Sánchez-Hidalgo JM, Rufián-Peña S, Durán-Martínez M, Arjona-Sánchez Á, Salcedo-Leal I, Lopez-Cillero P, et al. Risk factors of early recurrence in retroperitoneal liposarcoma. *Cirugia Espanola* (2018) 96:568–76. doi: 10.1016/j.ciresp.2018.06.002

17. Nathenson MJ, Barysauskas CM, Nathenson RA, Regine WF, Hanna N, Sausville E. Surgical resection for recurrent retroperitoneal leiomyosarcoma and liposarcoma. *World J Surg Oncol* (2018) 16:203. doi: 10.1186/s12957-018-1505-4

18. Zhao X, Li P, Huang X, Chen L, Liu N, She Y. Prognostic factors predicting the postoperative survival period following treatment for primary retroperitoneal liposarcoma. *Chin Med J* (2015) 128:85–90. doi: 10.4103/0366-6999.147822

19. Sargos P, Dejean C, de Figueiredo BH, Brouste V, Nguyen Bui B, Italiano A, et al. High-dose pre-operative helical tomotherapy (54 gy) for retroperitoneal liposarcoma. *Radiat Oncol (London England)* (2012) 7:214. doi: 10.1186/1748-717X-7-214

20. Lee SY, Goh BKP, Teo MCC, Chew MH, Chow PKH, Wong WK, et al. Retroperitoneal liposarcomas: The experience of a tertiary Asian center. *World J Surg Oncol* (2011) 9:12. doi: 10.1186/1477-7819-9-12

21. Milone M, Pezzullo LS, Salvatore G, Pezzullo MG, Leongito M, Esposito I, et al. Management of high-grade retroperitoneal liposarcomas: Personal experience. *Updates Surg* (2011) 63:119–24. doi: 10.1007/s13304-011-0061-z

22. Singer S, Antonescu CR, Riedel E, Brennan MF, Pollock RE. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. *Ann Surg* (2003) 238(3):358–71. doi: 10.1097/01.sla.0000086542.11899.38

23. Linehan DC, Lewis JJ, Leung D, Brennan MF. Influence of biologic factors and anatomic site in completely resected liposarcoma. *J Clin Oncol* (2000) 18:1637–43. doi: 10.1200/JCO.2000.18.8.1637

24. Wu Y-X, Liu J-Y, Liu J-J, Yan P, Tang B, Cui Y-H, et al. A retrospective, single-center cohort study on 65 patients with primary retroperitoneal liposarcoma. *Oncol Lett* (2018) 15:1799–810. doi: 10.3892/ol.2017.7533

25. Rhu J, Cho CW, Lee KW, Park H, Park JB, Choi Y-L, et al. Comparison of retroperitoneal liposarcoma extending into the inguinal canal and inguinoscrotal liposarcoma. *Can J Surg J Canadien Chirurgie* (2017) 60:399–407. doi: 10.1503/cjs.005917

26. Fernandez-Ruiz M, Rodriguez-Gil Y, Guerra-Vales JM, Manrique-Municio A, Moreno-Gonzalez E, Colina-Ruizdelgado F. Primary retroperitoneal liposarcoma: Clinical and histological analysis of ten cases. *Gastroenterologia y Hepatologia* (2010) 33:370–6. doi: 10.1016/j.gastrohep.2009.12.010

27. Han HH, Choi KH, Kim DS, Jeong WKDJ, Yang SC, Jang SJ, et al. Retroperitoneal giant liposarcoma. *Korean J Urol* (2010) 51:579–82. doi: 10.4111/kju.2010.51.8.579

28. Crisan N, Ivan CS, Bungardean C, Cebotaru C, Coman I. Retroperitoneal perirenal myxoid liposarcoma. *J Surg Case Rep* (2015) 2015:rju127–7. doi: 10.1093/jscr/rju127

29. Daldoul S, Zahaf B, Ghassen EH, Marwa B, Ben SY, Ben MM. Retroperitoneal liposarcoma: Diagnostic difficulties and therapeutic attitudes. *Surg Curr Res* (2017) 07. doi: 10.4172/2161-1076.1000302

30. Yaman. Renal liposarcoma of the sinus renalis. *Int Urol Nephrol* (1996) 28:477–80. doi: 10.1007/bf02550953

31. Susini T, Taddei G, Massi D, Massi G. Giant pelvic retroperitoneal liposarcoma. *Obstetrics Gynecol* (2000) 95:1002–4. doi: 10.1016/s0029-7844(00)00818-8

32. Sener A, Wehrli B, Bramwell V, Bella AJ, Izawa JI. Retroperitoneal liposarcoma and Li-fraumeni syndrome: A case report and review of management options. *UroOncology* (2004) 4:161–5. doi: 10.1080/15610950400006660

33. Mehrotra PK, Ramachandran CS, Goel D, Arora V. Inflammatory variant of a well-differentiated retroperitoneal liposarcoma: Case report of a rare giant variety. *Indian J Cancer* (2006) 43:36–8. doi: 10.4103/0019-509x.25774

34. Calo PG, Farris S, Tatti A, Tuveri M, Catani G, Nicolosi A. Primary mesenteric liposarcoma. *Rep case. Il Giornale di Chirurgia* (2007) 28:318–20.

35. Gaston KE, White RLJ, Homsi S, Teigland C. Nephron-sparing radical excision of a giant perirenal liposarcoma involving a solitary kidney. *Am Surgeon* (2007) 73:377–80. doi: 10.1177/000313480707300413

36. Gupta NP, Yadav R. Renal sparing surgery for perirenal liposarcoma: 24 months recurrence free follow up. *Int Braz J urol: Off J Braz Soc Urol* (2007) 33:188–91. doi: 10.1590/s1677-55382007000200009

37. Pérez-Ponce Y, Castellanos-Alejandre R, Guerrero-Romero JF, Estrada-León F, Torres-Lobatón A. Retroperitoneal liposarcoma as etiology of abdominal pain. *A Case Rep Literature Rev Cirugia y Cirujanos* (2008) 76:77–82.

38. Yildirim O, Namdaroglu OB, Menekse E, Albayrak AL. Giant well-differentiated liposarcoma of retroperitoneum. *Bratislavske lekarske listy* (2008) 109:418–20.

39. Benseler V, Obed A, Schubert T, Schlitt H-J, Bolder U. [Case report–surgical therapy of a retroperitoneal liposarcoma weighing 45 kg]. *Zentralblatt fur Chirurgie* (2009) 134:174–7. doi: 10.1055/s-2008-1076878

40. Goertz RS, Lenfers BH, Goertz GH. Huge liposarcoma of the left retroperitoneum. *Am J Surg* (2009) 197:e59–60. doi: 10.1016/j.amjsurg.2008.07.061

41. Salemis NS, Nisotakis K, Patouras P, Karagkiouzis G, Gourgiotis S. Retroperitoneal liposarcoma extending into the thigh. *Am J Surg* (2011) 201: e38–40. doi: 10.1016/j.amjsurg.2010.04.019

42. Colebunders B, Colpaert SDM, Mertens M, Willemsen P. Thoraco-abdominal wall reconstruction after surgical debulking of a giant retroperitoneal liposarcoma: A case report. *Acta chirurgica Belgica* (2011) 111:250–2. doi: 10.1080/00015458.2011.11680749

43. Makni A, Triki A, Fetirich F, Ksantini R, Chebbi F, Jouini M, et al. Giant retroperitoneal liposarcoma. *Rep 5 Cases. Annali Italiani di Chirurgia* (2012) 83:161–6.

44. Bansal VK, Misra MC, Sharma A, Chabbra A, Murmu LR. Giant retroperitoneal liposarcoma- renal salvage by autotransplantation. *Indian J Surg* (2013) 75:159–61. doi: 10.1007/s12262-012-0474-z

45. Sharma M, Mannan R, Bhasin TS, Manjari M, Punj R. Giant inflammatory variant of well differentiated liposarcoma: A case report of a rare entity. *J Clin Diagn Research: JCDR* (2013) 7:1720–1. doi: 10.7860/JCDR/2013/5998.3267

46. Nagy V, Bober J, Zavacky P, Brandebur OJ, Svajdler M. The recurrent primary retroperitoneal liposarcoma. *Bratislavske lekarske listy* (2013) 114:662–7. doi: 10.4149/bll_2013_141

47. Hoshi S, Hayashi N, Yagi M, Ookubo T, Muto A, Sugano O, et al. Long term survival in a case of concurrent retroperitoneal liposarcoma and renal cell carcinoma: A case report. *BMC Res Notes* (2014) 7:538. doi: 10.1186/1756-0500-7-538

48. Caizzone A, Saladino E, Fleres F, Paviglianiti C, Iaropoli F, Mazzeo C, et al. Giant retroperitoneal liposarcoma: Case report and review of the literature. *Int J Surg Case Rep* (2015) 9:23–6. doi: 10.1016/j.ijscr.2015.02.019

49. Kasashima H, Yamasaki Y, Morimoto Y, Akamaru Y, Yasumasa K, Kasugai T, et al. A case of retroperitoneal liposarcoma after delivery with expression of estrogen receptor: Report of a case. *Int J Surg Case Rep* (2015) 7C:99–103. doi: 10.1016/j.ijscr.2015.01.002

50. Reznichenko AA. Simultaneous renal cell carcinoma and giant retroperitoneal liposarcoma involving small intestine. *Case Rep Surg* (2016) 2016:6021909. doi: 10.1155/2016/6021909

51. Kobayashi T, Miura K, Ishikawa H, Soma D, Zhang Z, Yuza K, et al. Successful re-resection for locally recurrent retroperitoneal liposarcoma at four years after ex vivo tumor resection and autotransplantation of the liver: A case report. *Transplant Proc* (2016) 48:1215–7. doi: 10.1016/j.transproceed.2016.01.026

52. Machado MCC, Fonseca GM, de Meirelles LR, Zacchi FFS, Bezerra ROF. Primary liposarcoma of the pancreas: A review illustrated by findings from a recent case. *Pancreatology: Off J Int Assoc Pancreatol (IAP) . [et al]* (2016) 16:715–8. doi: 10.1016/j.pan.2016.07.003

53. Zeng X, Liu W, Wu X, Gao J, Zhang P, Shuai X, et al. Clinicopathological characteristics and experience in the treatment of giant retroperitoneal liposarcoma: A case report and review of the literature. *Cancer Biol Ther* (2017) 18:660–5. doi: 10.1080/15384047.2017.1345388

54. Tsiao S, Aydin N, Misra S. Neuropraxia following resection of a retroperitoneal liposarcoma. *Int J Surg Case Rep* (2017) 36:170–4. doi: 10.1016/j.ijscr.2017.05.032

55. Singal R, Trehan S, Mittal A, Roy M, Joshi K. A giant retroperitoneal sarcoma: Current pathology and successful surgically. *Acta Gastroenterologica Latinoamericana* (2018) 48:52–5.

56. Ioannidis A, Koutserimpas C, Konstantinidis M, Drikos I, Voulgaris P, Economou N. Dyspnea caused by a giant retroperitoneal liposarcoma: A case report. *Oncol Lett* (2018) 16:1539–42. doi: 10.3892/ol.2018.8791

57. Agrusa A, Di Buono G, Buscemi S, Randisi B, Gulotta L, Sorce V, et al. Dedifferentiated retroperitoneal large liposarcoma and laparoscopic treatment: Is it possible and safe? the first literature case report. *Int J Surg Case Rep* (2019) 57:113–7. doi: 10.1016/j.ijscr.2019.03.023

58. Argadjendra M, Napitupulu R, Yudadi R, Hoetama S, Wibowo HS. Kidney sparing giant retroperitoneal liposarcoma: Case report and literature review. *Int J Surg Case Rep* (2019) 56:70–3. doi: 10.1016/j.ijscr.2019.02.008

59. Huo D, Liu L, Tang Y. Giant retroperitoneal liposarcoma during pregnancy: A case report. *World J Surg Oncol* (2015) 13:145. doi: 10.1186/s12957-015-0555-0

60. Clar H, Leithner A, Gruber G, Werkgartner G, Beham A, Windhager R. Interdisciplinary resection of a giant retroperitoneal liposarcoma of 25 kg. *ANZ J Surg* (2009) 79:957. doi: 10.1111/j.1445-2197.2009.05160.x

61. Hashimoto Y, Hatakeyama S, Tachiwada T, Yoneyama T, Koie T, Kamimura N, et al. Surgical treatment of a giant liposarcoma in a Japanese man. *Adv Urol* (2010) 2010:943073. doi: 10.1155/2010/943073

62. Akhoondinasab MR, Omranifard M. Huge retroperitoneal liposarcoma. *J Res Med Sci* (2011) 16:565–7.

63. Bhat SP, Prasad KHL, Shetty R, Ballal R, Kumar SY, Hegde P. Giant inflammatory variant of well-differentiated liposarcoma of retroperitoneum: A rare case report. *Indian J Surg Oncol* (2013) 4:272–4. doi: 10.1007/s13193-013-0239-6

64. Oh SD, Oh SJ, Suh BJ, Shin JY, Oh CK, Park JK, et al. A giant retroperitoneal liposarcoma encasing the entire left kidney and adherent to adjacent structures: A case report. *Case Rep Oncol* (2016) 9:368–72. doi: 10.1159/000447488

65. Tanaka M, Kawahara T, Nishikoshi T, Hagiwara M, Imai K, Hasegawa K, et al. Successful surgical treatment for huge retroperitoneal liposarcoma involving the pancreas, right kidney, abdominal aorta and inferior vena cava. *J Surg Case Rep* (2017) 2017:rjx200. doi: 10.1093/jscr/rjx200

66. Abufkhaida BS, Alsalameh BK. Recurrent abdominal liposarcoma presenting with intestinal obstruction. *J Surg Case Rep* (2019) 2019:rjz188. doi: 10.1093/jscr/rjz188

67. Montenegro A, Varas M, Sanchez-Vizcaino E, Naval J, Loras C, Abad R. A giant retroperitoneal liposarcoma with renal involvement: A case report and literature review. *Gastroenterologia y Hepatologia* (2019) 42:490–1. doi: 10.1016/j.gastrohep.2019.01.003

68. Herzberg J, Niehaus K, Holl-Ulrich K, Honarpisheh H, Guraya SY, Strate T. Giant retroperitoneal liposarcoma: A case report and literature review. *J Taibah Univ Med Sci* (2019) 14:466–71. doi: 10.1016/j.jtumed.2019.08.005

69. Yang J, Zhao Y, Zheng CH, Wang Q, Pang XY, Wang T, et al. Huge retroperitoneal liposarcoma with renal involvement requires nephrectomy: A case report and literature review. *Mol Clin Oncol* (2016) 5:607–9. doi: 10.3892/mco.2016.1017

70. McCallum OJ, Burke JJ2nd, Childs AJ, Ferro A, Gallup DG. Retroperitoneal liposarcoma weighing over one hundred pounds with review of the literature. *Gynecologic Oncol* (2006) 103:1152–4. doi: 10.1016/j.ygyno.2006.08.005

71. Keil S, Bruners P, Brehmer B, Mahnken AH. Percutaneous radiofrequency ablation for treatment of recurrent retroperitoneal liposarcoma. *Cardiovasc Interventional Radiol* (2008) 31 Suppl 2:S213–6. doi: 10.1007/s00270-007-9263-7

72. Sato Y, Yamamoto S, Fujita S. Retroperitoneal liposarcoma with colonic involvement: a case report. *Japanese J Clin Oncol* (2014) 44:374–8. doi: 10.1093/jjco/hyu009

73. Bruce NR, Tilley ZW, Carlson JT, Barreto Andrade JC. Management of T-cell large granular lymphocyte leukemia and concurrent retroperitoneal liposarcoma. *J Surg Case Rep* (2018) 2018) 7:1–3. doi: 10.1093/jscr/rjy142

74. Ghose J, Bhamre R, Mehta N, Desouza A, Patkar S, Dhareshwar J, et al. Resection of the inferior vena cava for retroperitoneal sarcoma: Six cases and a review of literature. *Indian J Surg Oncol* (2018) 9:538–46. doi: 10.1007/s13193-018-0796-9

75. Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The clavien-dindo classification of surgical complications: Five-year experience. *Ann Surg* (2009) 250:187–96. doi: 10.1097/SLA.0b013e3181b13ca2

76. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, et al. Descriptive epidemiology of sarcomas in Europe: Report from the RARECARE project. *Eur J Cancer* (2013) 49:684–95. doi: 10.1016/j.ejca.2012.09.011

77. Trans-Atlantic RPS Working Group. Management of primary retroperitoneal sarcoma (RPS) in the adult: A consensus approach from the trans-Atlantic RPS working group. *Ann Surg Oncol* (2015) 22:256–63. doi: 10.1245/s10434-014-3965-2

78. Bonvalot S, Raut CP, Pollock RE, Rutkowski P, Strauss DC, Hayes AJ, et al. Technical considerations in surgery for retroperitoneal sarcomas: Position paper

from e-surge, a master class in sarcoma surgery, and EORTC-STBSG. *Ann Surg Oncol* (2012) 19:2981–91. doi: 10.1245/s10434-012-2342-2

79. Gronchi A, Lo Vullo S, Fiore M, Mussi C, Stacchiotti S, Collini P, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol* (2009) 27:24–30. doi: 10.1200/JCO.2008.17.8871

80. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY, et al. Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control. *J Clin Oncol* (2009) 27:31–7. doi: 10.1200/JCO.2008.18.0802

81. Macneill AJ, Gronchi A, Miceli R, Bonvalot S, Swallow CJ, Hohenberger P, et al. Postoperative morbidity after radical resection of primary retroperitoneal sarcoma. *Ann Surg* (2018) 267:959–64. doi: 10.1097/SLA.0000000000002250

82. Callegaro D, Fiore M, Gronchi A. Personalizing surgical margins in retroperitoneal sarcomas. *Expert Rev Anticancer Ther* (2015) 15:553–67. doi: 10.1586/14737140.2015.1028375

83. Gronchi A, Strauss DC, Miceli R, Bonvalot S, Swallow CJ, Hohenberger P, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS). A report on 1007 patients from the multi-institutional collaborative RPS working group. *Ann Surg* (2016) 263:1002–9. doi: 10.1097/SLA.0000000000001447

84. Lochan R, French J, Manas D. Surgery for retroperitoneal soft tissue sarcomas: aggressive re-resection of recurrent disease is possible. *Ann R Coll Surgeons Engl* (2011) 93:39–43. doi: 10.1308/003588410X12771863936729

85. Swallow CJ, Strauss DC, Bonvalot S, Rutkowski P, Desai A, Gladdy RA, et al. Management of primary retroperitoneal sarcoma (RPS) in the adult: An updated consensus approach from the transatlantic Australasian RPS working group. *Ann Surg Oncol* (2021) 28(12):7873–88. doi: 10.1245/s10434-021-09654-z

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 13 September 2022
DOI 10.3389/fonc.2022.978823

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Chi-Leung Chiang,
The University of Hong Kong,
SAR China
Yang Deng,
Shandong First Medical University,
China

*CORRESPONDENCE
Jinlong Liu
liujl800813@163.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 26 June 2022
ACCEPTED 09 August 2022
PUBLISHED 13 September 2022

CITATION
Pei Y, Li W, Wang Z and Liu J (2022) Successful conversion therapy for unresectable hepatocellular carcinoma is getting closer: A systematic review and meta-analysis.
Front. Oncol. 12:978823.
doi: 10.3389/fonc.2022.978823

Successful conversion therapy for unresectable hepatocellular carcinoma is getting closer: A systematic review and meta-analysis

Yinxuan Pei, Weiwei Li, Zixiang Wang and Jinlong Liu*

Department of Hepatobiliary Surgery, Affiliated Hospital of Chengde Medical University, Chengde, China

Background: Conversion therapy provides selected patients with unresectable hepatocellular carcinoma the opportunity to undergo a curative hepatectomy and achieve long-term survival. Although various regimens have been used for conversion therapy, their conversion rate and safety remain uncertain. Therefore, we conducted some meta-analyses to evaluate the efficacy and safety of several conversion regimens in order to elucidate the optimal regimen.

Method: We performed systematic literature research on PubMed, Embase, and the Web of Science until July 30, 2022. Chemotherapy, transcatheter arterial chemoembolization (TACE), molecular therapy (targeted therapy, immunotherapy, or a combination of both), and combined locoregional-systemic therapy were the conversion regimens we targeted.

Results: Twenty-four studies were included. The pooled conversion rates for chemotherapy, TACE, molecular therapy, and combined locoregional-systemic therapy were 13% (95% confidence interval [CI], 7%–20%; I^2 = 82%), 12% (95% CI, 9%–15%; I^2 = 60%), 10% (95% CI, 3%–20%; I^2 = 90%), and 25% (95% CI, 13%–38%; I^2 = 89%), respectively. The pooled objective response rates (ORR) for chemotherapy, TACE, molecular therapy, and combined locoregional-systemic therapy were 19% (95% CI, 12%–28%; I^2 = 77%), 32% (95% CI, 15%–51%; I^2 = 88%), 30% (95% CI, 15%–46%; I^2 = 93%), and 60% (95% CI, 41%–77%; I^2 = 91%), respectively. The pooled grade ≥3 AEs for chemotherapy, TACE, molecular therapy, and combined locoregional-systemic therapy were 67% (95% CI, 55%–78%; I^2 = 79%), 34% (95% CI, 8%–66%; I^2= 92%), 30% (95% CI, 18%–43%; I^2 = 84%), and 40% (95% CI, 23%–58%; I^2 = 89%), respectively. Subgroup analyses showed the conversion rate, ORR and grade ≥3 AE rate for tyrosine kinase inhibitor (TKI) combined with immune checkpoint inhibitor (ICI) and locoregional therapy (LRT) were 33% (95% CI, 17%-52%; I^2 = 89%), 73% (95% CI, 51%–91%; I^2 = 90%), 31% (95% CI, 10%-57%; I^2 = 89%), respectively.

Conclusion: Combined locoregional-systemic therapy, especially TKI combined with ICI and LRT, may be the most effective conversion therapy regimen, associated with a significant ORR, conversion potential, and an acceptable safety profile.

KEYWORDS

hepatocellular carcinoma, conversion therapy, chemotherapy, transcatheter arterial chemoembolization, targeted therapy, immunotherapy, combined locoregional-systemic therapy, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and ranks third in terms of the mortality rate of malignant tumors worldwide in 2020 (1). Apart from liver transplantation, which is limited by a lack of donors, hepatectomy is the only curative therapy that can achieve long-term survival for early HCC. Regrettably, >70% of individuals with HCC are diagnosed in a mid- or advanced stage due to the lack of symptoms in the early stages of the disease (2). As a result, these patients are considered unresectable and miss the window for radical hepatectomy (3, 4).

Current treatment options for intermediate and advanced HCC are non-surgical, such as locoregional therapy (LRT), and systemic therapy, which offer only poor long-term survival. Surprisingly, some selected patients with unresectable HCC (uHCC) have experienced tumor shrinkage and downstaging after LRT and systemic therapy, thus meeting the criteria for resectability (5, 6). This treatment strategy, which aims to convert uHCC into resectable HCC, is known as conversion therapy. Patients with uHCC who have undergone successful conversion and subsequent resection have a 5-year survival rate of >50% (7, 8), which is similar to the 5-year survival rate for patients with resectable HCC who have undergone surgical resection (9). The LRTs used for conversion therapy include transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and transarterial radioembolization (TARE). The systemic treatments used for conversion therapy include chemotherapy, targeted therapy, and immunotherapy.

Recently, with the development and application of the new tyrosine kinase inhibitor (TKI) and immune checkpoint inhibitor (ICI), the efficacy of targeted therapies and immunotherapies for uHCC has improved compared to the past. Furthermore, the improved efficacy makes the targeted therapy and immunotherapy increasingly important in conversion therapy strategies for uHCC. On this basis, combinations of targeted therapies and immunotherapies, as well as combined locoregional-systemic therapy, have been used as conversion therapies. To date, a number of conversion therapy strategies have been investigated, but the best therapeutic treatment options remain unclear. Therefore, we conducted several meta-analyses to systematically evaluate the safety and efficacy of representative treatment strategies (chemotherapy, TACE, molecular therapy, and combined locoregional-systemic therapy) as conversion therapies for HCC in order to elucidate the optimal regimen.

Methods

All items in our meta-analyses were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (10).

Search strategy

In these meta-analyses, relevant studies were systematically searched for in PubMed, Embase, and the Web of Science up to July 30, 2022. The search strings used were as follows: ("unresectable" OR "intermediate-stage" OR "advanced") AND ("liver cancer" OR "hepatoma" OR "hepatic carcinoma" OR "hepatocellular carcinoma" OR "hepatocarcinoma") AND (chemotherapy OR ("loco-regional therap*" OR "locoregional therap*") OR (TACE OR "transcatheter arterial chemoembolization") OR ("hepatic arterial infusion chemotherapy" OR HAIC) OR (radiotherapy OR ("Transarterial Radioembolization" OR TARE) OR yttrium-90 OR ("selective internal radiation therapy" OR SIRT) OR ("Stereotactic Body Radiation Therapy" OR SBRT)) OR ("Targeted therapy" OR "tyrosine kinase inhibitor*" OR "Immune checkpoint inhibitor*" OR "systemic therap*") OR [(Triple therapy) OR (combination therapy) OR combined)] AND [("hepatic resection" OR "liver resection" OR "hepatectomy"[Mesh]) OR resectable]. In addition, references listed in published articles that may be relevant to this review were manually searched.

Literature selection

Included studies were required to meet the following criteria (1): enrolled patients who were initially diagnosed with potentially resectable uHCC (e.g., an Eastern Cooperative Oncology Group performance status [ECOG PS] score of 0–2 points and a Child–Pugh classification of A or B, despite the combination of extrahepatic metastases, macrovascular invasion [MVI], multiple tumors, or insufficient future liver remnant [FLR]); (2) the intervention included ≥1 of the treatments we studied (chemotherapy, TACE, molecular therapy, and combined locoregional-systemic therapy); (3) the outcomes included the conversion rate or the number of people successfully converted, the objective response rate (ORR), and the grade ≥ 3 treatment-related adverse events (AEs) rate; and (4) study types included randomized controlled trials (RCTs), non-RCTs, single-arm studies, cohort studies, case–control trials, or case series. Meanwhile, the exclusion criteria were as follows: (1) studies that included participants diagnosed with secondary liver cancer; (2) studies with mostly the same population (if multiple studies were found, the most recent or most detailed study was adopted); (3) incomplete or unavailable target outcome data; and (4) reviews, comments, conference, abstracts, letters, case reports, and animal experiments. Two authors independently browsed the titles and abstracts of all articles to identify articles relevant to our study. Finally, studies included in the meta-analysis were screened out by reading their full texts. Any disagreements were resolved through discussions with a third investigator.

Data extraction

The primary outcome was the conversion rate, and the secondary outcomes were the ORR and grade ≥ 3 AE rate. The relevant data were extracted by two authors independently from the included studies and filled into a predesigned Excel sheet (Microsoft, Redmond, WA, USA). The data collected were as follows: (1) the first author, year of publication, country, study design, and the number of people receiving conversion therapy, and (2) conversion therapy modalities and schedule, conversion rate, ORR, grade ≥ 3 AE rate, reason of unresectability, and criteria of resectability. Any disagreements were resolved through discussions with a third investigator.

Quality assessment

Because single-arm meta-analyses were used to quantify the pooled results, we used the methodological index for non-randomized studies (MINORS) tool (11) to assess the methodological quality of RCTs and non-RCTs as single-arm studies. Similarly, we used the Institute of Health Economics Quality Appraisal (IHEQA) Checklist (12) to assess the methodological quality of cohort and case–control studies as case series.

Statistical analysis

Data analysis was performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ indicated a statistically significant result. Heterogeneity was assessed using Cochran's Q test and I^2 test, and $I^2 > 50\%$ or $P < 0.1$ indicated significant heterogeneity. When $I^2 > 50\%$, a random-effects model was used; if $I^2 \leq 50\%$, a fixed-effects model was used. Then, the pooled event rate (conversion rate, ORR, and grade ≥ 3 AE rate) and 95% confidence interval (95% CI) were calculated using the "meta" package of R. In addition, funnel plots, and Egger's tests were used to assess the publication biases.

Results

Study identification and characteristics

The initial search identified 4,984 references. A total of 3,225 records remained after removing duplicates, and 3,165 articles were further excluded by title and abstract screening. Subsequently, the remaining 60 articles were assessed for eligibility by reading their full texts, and 36 were further excluded (including three studies with duplicate participants, 15 studies with treatments mixed with other treatments, nine with insufficient data, and nine with no results of interest). Finally, 24 studies met the inclusion criteria and were included in these meta-analyses. Figure 1 illustrates the flowchart for literature screening. The characteristics of the included studies are summarized in Table 1. In total, four studies were included in the chemotherapy group (7, 13–15), seven were included in the TACE group (8, 16–21), eight were included in the molecular therapy group (22–29), and seven were included in the combined locoregional-systemic therapy group (23, 24, 30–34). Nineteen studies (7, 8, 13, 15–17, 19–22, 24, 25, 27–29, 31–34) were considered to be of acceptable quality according to the IHEQA checklist, and the remaining five studies (14, 18, 23, 26, 30) were considered to be of moderate to high quality according to the MINORS tool. The details are summarized in the Supplementary Materials.

Chemotherapy

Four studies (7, 13–15), including seven subgroups, reported that the treatment modality was chemotherapy. The conversion rate, ORR, and the rate of grade ≥ 3 AEs were reported in seven

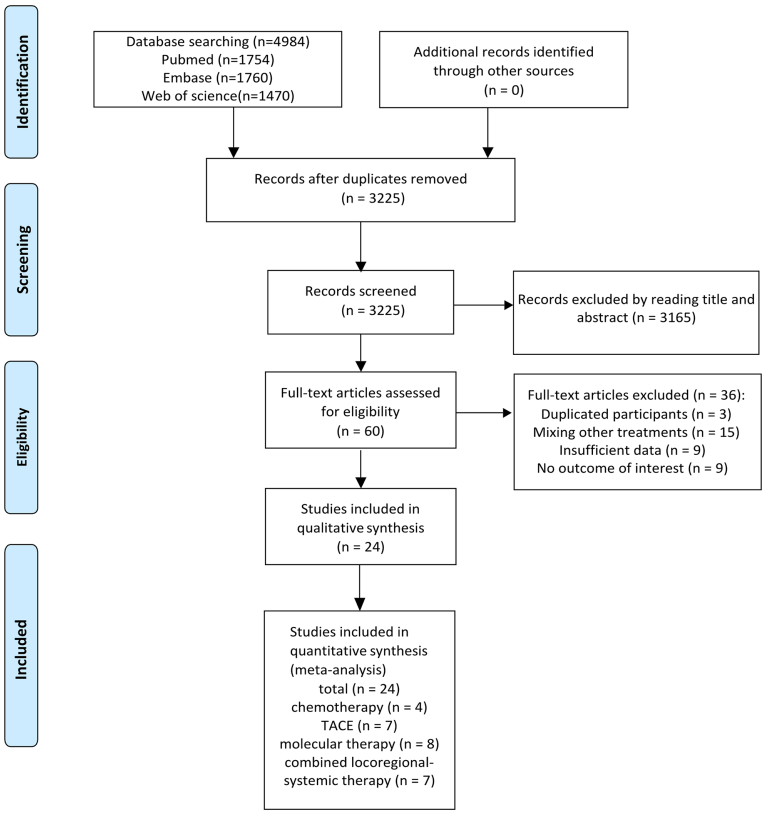

FIGURE 1
The flowchart for the study search and screening.

subgroups of all studies, five subgroups of three studies (13–15), and four subgroups of two studies (14, 15), respectively. All studies included a total of 650 patients with uHCC. Most participants had extrahepatic metastases, vascular invasion, or multiple tumors. The Child–Pugh classification was mostly class A, and the EOCG PS was mostly 0–1 points. When focusing on treatment alternatives, all studies utilized a combination chemotherapy regimen (i.e., PIAF, cisplatin, interferon-2b, doxorubicin, and 5-fluorouracil), and two studies (7, 14) chose a single-agent doxorubicin chemotherapy regimen. The year of publication of the included studies ranged from 2002 to 2013.

The conversion rate for all studies ranged from 4% (14) to 33% (15). The pooled conversion rate was 13% (95% CI, 7%–20%; I^2 = 82%). The conversion rate of PIAF was 15% (95% CI, 8%–25%; I^2 = 83%) and that of doxorubicin alone was 7% (95% CI, 2%–14%; I^2 = 59%). The conversion rate of PIAF showed a non-significant trend of improvement compared to that of doxorubicin (P = 0.12) (Figure 2A).

The ORR ranged from 10% (14) to 36% (15), and the pooled ORR was 19% (95% CI, 12%–28%; I^2 = 77%) (Figure 2B).

The pooled rate of grade ≥ 3 AEs ranged from 58% (15) to 82% (14), and the pooled rate was 67% (95% CI, 55%–78%; I^2 = 79%) (Figure 2C).

TACE

TACE was reported as an intervention in seven studies (8, 16–21) covering nine subgroups. Of these, nine subgroups of all studies reported conversion rates, six subgroups of four studies (18–21) reported ORRs, and three subgroups of two studies (18, 20) reported AEs of grade ≥ 3. In all studies, among 1,809 patients diagnosed with uHCC, the majority of participants had no extrahepatic metastases or MVI. In addition, most were classified as Child–Pugh class A and had an ECOG PS of 0–1 points. Considering anti-neoplastic drugs, all studies except Fan et al. (8) used doxorubicin or epirubicin. A few studies also used platinum, mitomycin (8, 18, 21), and 5-fluorouracil (8). Lipiodol or gelatin sponge was used in seven subgroups of all studies (conventional TACE [c-TACE]) to embolize target vessels, and drug-eluting beads (drug-eluting beads TACE [DEB-TACE]) were used in two subgroups of two studies (19, 20). The year of study publication ranged from 2012 to 2021, except for that by Fan et al. (8), which was published in 1998.

The conversion rate for all studies ranged from 5% (20) to 21% (20). The pooled conversion rate was 12% (95% CI, 9%–15%; I^2 = 60%). Subgroup analysis was performed depending on c-TACE/DEB-TACE. In the cTACE group, the conversion rate

TABLE 1 Characteristics of included studies.

Study	Year	Group of interventions	Subgroup of interventions	N	Reason of unresectability	Definition of successful conversion	Design
Leung (13)	2002	CT	PIAF	149	Extrahepatic metastasis; MVI; Extensive disease	Downstaging to resectable	Case series
Lau-cohort 1 (7)	2004	CT	PIAF	128	Multiple tumors; MVI; Extensive bilobar involvement	Tumor shrinks and FLR increases to resectable	Case series
Yeo-cohort 1 (14)	2005	CT	PIAF	86	Extrahepatic metastasis	Downstaging to resectable	RCT
Kaseb-cohort 1 (15)	2013	CT	PIAF	84	Extrahepatic metastasis; MVI	Resectability was assessed by experienced hepatobiliary surgeons	Retrospective cohort
Kaseb-cohort 2 (15)	2013	CT	PIAF*	33	Extrahepatic metastasis; MVI	Resectability was assessed by experienced hepatobiliary surgeons	Retrospective cohort
Lau-cohort 2 (7)	2004	CT	Doxorubicin	76	Multiple tumors; MVI; Extensive bilobar involvement	Tumor shrinks and FLR increases to resectable	Case series
Yeo-cohort 2 (14)	2005	CT	Doxorubicin	94	Extrahepatic metastasis;	Downstaging to resectable	RCT
Fan (8)	1998	TACE	cTACE	360	Insufficient FLR; Oversized tumors	Tumor shrinks to resectable	Case series
Shi (16)	2012	TACE	cTACE	420	Insufficient FLR; Oversized tumors	Tumor shrinks to resectable	Case series
Zhang (17)	2016	TACE	cTACE	831	Multiple tumors; Insufficient FLR;	R0 resection	Retrospective cohort
He (18)	2017	TACE	cTACE	41	Oversized tumors	Tumor shrinks to resectable	nRCT
Wu-cohort 1 (19)	2018	TACE	cTACE	30	BCLC stage B/C	Downstaging to resectable	Retrospective cohort
Chiu-cohort 1 (20)	2020	TACE	cTACE	19	MVI	Downstaging to resectable	Retrospective cohort
Li (21)	2021	TACE	cTACE	42	Insufficient FLR	Adequate FLR	Retrospective cohort
Wu-cohort 2 (19)	2018	TACE	DEB-TACE	24	BCLC stage B/C	Downstaging to resectable	Retrospective cohort
Chiu-cohort 2 (20)	2020	TACE	DEB-TACE	42	MVI	Downstaging to resectable	Retrospective cohort
Yoshimoto (22)	2018	MT	TKI	38	Advanced HCC	Tumor shrinks to resectable	Case series
He-cohort 1 (23)	2019	MT	TKI	122	MVI	Downstaging to resectable	RCT
He-cohort 1 (24)	2021	MT	TKI	86	Advanced HCC; BCLC stage C	Tumor shrinks to resectable	Retrospective cohort
Shindoh (25)	2021	MT	TKI	107	Advanced HCC	R0 resection	Case series
Zhang (26)	2020	MT	TKI+ICI	33	MVI	Adequate FLR	Prospective single-arm
Zhu (27)	2021	MT	TKI+ICI	63	Mid- or advanced HCC; Insufficient FLR	R0 resection with adequate FLR; Good physical condition	Case series
Huang (28)	2021	MT	TKI+ICI	60	Extrahepatic metastases; MVI	Downstaging to resectable	Case series
Xie (29)	2021	MT	TKI+ICI	60	Confirmed histologically or radiologically	Downstaging to resectable with adequate FLR	Case series
He (30)	2018	LRT+systemic treatment	TKI+LRT	35	MVI	Downstaging to resectable	Prospective single-arm
He-cohort 2 (23)	2019	LRT+systemic treatment	TKI+LRT	125	MVI	Downstaging to resectable	RCT
Chen-cohort 1 (31)	2021	LRT+systemic treatment	TKI+LRT	72	Mid- or advanced-stage HCC; Insufficient FLR	Downstaging to resectable	Retrospective cohort

(Continued)

TABLE 1 Continued

Study	Year	Group of interventions	Subgroup of interventions	N	Reason of unresectability	Definition of successful conversion	Design
He-cohort 2 (24)	2021	LRT+systemic treatment	TKI+ICI+LRT	71	Advanced HCC; BCLC stage C	Tumor shrinks to resectable	Retrospective cohort
Yang (32)	2021	LRT+systemic treatment	TKI+ICI+LRT	38	Technical and/or oncological reasons	Downstaging to resectable	Case series
Zhang (33)	2021	LRT+systemic treatment	TKI+ICI+LRT	25	BCLC stage C	Adequate FLR	Case series
Wu (34)	2021	LRT+systemic treatment	TKI+ICI+LRT	62	Extensive bilobar involvement; MVI; Extrahepatic metastases	R0 resection with adequate FLR; Good physical condition	Case series
Chen-cohort 2 (31)	2021	LRT+systemic treatment	TKI+ICI+LRT	70	Mid- or advanced-stage HCC; Insufficient FLR	Downstaging to resectable	Retrospective cohort

N, number of patients with unresectable hepatocellular carcinoma; CT, chemotherapy; MT, Molecular therapy; LRT, locoregional therapy; PIAF, Cisplatin, interferon α-2b, 5-fluorouracil and doxorubicin; MVI, Macrovascular invasion; TACE, transcatheter arterial chemoembolization; cTACE, conventional transcatheter arterial chemoembolization; DEB-TACE, drug-eluding beads transcatheter arterial chemoembolization, TKI, Tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; FLR, future liver remnant;
*Modified PIAF.

was 11% (95% CI, 8%–15%; I^2 = 63%), while, in the DEB-TACE group, the conversion rate was 20% (95% CI, 11%–30%; I^2 = 0). DEB-TACE had a higher conversion rate than c-TACE, but the difference was not statistically significant (P = 0.07) (Figure 3A).

The ORR ranged from 10% (18) to 62% (19), and the pooled ORR was 32% (95% CI, 15%–51%; I^2 = 88%) (Figure 3B).

The rate of grade ≥ 3 AEs ranged from 17% (20) to 66% (18), and the pooled rate was 34% (95% CI, 8%–66%), with significant heterogeneity (I^2 = 92%) (Figure 3C).

Molecular therapy

There were eight studies (22–29), including eight subgroups, which adopted molecular therapy as the arm-treatment. All eight subgroups of all studies reported the conversion rate, six subgroups of six studies (23–26, 28, 29) reported ORR, and four subgroups of four studies (23, 25, 28, 29) reported AEs of grade ≥ 3. A total of 569 patients with uHCC were enrolled in all trials. Most participants were diagnosed with extrahepatic metastases, MVI, or multiple tumors. Meanwhile, almost all of them were classified as Child–Pugh class A and had an ECOG PS of 0–1 points. Four studies (22–25) adopted TKI alone, and four studies (26–29) adopted TKI combined with ICI. The TKIs used in most studies were sorafenib (22, 23) and lenvatinib (24–29), with only one study using apatinib (27). The ICIs were various anti–programmed cell death protein 1 antibodies (e.g., sindilizumab, pabrolizumab, camrelizumab, and toripalimab). The years of study publication ranged from 2018 to 2021.

The conversion rate of included studies ranged from 0% (24) to 42% (26), and the pooled conversion rate was 10% (95% CI, 3%–20%; I^2 = 90%). A subgroup analysis was performed based on monotherapy with TKI alone or TKI combined with ICI. The conversion rate was 19% (95% CI, 8%–33%; I^2 = 78%) in the group receiving TKI combined with ICI and 3% (95% CI, 0–10%; I^2 = 86%) in the TKI-alone group. The conversion rate in the group receiving TKI combined with ICI was significantly higher than that in the TKI-alone group (P < 0.01) (Figure 4A).

The ORR ranged from 6% (23) to 53% (29) and the pooled ORR was 30% (95% CI, 15%–46%; I^2 = 93%). The ORR was 44% (95% CI, 32%–56%; I^2 = 59%) in TKI combined with ICI group and 18% (95% CI, 4%–38%; I^2 = 95%) in the TKI-alone group. The ORR of TKI combined with ICI was significantly higher than that of the TKI-alone (P = 0.03) (Figure 4B).

The grade ≥ 3 AE rate ranged from 13% (29) to 42% (23), and the pooled rate was 30% (95% CI, 18%–43%; I^2 = 84%). The grade ≥ 3 AE rate was 25% (95% CI, 5%–52%; I^2 = 90%) in TKI combined with ICI group and 34% (95% CI, 21%–49%; I^2 = 82%) in the TKI-alone group. No significant difference existed in the grade ≥ 3 AE rate between TKI combined with ICI group and the TKI-alone group (P = 0.53) (Figure 4C).

Combined locoregional-systemic therapy

Eight subgroups in seven studies (23, 24, 30–34) reported combined locoregional-systemic therapy. The conversion rates and ORR were available for eight subgroups and seven subgroups from all studies, respectively, and five subgroups from five studies (23, 30, 32–34) investigated the rates of grade ≥ 3 AEs. There were 498 patients with uHCC in all the studies. Most patients had the following baseline characteristics: concurrent extrahepatic metastases, MVI, or multiple tumors; Child–Pugh class A; Barcelona Clinic Liver Cancer (BCLC) stage C; and ECOG PS 0–1 points. For treatment strategies, five studies (24, 31–34) adopted TKI combined with ICI and LRT, and three studies (23, 30, 31) adopted TKI combined with LRT. The TKI used was lenvatinib (24, 31–34) or sorafenib (23, 30),

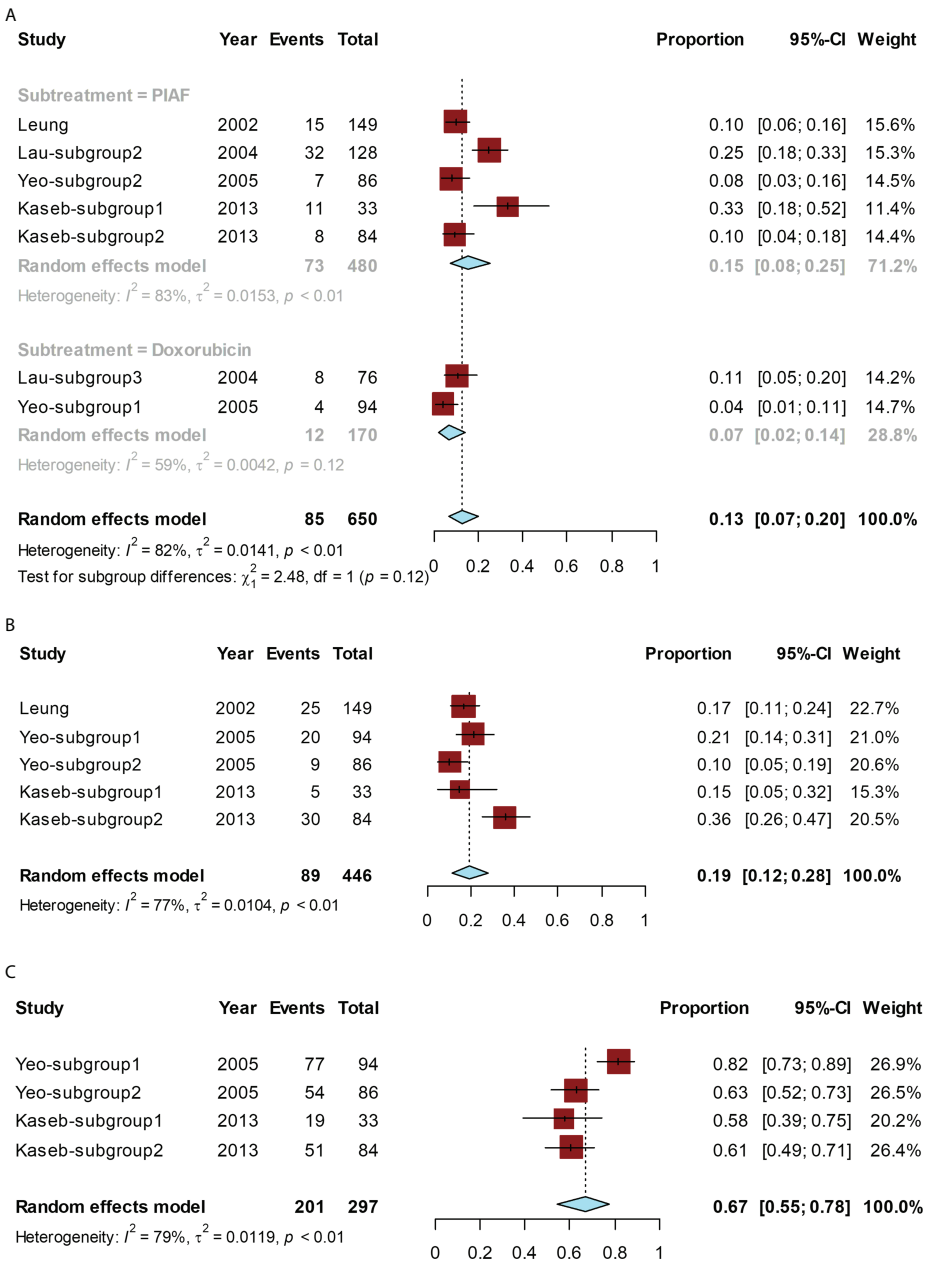

FIGURE 2
Forest plot for the chemotherapy group. The pooled conversion rate and subgroup analysis of the conversion rate according to PIAF or doxorubicin **(A)**, pooled ORR **(B)**, and the pooled rate of grade ≥ 3 AEs **(C)**.

and the ICI were various programmed cell death protein 1 monoclonal antibodies. For TACE, two studies (32, 34) used c-TACE, and one study (31) used DEB-TACE. For HAIC, all studies used the FOLFOX regimen. The years of study publication ranged from 2018 to 2021.

The conversion rates of available studies ranged from 11% (31) to 60% (33), and the pooled rate was 25% (95% CI, 13%–38%; I^2 = 89%). A subgroup analysis was performed according to the combination of treatments. The pooled conversion rate for the TKI combined with ICI and LRT was 33% (95% CI, 17%-52%; I^2 = 89%), which was significantly higher than that for TKI combined with LRT (12% [95% CI, 8%-17%; I^2 = 0%]) (P = 0.01) (Figure 5A).

The ORR of included studies ranged from 28% (31) to 96% (33), and the pooled ORR was 60% (95% CI, 41%–77%; I^2 = 91%). Subgroup analysis suggested that the pooled ORR of TKI

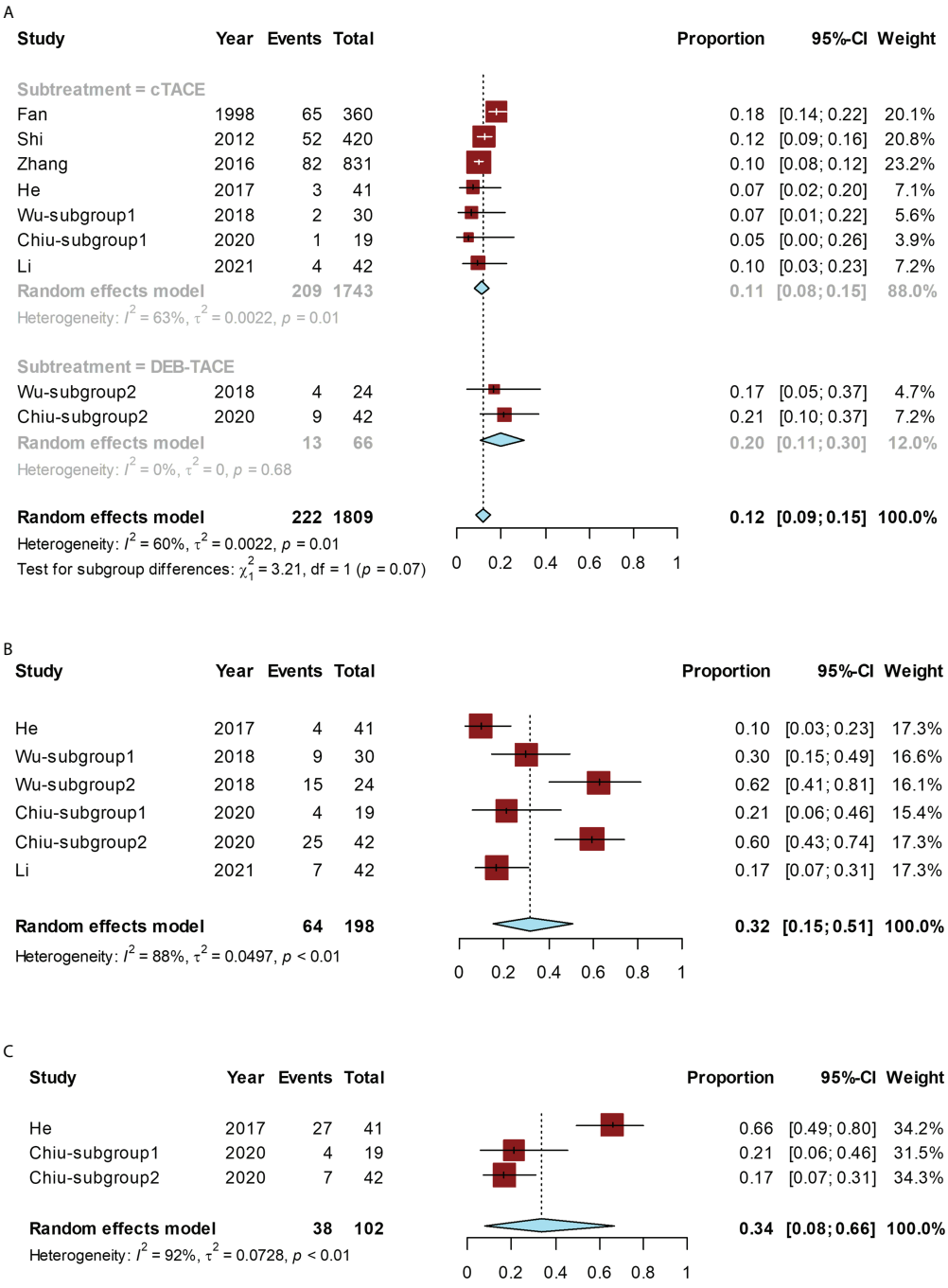

FIGURE 3
Forest plot for the TACE group. The pooled conversion rate and subgroup analysis of the conversion rate according to cTACE or DEB-TACE **(A)**, pooled ORR **(B)**, or pooled rate of grade ≥ 3 AEs **(C)**. cTACE, conventional transcatheter arterial chemoembolization; DEB-TACE, drug-eluding beads transarterial chemoembolization.

combined with ICI and LRT was 73% (95% CI, 51%–91%; I^2 = 90%), while the pooled ORR of TKI combined with LRT was 41% (95% CI, 25%–57%; I^2 = 85%) (Figure 5B). The ORR of TKI combined with ICI and LRT was significantly higher than that of TKI combined with LRT (P = 0.02).

The grade ≥ 3 AE rate of included studies ranged from 15% (34) to 55% (32), and the pooled grade ≥ 3 AE rate was 40% (95% CI, 23%–58%; I^2 = 89%) (Figure 5C). The grade ≥ 3 AE rate between the TKI combined with ICI and LRT group (31% [95% CI, 10%-57%; I^2 = 89%]) and the TKI combined with LRT group

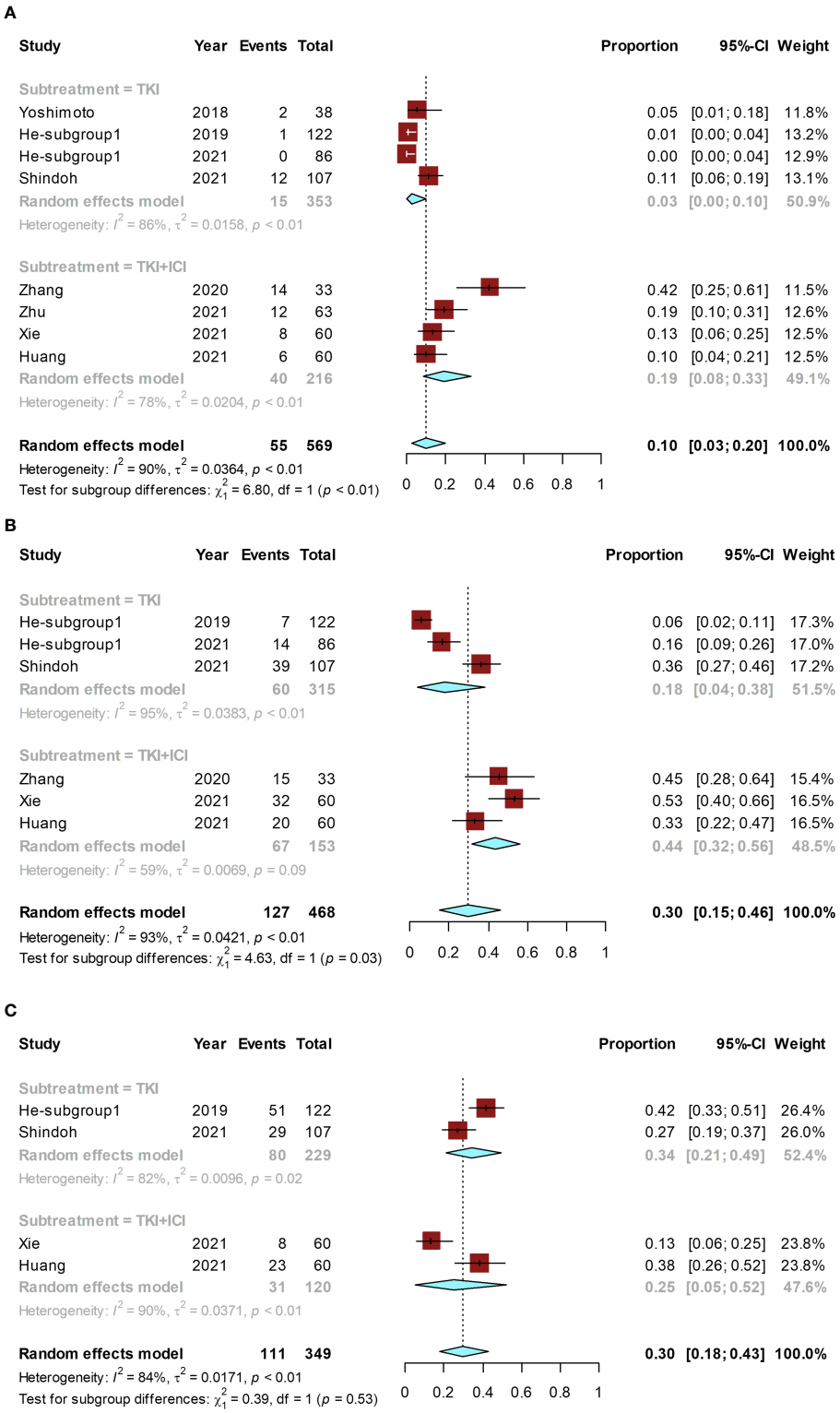

FIGURE 4
Forest plot for the molecular therapy group. Pooled rates and the subgroup analysis of conversion rate according to the use of TKI alone or TKI combined with ICI: pooled conversion rate **(A)**, pooled ORR **(B)**, and the pooled rate of grade ≥ 3 AEs **(C)**. TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

(53% [95% CI, 45%-61%; I^2 = 0%]) was not statistically significantly different (P = 0.11).

Publication bias

No significant publication bias existed according to the funnel plots (Figure 6) and Egger's test (Supplementary Figure S1) based on an analysis of the conversion rate of chemotherapy (P = 0.625), TACE (P = 0.776), molecular therapy (P = 0.087), and combined locoregional-systemic therapy (P = 0.190) groups.

Discussion

With the advent and development of new biologic agents and the exploration of treatment strategies, uHCC, once considered incurable, can become resectable with conversion therapy and achieve survival benefits comparable to those achieved with resection of early-stage HCC (7–9). There are many options for conversion therapy, but the best choice is not yet clear.

Our meta-analyses summarized the efficacy and safety of four representative types of conversion therapy for uHCC. Among these, chemotherapy, TACE, and molecular therapies had lower and similar conversion rates, whereas combined locoregional-systemic therapy had a significantly higher conversion rate. Notably, subgroup analysis showed no significant differences in conversion potential between different strategies of the same monotherapy. However, the conversion rate of the combined therapy was significantly better than that of the monotherapy. The increased conversion potential of combined therapy could be since the fact that different treatments have different anti-tumor mechanisms. In particular, TKI combined with ICI and LRT has the highest conversion rate (33%) compared to any other treatment strategy, which is close to the 39.1% rate of conversion surgery for FOLFOXIRI plus bevacizumab as a conversion therapy used for patients with initially unresectable metastatic colorectal cancer (35), which is exciting.

The ORRs achieved with chemotherapy, TACE, and molecular therapy remained similar. Similarly, the ORR for combined locoregional-systemic therapy remained significantly higher than the ORRs of the aforementioned other therapies. Similar to the trend in the subgroup analysis of the conversion rate, combined therapy was associated with a higher ORR, and TKI combined with ICI and LRT could achieve the highest ORR. To some extent, this result suggested that strategies that can have a higher ORR may imply a higher conversion potential.

In terms of safety, we were mainly concerned about serious (grade ≥ 3) treatment-related AEs. The chemotherapy group had the worst safety profile, with around 70% of patients experiencing significant side effects. Given the low ORR and conversion rates of chemotherapy, its poor safety profile seems unacceptable today. Safety was similar and acceptable in both the TACE group, the molecular therapy group, and the combined locoregional-systemic therapy group. Interestingly, the subgroup analysis showed increased safety risks with combination therapies compared to monotherapy, but the trend was insignificant. For the combined therapy, the safety of TKI combined with ICI was comparable to that of TKI combined with LRT. Furthermore, no increased security risks were identified even when comparing TKI combined with ICI and LRT with TKI combined with LRT.

Our findings additionally reflect the history and development of conversion therapy for uHCC to some extent. In the early stages, the options used as conversion therapy were mainly chemotherapy and LRT, represented by TACE. For chemotherapy, there are combination chemotherapy regimens (such as PIAF) and single-agent chemotherapy regimens (such as doxorubicin). Chemotherapy is currently rarely considered as conversion therapy for HCC due to its low conversion potential and high safety risks. However, LRT is continuing to develop. Representative TACE is currently used as the first-line treatment for intermediate to advanced HCC (36–38). In recent years, a new TACE approach (DEB-TACE) has been developed with the ability to increase the intravascular drug concentration and reduce the amount of chemotherapeutic drugs entering the systemic circulation (39). This ability might be why DEB-TACE was associated with greater conversion and improved safety compared to cTACE, although the difference was not statistically significant. Several studies (40–42) has shown that TARE could lead to tumor shrinkage and downstaging. However, due to liver resection mixed with liver transplantation following tumor downstaging, the role of TARE as conversion therapy for uHCC could not be accurately clarified.

Sorafenib was approved by the U.S. Food and Drug Administration for advanced uHCC in 2007. Sorafenib application extends the median survival time for patients with uHCC (43). However, the ORR of the included studies with sorafenib as the conversion therapy was only 6%, which implies a very low conversion potential (2%) (22, 23). Recently, significant progress has been made in developing new anti-tumor molecular drugs, including other TKIs and ICIs. Although the efficacy of single agents remains limited, TKI combined with ICI significantly improved the conversion rate but was accompanied by an increased incidence of AEs. The inference that drugs with different anti-tumor mechanisms have increased conversion potential when used in combination seems reasonable. It might have been based on this inference that the combination of LRT and systemic therapy has recently received more attention, with higher conversion rates as expected. In particular, triple therapy consisting of TKIs combined with ICIs plus an LRT began to be extensively studied in 2021, with a higher conversion rate than any other.

Admittedly, some limitations should be pointed out. First, a high degree of heterogeneity exists in this meta-analysis. Its sources may be as follows (1): differentiation of unresectable causes and

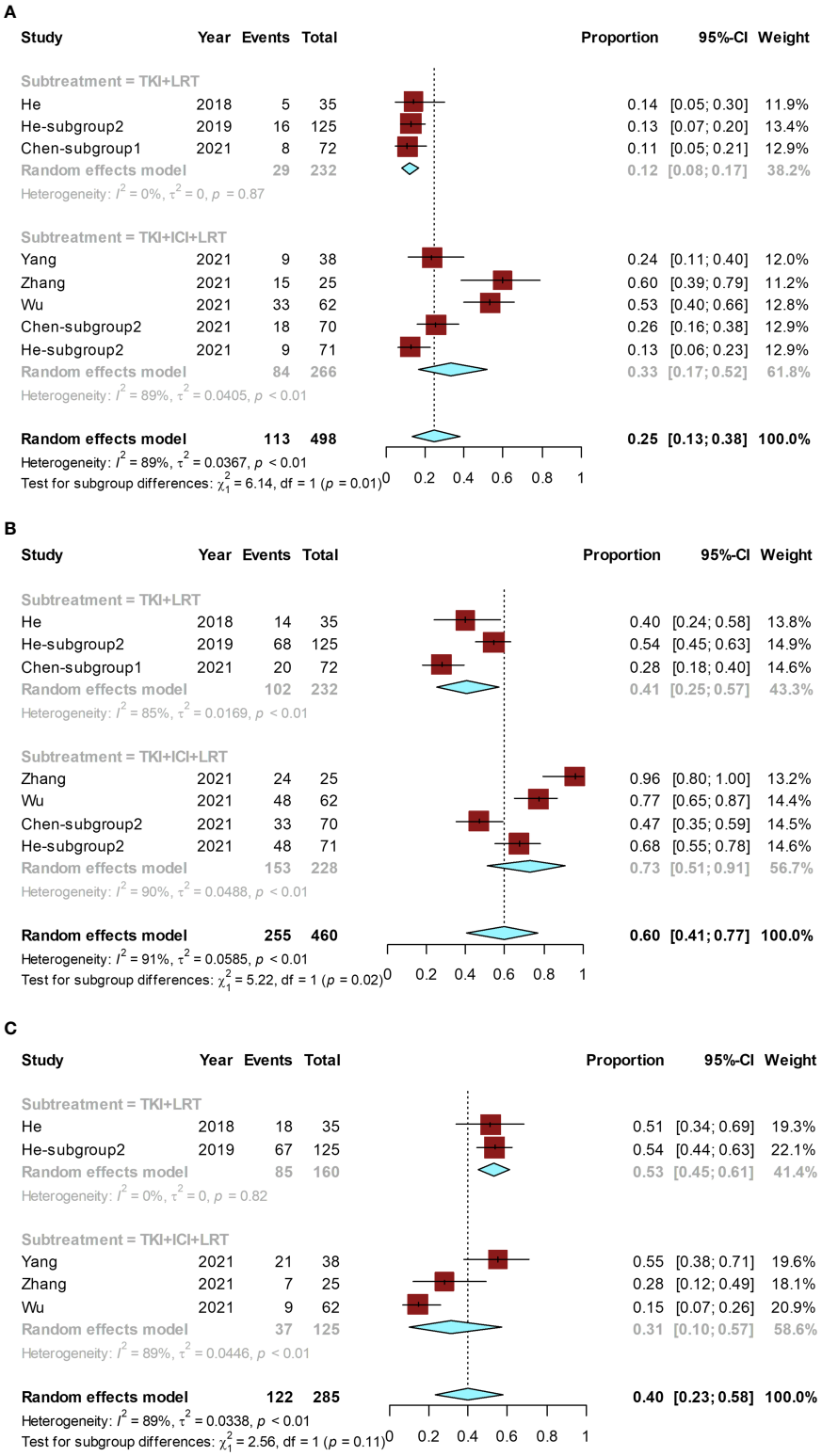

FIGURE 5
Forest plot for the combined locoregional-systemic therapy group. The pooled conversion rate and subgroup analysis **(A)**, pooled ORR and its subgroup analysis **(B)**, and the pooled rate of grade ≥ 3 AEs and its subgroup **(C)**. These subgroup analyses were conducted according to combination of treatments. LRT, locoregional therapy.

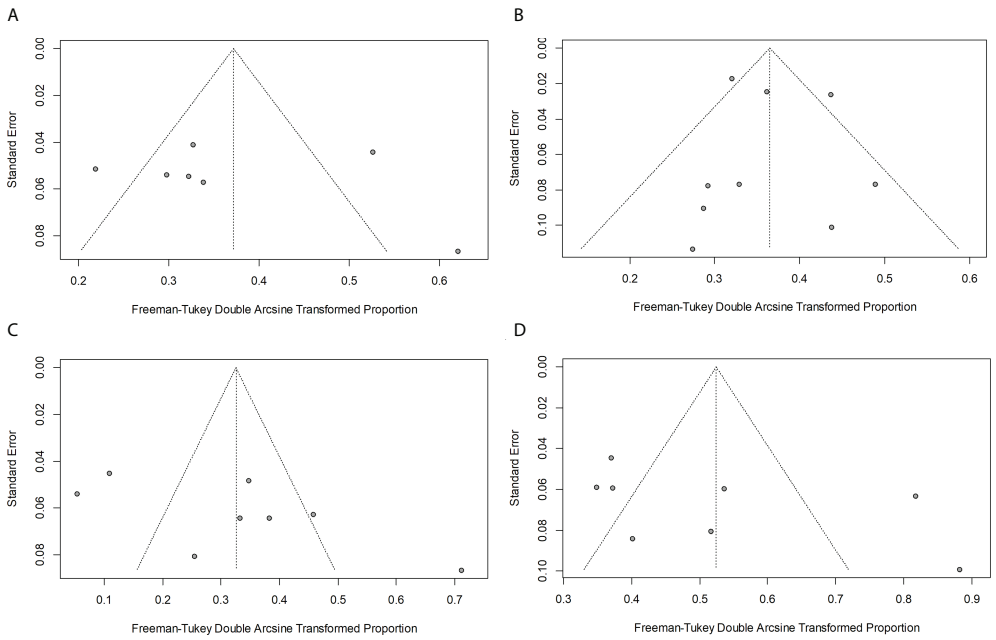

FIGURE 6
Funnel plots for the conversion rates of chemotherapy **(A)**, TACE **(B)**, molecular therapy **(C)**, and combined locoregional-systemic therapy **(D)**.

inconsistent criteria for resectability, and (2) there are no fixed criteria for the choice of treatment regimen and drug dose. So, subgroup analysis was performed to explore the stability of the results and further interpret the results. Second, most included studies were not using conversion rates as the primary endpoint since conversion therapy for HCC has only recently received attention. In addition, the population characteristics of the groups were inconsistent. All of our studies included patients with extrahepatic metastases, except for the TACE group, which did not include patients with extrahepatic metastases. The inconsistency in population characteristics might be primarily due to the different indications for different treatment strategies. So, our study focused on each treatment strategy.

The exploration of transformation therapy for uHCC is in the ascendant. Prospective controlled trials with large samples of different combinations of conversion strategies should be performed more often to provide better-quality evidence for clinical practice. Following conversion therapy strategies, criteria for resectability and study endpoints have yet to be further harmonized for uHCC. In the future, individualized protocols and studies for conversion therapy may receive more attention due to the biological heterogeneity of primary HCC.

Conclusion

Our findings demonstrated that combined locoregional-systemic therapy, may be the most effective conversion therapy regimen for uHCC at present, which is associated with a significant ORR and conversion potential, along with an acceptable safety profile.

Author contributions

JL and YP contributed to the conception and design of the study. YP and WL conducted the literature search and extracted the data. ZW was involved in the resolution of all the arguments. YP conducted the data analysis and wrote the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Hebei Provincial Key Research and Development Program Project (21377767D) and the Hebei Provincial Postgraduate Innovation Fund (CXZZSS2022137).

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.978823/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, et al. Hepatocellular carcinoma: Consensus recommendations of the national cancer institute clinical trials planning meeting. *J Clin Oncol* (2010) 28(25):3994–4005. doi: 10.1200/jco.2010.28.7805

3. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2019) 30(5):871–3. doi: 10.1093/annonc/mdy510

4. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. Easl-eortc clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* (2012) 56(4):908–43. doi: 10.1016/j.jhep.2011.12.001

5. Tang ZY, Liu KD, Bao YM, Lu JZ, Yu YQ, Ma ZC, et al. Radioimmunotherapy in the multimodality treatment of hepatocellular carcinoma with reference to second-look resection. *Cancer* (1990) 65(2):211–5. doi: 10.1002/1097-0142(19900115)65:2<211::aid-cncr2820650205>3.0.co;2-g

6. Sitzmann JV, Order SE, Klein JL, Leichner PK, Fishman EK, Smith GW. Conversion by new treatment modalities of nonresectable to resectable hepatocellular cancer. *J Clin Oncol* (1987) 5(10):1566–73. doi: 10.1200/jco.1987.5.10.1566

7. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. *Ann Surg* (2004) 240(2):299–305. doi: 10.1097/01.sla.0000133123.11932.19

8. Fan J, Tang ZY, Yu YQ, Wu ZQ, Ma ZC, Zhou XD, et al. Improved survival with resection after transcatheter arterial chemoembolization (Tace) for unresectable hepatocellular carcinoma. *Digestive Surg* (1998) 15(6):674–8. doi: 10.1159/000018676

9. Sitzmann JV, Abrams R. Improved survival for hepatocellular cancer with combination surgery and multimodality treatment. *Ann Surg* (1993) 217(2):149–54. doi: 10.1097/00000658-199302000-00009

10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Res ed)* (2021) 372:n71. doi: 10.1136/bmj.n71

11. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. *ANZ J Surg* (2003) 73(9):712–6. doi: 10.1046/j.1445-2197.2003.02748.x

12. Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. *J Clin Epidemiol* (2016) 69:199–207.e2. doi: 10.1016/j.jclinepi.2015.07.010

13. Leung TW, Tang AM, Zee B, Yu SC, Lai PB, Lau WY, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. *Cancer* (2002) 94(2):421–7. doi: 10.1002/cncr.10236

14. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase iii study of doxorubicin versus Cisplatin/Interferon alpha-2b/Doxorubicin/Fluorouracil (Piaf) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Institute* (2005) 97(20):1532–8. doi: 10.1093/jnci/dji315

15. Kaseb AO, Shindoh J, Patt YZ, Roses RE, Zimmitti G, Lozano RD, et al. Modified Cisplatin/Interferon α-2b/Doxorubicin/5-Fluorouracil (Piaf) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. *Cancer* (2013) 119(18):3334–42. doi: 10.1002/cncr.28209

16. Shi XJ, Jin X, Wang MQ, Wei LX, Ye HY, Liang YR, et al. Effect of resection following downstaging of unresectable hepatocelluar carcinoma by transcatheter arterial chemoembolization. *Chin Med J* (2012) 125(2):197–202. doi: 10.3760/cma.j.issn.0366-6999.2012.02.007

17. Zhang Y, Huang G, Wang Y, Liang L, Peng B, Fan W, et al. Is salvage liver resection necessary for initially unresectable hepatocellular carcinoma patients downstaged by transarterial chemoembolization? ten years of experience. *Oncol* (2016) 21(12):1442–9. doi: 10.1634/theoncologist.2016-0094

18. He MK, Le Y, Li QJ, Yu ZS, Li SH, Wei W, et al. Hepatic artery infusion chemotherapy using mfolfox versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: A prospective non-randomized study. *Chin J Cancer* (2017) 36(1):83. doi: 10.1186/s40880-017-0251-2

19. Wu B, Zhou J, Ling G, Zhu D, Long Q. Callispheres drug-eluting beads versus lipiodol transarterial chemoembolization in the treatment of hepatocellular carcinoma: A short-term efficacy and safety study. *World J Surg Oncol* (2018) 16(1):69. doi: 10.1186/s12957-018-1368-8

20. Chiu SH, Chang PY, Shih YL, Huang WY, Ko KH, Chang WC, et al. Efficacy and safety of supplemental transarterial chemoembolization through extrahepatic collateral arteries with drug-eluting beads: Treatment for unresectable hepatocellular carcinoma. *Drug design Dev Ther* (2020) 14:5029–41. doi: 10.2147/dddt.S266470

21. Li B, Qiu J, Zheng Y, Shi Y, Zou R, He W, et al. Conversion to resectability using transarterial chemoembolization combined with hepatic arterial infusion chemotherapy for initially unresectable hepatocellular carcinoma. *Ann Surg Open* (2021) 2(2):e057. doi: 10.1097/as9.0000000000000057

22. Yoshimoto T, Imura S, Morine Y, Ikemoto T, Arakawa Y, Iwahashi S, et al. The outcome of sorafenib therapy on unresectable hepatocellular carcinoma: Experience of conversion and salvage hepatectomy. *Anticancer Res* (2018) 38(1):501–7. doi: 10.21873/anticanres.12250

23. He M, Li Q, Zou R, Shen J, Fang W, Tan G, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: A randomized clinical trial. *JAMA Oncol* (2019) 5(7):953–60. doi: 10.1001/jamaoncol.2019.0250

24. He MK, Liang RB, Zhao Y, Xu YJ, Chen HW, Zhou YM, et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. *Ther Adv Med Oncol* (2021) 13:17588359211002720. doi: 10.1177/17588359211002720

25. Shindoh J, Kawamura Y, Kobayashi Y, Kobayashi M, Akuta N, Okubo S, et al. Prognostic impact of surgical intervention after lenvatinib treatment for advanced hepatocellular carcinoma. *Ann Surg Oncol* (2021) 28(12):7663–72. doi: 10.1245/s10434-021-09974-0

26. Zhang W, Hu B, Han J, Wang H, Wang Z, Chen M, et al. Preliminary report on the study of conversion therapy of advanced hepatocellular carcinoma combined pd-1 inhibitors with multi-target tyrosine kinase inhibitors. *Chin J Hepatobiliary Surg* (2020) 26:947–8. doi: 10.3760/cma.j.cn113884-20201203-00611

27. Zhu XD, Huang C, Shen YH, Ji Y, Ge NL, Qu XD, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase

inhibitor and anti-Pd-1 antibody combinations. *Liver Cancer* (2021) 10(4):320–9. doi: 10.1159/000514313

28. Huang C, Zhu XD, Shen YH, Wu D, Ji Y, Ge NL, et al. Organ specific responses to first-line lenvatinib plus anti-Pd-1 antibodies in patients with unresectable hepatocellular carcinoma: A retrospective analysis. *biomark Res* (2021) 9(1):19. doi: 10.1186/s40364-021-00274-z

29. Xie D, Sun Q, Wang X, Zhou J, Fan J, Ren Z, et al. Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world. *Ann Trans Med* (2021) 9(8):652. doi: 10.21037/atm-20-7037

30. He MK, Zou RH, Li QJ, Zhou ZG, Shen JX, Zhang YF, et al. Phase ii study of sorafenib combined with concurrent hepatic arterial infusion of oxaliplatin, 5-fluorouracil and leucovorin for unresectable hepatocellular carcinoma with major portal vein thrombosis. *Cardiovasc interventional Radiol* (2018) 41(5):734–43. doi: 10.1007/s00270-017-1874-z

31. Chen S, Wu Z, Shi F, Mai Q, Wang L, Wang F, et al. Lenvatinib plus tace with or without pembrolizumab for the treatment of initially unresectable hepatocellular carcinoma harbouring pd-L1 expression: A retrospective study. *J Cancer Res Clin Oncol* (2021) 148(8):2115–25. doi: 10.1007/s00432-021-03767-4

32. Yang X, Xu H, Zuo B, Yang X, Bian J, Long J, et al. Downstaging and resection of hepatocellular carcinoma in patients with extrahepatic metastases after stereotactic therapy. *Hepatobiliary Surg Nutr* (2021) 10(4):434–42. doi: 10.21037/hbsn-21-188

33. Zhang J, Zhang X, Mu H, Yu G, Xing W, Wang L, et al. Surgical conversion for initially unresectable locally advanced hepatocellular carcinoma using a triple combination of angiogenesis inhibitors, anti-Pd-1 antibodies, and hepatic arterial infusion chemotherapy: A retrospective study. *Front Oncol* (2021) 11:729764. doi: 10.3389/fonc.2021.729764

34. Wu JY, Yin ZY, Bai YN, Chen YF, Zhou SQ, Wang SJ, et al. Lenvatinib combined with anti-Pd-1 antibodies plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: A multicenter retrospective study. *J hepatocell carcinoma* (2021) 8:1233–40. doi: 10.2147/jhc.S332420

35. Tomasello G, Petrelli F, Ghidini M, Russo A, Passalacqua R, Barni S. Folfoxiri plus bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: A systematic review and pooled analysis. *JAMA Oncol* (2017) 3(7):e170278. doi: 10.1001/jamaoncol.2017.0278

36. Vogel A, Martinelli EEGCEa and Committee EG. Updated treatment recommendations for hepatocellular carcinoma (Hcc) from the esmo clinical practice guidelines. *Ann Oncol* (2021) 32(6):801–5. doi: 10.1016/j.annonc.2021.02.014

37. Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, et al. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 edition). *Liver Cancer* (2020) 9(6):682–720. doi: 10.1159/000509424

38. Xie DY, Ren ZG, Zhou J, Fan J, Gao Q.2019 Chinese Clinical guidelines for the management of hepatocellular carcinoma: Updates and insights. *Hepatobiliary Surg Nutr* (2020) 9(4):452–63. doi: 10.21037/hbsn-20-480

39. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics. *J Hepatol* (2007) 46(3):474–81. doi: 10.1016/j.jhep.2006.10.020

40. Labgaa I, Tabrizian P, Titano J, Kim E, Thung SN, Florman S, et al. Feasibility and safety of liver transplantation or resection after transarterial radioembolization with yttrium-90 for unresectable hepatocellular carcinoma. *HPB* (2019) 21(11):1497–504. doi: 10.1016/j.hpb.2019.03.360

41. Iñarrairaegui M, Pardo F, Bilbao JI, Rotellar F, Benito A, D'Avola D, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. *Eur J Surg Oncol* (2012) 38(7):594–601. doi: 10.1016/j.ejso.2012.02.189

42. Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, et al. Yttrium-90 microspheres (Therasphere) treatment of unresectable hepatocellular carcinoma: Downstaging to resection, rfa and bridge to transplantation. *J Surg Oncol* (2006) 94(7):572–86. doi: 10.1002/jso.20609

43. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *New Engl J Med* (2008) 359 (4):378–90. doi: 10.1056/NEJMoa0708857

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 29 September 2022
DOI 10.3389/fonc.2022.973857

OPEN ACCESS

EDITED BY
Guoying Wang,
First Affiliated Hospital of Guangzhou Medical University, China

REVIEWED BY
Yan Zhou,
Tianjin Third Central Hospital, China
Gaëtan-Romain Joliat,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

*CORRESPONDENCE
Xu Che
drchexu@126.com
Jianguo Zhou
zjgty@hotmail.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 22 June 2022
ACCEPTED 15 September 2022
PUBLISHED 29 September 2022

CITATION
Wang C, Huang X, Lan X, Lan D, Huang Z, Ye S, Ran Y, Bi X, Zhou J and Che X (2022) Research progress of spontaneous ruptured hepatocellular carcinoma: Systematic review and meta-analysis.
Front. Oncol. 12:973857.
doi: 10.3389/fonc.2022.973857

Research progress of spontaneous ruptured hepatocellular carcinoma: Systematic review and meta-analysis

Chunling Wang[1†], Xiaozhun Huang[2†], Xiaofeng Lan[3†], Dongmei Lan[3], Zhangkan Huang[2], Shu Ye[2], Yihong Ran[2], Xinyu Bi[4], Jianguo Zhou[4*] and Xu Che[2*]

[1]Department of Hospital-Acquired Infection Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China, [2]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China, [3]Department of Internal Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China, [4]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Spontaneously ruptured hepatocellular carcinoma (rHCC) with hemorrhage is characterized by rapid onset and progression. The aim of this systematic review was to explore the current studies on rHCC with hemorrhage and determine the optimum treatment strategy.

Method: The PubMed, Web of Science, Embase, and the Cochrane Library databases were searched for studies reporting survival outcomes with comparison between emergency resection (ER) and transarterial embolization following staged hepatectomy (SH) were included by inclusion and exclusion criteria, the perioperative and survival data were statistically summarized using Review Manager 5.3 software.

Result: A total of 8 retrospective studies were included, with a total sample size of 556, including 285 (51.3%) in the ER group and 271 (48.7%) in the SH group. The perioperative blood loss and blood transfusion volume in the SH group were less than those in the ER group, and there were no significant differences in the operative time, incidence of complications, mortality and recurrence rate of tumors between the two groups. The 1-, 2-, 3-year overall survival and 1-, 2-, 3-, 5-year disease-free survival of the ER group were not significantly different

from those of the SH group, and the 5-year overall survival rate of ER group was lower than that of the SH group (hazard ratios=1.52; 95% confidence intervals: 1.14-2.03, P=0.005).

Conclusion: There was no significant difference in the short-term efficacy of ER or SH in the treatment of ruptured HCC, and SH was superior to ER in the long-term survival.

KEYWORDS

hepatocellular carcinoma, spontaneously ruptured, hepatectomy, survival, prediction model

1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the second most common cause of cancer-related deaths (1). Spontaneous rupture is a rare but fatal complication of HCC that is characterized by coagulation disorders, hemodynamic instability, and hepatic insufficiency. Ruptured hepatocellular carcinoma (rHCC) is more common in patients with advanced liver disease and heavy tumor burden, which is reflected tumor size, number of tumors, portal vein cancer embolism, and microvascular invasion.

The current treatment strategies for rHCC include emergency resection (ER), anhydrous alcohol injection, hepatic artery ligation, transcatheter artery embolization (TAE), and conservative symptomatic supportive care. Radical resection is a curative option for rHCC, and its goal is to stop bleeding in time and salvage liver function. However, given the poor general condition and liver function of patients with rHCC, the tumor is usually unresectable, large, or multifocal, and may be accompanied by major intrahepatic vascular invasion and extrahepatic metastases. This not only obviates the use of exploratory laparotomy for radical resection but also increases the risk of serious postoperative complications. TAE is superior to laparotomy in terms of maintaining hemostasis, and prolongs patient survival (2). Nevertheless, ER or TAE following staged hepatectomy (SH) is still a controversial treatment strategy for rHCC (3, 4).

According to the AJCC TNM staging, HCC with spontaneous rupture is classified as T4 stage regardless of primary tumor size and relationship to blood vessels (5, 6). However, some studies show that classifying all cases of rHCC as T4 may not accurately reflect the true prognosis (7–9). Therefore, it is critical to identify novel indicators or models to predict the prognosis of rHCC in order to guide clinical management. In this systemic review and meta-analysis, the research progress and prognostic models of spontaneous rHCC based on the available clinical evidence will be discussed.

2 Materials and methods

The present meta-analysis was performed according to the criteria defined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (10).

2.1 Databases and search strategies

The present meta-analysis was performed according to the criteria defined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. PubMed, Web of Science, Embase, and Cochrane Library databases were searched for articles that were available until February 25, 2022. Medical subject headings combined with free text words were used to search for randomized clinical trial (RCT) and observational studies. The following medical heading terms and their combinations were used: ((hepatocellular carcinoma [Title/Abstract]) AND (rupture [Title/Abstract])) AND ((hepatectomy [Title/Abstract]) OR (resection [Title/Abstract])).

2.2 Literature inclusion and exclusion criteria

Inclusion criteria (1): Published articles comparing the short and long-term outcomes of emergency resection (ER) or staged hepatectomy (SH) after hepatocellular carcinoma (rHCC) rupture; (2) Pathologically confirmed diagnosis of HCC in the study population; (3) Studies include at least one outcome measure relevant to the study.

Exclusion criteria: (1) Unextractable data; (2) Editorials, editorial letters, comments, case reports, or other types of publications; (3) Animal experiments.

2.3 Data extraction and outcome measures

After removing the duplicate articles, the titles and abstracts of the remaining articles were evaluated, and studies were sequentially excluded according to the eligibility criteria. The complete text of the selected articles was examined independently by two investigators, and any discrepancy was resolved by consensus. The main indicators included perioperative conditions (duration of surgery, amount of bleeding, amount of blood transfusion), postoperative outcomes (morbidity, mortality, recurrence rate), overall survival (OS), and disease-free survival (DFS).

2.4 Quality assessment and statistical analysis

The data were checked for completeness, plausibility, and integrity before incorporating them into a single database. The methodological quality of the retrospective studies was assessed using the modified Newcastle–Ottawa scale, which is based on patient selection, comparability of the study groups and outcome assessment. The studies were scored from 0–9, and scores ≥6 were considered high quality. Discrepancies, if any, were resolved by consensus. The meta-analysis was performed using the Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). Continuous and dichotomous variables were expressed as weighted mean difference (*WMD*) and odds ratio (*OR*) respectively. Results were reported with 95% confidence intervals (*CI*). Statistical heterogeneity among the included studies was assessed using the chi-squared test with $P < 0.05$ as the threshold of significance, and quantified using the I^2 statistic. The random effects model was used for pooled analyses in case of significant heterogeneity between the studies, and the fixed effects model was used otherwise. Bias in publication was tested using the Stata version 12.0 software (Stata Corporation, College Station, TX, USA).

3 Result

3.1 Search results

A total of 963 articles were initially retrieved and 366 duplicate studies were removed. The remaining 574 articles were screened on the basis of their titles and abstracts, and the irrelevant studies, case reports, and studies analyzing molecular mechanisms were excluded. The full texts of 23 articles were evaluated, and 8 articles (2–4, 11–15) were finally selected. The literature search and study selection criteria are schematically illustrated in Supplementary Figure 1.

3.2 Characteristics of the included studies

The characteristics of the 8 articles are summarized in Supplementary Table 1. All studies were retrospective, and published from 2006 to 2020. Except for the study by Buczkowski et al. (15) that was conducted in Canada, all studies were from China. The studies included 556 cases, of which 285 (51.3%) had ER and 271 (48.7%) had SH.

3.3 The methodological quality of the included studies

Based on the mNOS scores, the studies included in this meta-analysis were of high quality (Supplementary Table 2). Two studies (3, 4) scored 9, one study (12) scored 8, four studies (2, 11, 14, 15) scored 7, and only one study (13) scored 6 points. Four trials (3, 4, 12, 15) reported follow-up time, seven studies (2–4, 11, 12, 14, 15) reported perioperative outcome measures, and all studies reported survival data of at least 1 year.

3.4 Perioperative relevant outcome measures

Data of operation time was reported for the ER and SH groups in 4 studies (2–4, 15) using *WMD*. There was low heterogeneity among the studies (I^2=5%), and the fixed-effects model showed no significant difference between the two groups (*WMD*=0.76 min, 95%*CI*: 9.28-7.76, *P*=0.86, Supplementary Figure 2A).

Five studies (2–4, 11, 15) reported perioperative blood loss and 4 studies (2–4, 15) reported blood transfusion, and the results showed that the ER group lost more blood than the SH group (*WMD*=683.61 mL, 95%*CI*: 283.36-1083.86, *P*=0.0008, Supplementary Figure 2B). Therefore, the need for blood transfusion was also significantly higher in the ER group (*WMD*=453.43 mL, 95%*CI*: 250.27-656.58, *P*<0.0001, Supplementary Figure 2C). Significant heterogeneity was observed for the blood loss results (I^2=82%, *P*=0.0002), and moderate heterogeneity was found in the rate of blood transfusion (I^2=49%, *P*=0.12). The sensitivity analysis reduced heterogeneity but do not change the statistical results.

Five studies (3, 4, 11, 14, 15) reported the incidence of perioperative complications, and the results showed that the complication rates of the ER and SH group were similar (23.6%

vs. 40.9%; *OR*=0.94, 95%*CI*: 0.51-1.66, *P*=0.82, Supplementary Figure 2D), and there was no heterogeneity (I^2 =0). The incidence of postoperative liver failure was reported in 5 articles, and no statistically significant difference between the two groups (3.6% vs. 2.3%; *OR*=1.19, 95% *CI*: 0.40 to 3.57, *P*=0.75, Supplementary Figure 2E) or any heterogeneity among the studies was observed (I^2 =0).

Case fatality was reported in 6 studies (3, 4, 11, 12, 14, 15) which showed significantly higher rates in the ER group compared to the SH group (7.97% vs. 1.29%; *OR*=3.10, 95%*CI*: 1.21-7.97; *P*=0.02). Slight heterogeneity was observed (I^2 =23%), and sensitivity analysis showed that after excluding the studies of Ou et al. (4) and Buczkowski et al. (15), there was no significant difference between the mortality rates of the ER and SH groups (4.76% versus 1.81%; *OR*=1.28, 95% *CI*: 0.40-4.12, *P*=0.68, Supplementary Figure 2F). In addition, no heterogeneity was found among the studies (I^2=0, *P*=0.49).

3.5 Postoperative tumor outcome measures

Four studies (2–4, 15) reported tumor recurrence, and χ^2 test suggested no heterogeneity (I^2 = 0) among the studies. The fixed-effects model showed that the difference in total recurrence rate between the two groups was not statistically significant (69.3% vs. 64.3%); *OR*=1.11, 95%*CI*: 0.64-1.93, *P*=0.71, Supplementary Figure 3A). Four articles (2–4, 11) reported peritoneal metastases or recurrence, and showed no heterogeneity (I^2 =0). Fixed-effects model showed that the recurrence rate of peritoneal metastases was lower in the ER group, albeit not significantly (15.6% versus 17.1%; *OR*=0.80, 95%*CI*: 0.43-1.5, *P*=0.49, Supplementary Figure 3B).

3.6 Survival outcomes

All 8 included studies reported 1- and 2-year OS rates; 6 studies (2–4, 11, 12, 14) reported 3-year survival rates; and only 5 studies (2, 4, 11, 12, 14) had the 5-year OS data. The 1-, 2-, and 3-year OS rates were not significantly different between the ER and SH groups (*P*>0.05), and the respective hazard ratios (*HR*) were 1.06 (95% *CI*: 0.62-1.81, Supplementary Figure 4A), 1.38 (95% *CI*: 0.94-2.03, Supplementary Figure 4B) and 1.05 (95% *CI*: 0.64-1.72, Supplementary Figure 4C). The χ^2 test showed lack of heterogeneity between the studies (1 year OS: I^2=0, *P*=0.84; 2 years OS: I^2=0, *P*= 0.10; 3 years OS: I^2=38%, *P*=0.84), and sensitivity analysis did not alter the statistical results. However, the 5-year OS of the ER group was significantly lower than that of the SH group (*HR* =1.52, 95% *CI*: 1.14-2.03, *P*=0.005, Supplementary Figure 4D), and there was no heterogeneity between the studies (I^2=0, *P*=0. 92).

Four studies (2–4, 11) reported the 1-, 2- and 3-year DFS, and only 3 studies (2, 4, 11) reported the DFS for 5 years. The 1-, 2-, 3- and 5-year DFS rates were similar in the ER and SH groups (*P*>0.05), with respective *HR* of 1.21 (95% *CI*: 0.78-1.87, Supplementary Figure 5A), 1.19 (95% *CI*: 0.86-1.65, Supplementary Figure 5B), 1.2 (95%*CI*: 0.88-1.63, Supplementary Figure 5C) and 1.27 (95%*CI*: 0.96-1.69, Supplementary Figure 5D). There was no heterogeneity between the studies (1 year DFS: I^2 =0, *P*=0. 68; 2 years DFS: I^2=0, *P*=0.85; 3 years DFS: I^2=0, *P*=0.99; 5 DFS: I^2=0, *P*=0.45).

3.7 Sensitivity analysis and publication bias

Sensitivity analysis included the studies with mNOS scores of 7 and above. There was no change in the statistical results of the recent postoperative outcome measures and survival data. After two studies, the case fatality rate was not SH group due to the removal of Ou et al. (4) and Buczkowski et al. (15). Tested by Begg's rank-related test (*P* =0.368, Supplementary Figure 6A) and Egger linear regression method (*P* =0.067, Supplementary Figure 6B) showed no publication bias in the studies included in this meta-analysis.

4 Discussion

4.1 Risk factors for rHCC

The current hypothesis is that the rapid expansion and invasion of the hepatic tumor leads to intra-plasmal hemorrhage of the tumor and obstructs the hepatic venous outflow tract, which causes intra-tumoral hypertension and eventual rupture (16–18). The risk factors of rHCC include cirrhosis, hypertension, tumors larger than 5 cm in diameter, thrombosis and extrahepatic infiltrates (16, 17, 19). Therefore, HCC patients with underlying diseases such as hypertension and cirrhosis, tumor > 5 cm in diameter, and extrahepatic infiltrates should be considered at high risk of tumor rupture, and radical resection should be performed at the earliest as long as the preoperative clinical evaluation is consistent with the surgical requirements.

4.2 Short-term survival of rHCC

A systematic review (20) pooled clinical data of 4941 patients with rHCC from 67 studies in a systematic review, and found that the average 30-day and 6-month survival rates were 66.9% and 53.6% respectively. The main causes of death were bleeding-related complications (34.3%) and liver failure (30.0%). In addition, the 30-day survival rate was 34.8% for the patients

who received conservative medical care and did not undergo surgery or any other intervention, and 70.1% for patients who received transcatheter arterial chemoembolization (TACE) or TAE. Due to its minimal invasiveness, high selectivity, reproducibility, and low relative risk, TAE has a better hemostasis effect on patients with rHCC compared to simple open hemostasis, and can therefore prolong patient survival (2). Partial hepatectomy can remove ruptured tumors, clean the abdominal cavity, and achieve radical resection. Furthermore, compared to TAE or conservative medical treatment, radical resection is associated with lower mortality and better prognosis (21), and can improve the 30-day survival rate of rHCC patients to 95.5% or even 100% (20).

Due to the low incidence and heterogeneity of rHCC, the choice between ER or SH in patients with potentially resectable spontaneous rHCC is controversial. Zheng YJ et al. (22) conducted a meta-analysis of 7 retrospective studies comparing the outcomes of early hepatectomy (EH) or delayed hepatectomy (DH) on 385 patients with spontaneous rHCC, and found that DH (7 days after rupture) can reduce intraoperative bleeding, intraoperative blood transfusion, and 30-day mortality rate, and improve the 1-year, 2-year, and 3-year OS rate. There was no difference between the 5-year OS of the two groups. However, Zheng YJ et al. (22) defined EH as that performed within 3 days after the rupture of HCC, and DH as resection after 7 days of conservative treatment and/or scavenged hemostasis. However, the definition of operation time was vague, which could not fully meet the inclusion criteria of the meta-analysis, resulting in obvious selection bias. In addition, there was systematic error in extracting information from literature, the *HR* for 1-, 2-, 3-, and 5-year OS of rHCC patients reported by Zhong et al. (12) was 1.42 (95% *CI*: 0.35 to 5.82), and that reported by Buczkowski et al. (15) for 1-, 2- and 3-year OS was 3.74 (95%CI: 0.55 to 25.55). In addition, two studies (3, 11) published in 2019 and 2020 were not included in the meta-analysis.

4.3 Long-term survival of rHCC

Moris D et al. (20) summarized the long-term prognosis of patients with rHCC from 67 reports, and concluded that tumor recurrence and metastasis were the most frequent cause of death (17.2% of the overall cohort). As expected, surgical resection led to more favorable long-term outcomes. The 1-, 3- and 5-year OS in the ER group were 40%-94.6%, 41.1%-49.5%, and 23.3%-27.8% respectively, compared to 57.1%-90%, 19%-67.5%, and 7.6%-67.5% in the SH group.

The current meta-analysis showed the 1-, 2- and 3-year OS and the 1-, 2-, 3- and 5-year DFS rates were similar in ER and SH groups (all $P>0.05$), whereas the 5-year OS rate was significantly lower in the ER group (*HR*=1.52; 95%*CI*: 1.14-2.03, $P=0.005$). Although some studies have reached conclusions consistent with these results, they are limited by the small sample size and insufficient follow-up duration (2). One possible reason of the comparable 3-year survival rates of ER and SH is that the amount of intraperitoneal hemorrhage is counted in the ER group, and the time from TAE to resection varies from 1 day to 2 months. The hemorrhage partially absorbed and removed in the SH group, which may explain similar survival prognosis of both groups within 3 years. However, the 5-year OS in the ER group was significantly shorter than that in the SH group. It is difficult at present to provide a convincing explanation for this difference, which may not be due to the treatment at the time of HCC rupture but rather due to the follow-up treatment measures after radical resection. This hypothesis will have to be validated with larger samples and longer follow-up evaluation. Therefore, based on the aggregated data, rHCC should not be considered a "single clinical event" and "rupture" should not be considered as the only adverse prognostic factor.

4.4 Survival prediction of rHCC

Given the paucity of studies on spontaneously rHCC after radical resection, and the significant heterogeneity between cases with non-ruptured and rHCC, it is still unclear whether liver tumor rupture affects long-term survival. In addition, the survival benefits of the different treatment methods are not consistent. Therefore, it is essential to identify novel prognostic markers or models for rHCC in order to aid clinical decision-making (Table 1).

4.4.1 TAE for rHCC

Since HCC rupture causes acute bleeding, the primary goal of treatment is to stem the bleeding and prevent internal hemorrhage. TAE is a minimally invasive and reproducible approach with a good hemostasis effect in patients with hepatic tumor rupture. However, it is not suitable for all patients with rHCC.

4.4.1.1 Prediction of prognosis of TAE treatment of rHCC by imaging and clinical scoring systems

Compared to single abdominal hemostasis, emergency TAE has a better hemostasis effect on patients with rHCC, and can prolong patient survival (2). However, Ngan H et al. (23) reported that emergency TAE provided little survival benefit to patients with total bilirubin levels > 2.92 mg/dL, and Okazaki et al. (24) considered total bilirubin level > 3 mg/dL to be a contraindication to TAE. Lee et al. (25) devised a scoring system by combining imaging and clinical laboratory parameters to predict the case fatality rate in patients with rHCC at 30 days after TAE, and identified bilobar tumors, total bilirubin > 2.5 mg/dL and albumin < 30 g/L as independent predictors of 30-

TABLE 1 The models of predicting the prognosis of rHCC.

	Model	Author	Sample/Method	Risk factor		Outcome
TAE for rHCC	Prediction of prognosis of TAE treatment of rHCC by imaging and clinical scoring systems	Ngan H et al	33/Mantel-Cox test	Total bilirubin=2.9 mg/dl		mOS 1 week
				Total bilirubin<2.9 mg/dl		mOS 15 weeks
		Okazaki M et al	38/Mantel-Cox test	Total bilirubin=3.0 mg/dl		mOS 13 days
				Total bilirubin ≤3.0 mg/dl		mOS 165 days
		Lee KH et al	111/Multiple logistic regression model	Bilobar tumor distribution (3points)	High risk≥4points	30 days mortality 86.8%
				Total bilirubin=2.5mg/dL (2points)	Moderate risk=3points	30 days mortality 31.8%
				Albumin <30g/L (1points)	Low risk ≤ 2points	30 days mortality 2.6%
		Fan WZ et al	94/Cox regression analysis	Shock index	≥0.6=<1	mOS 12.0 ± 1.0 days
					≥1	mOS 52.0 ± 7.2 days
				Child-Pugh score	10/11	mOS 51.0 ± 13.9 days
					12/13	mOS 28.0 ± 3.7 days
				Portal vein tumor thrombus	Main	mOS 14.0 ± 2.0 days
					Lobar	mOS 34.0 ± 5.1 days
					Segmental	mOS 52.0 ± 6.9 days
	MELD predicts TAE for rHCC	Jundt MC et al	24/Log-rank test	MELD-Na score=16		mOS 9 days, 30 days mortality 67%
				MELD-Na score ≤ 16		mOS 166.5 days, 30 days mortality 21%
Partial liver resection for rHCC	TAA	Wu JJ et al	139/Log-rank test	Scores according to the tumor size	High risk 10-13 points	1 year OS 30.2%
				Scores according to the AFP	Moderate risk 6-9 points	1 year OS 43.2%
				Scores according to the ALP	Low risk 0-5 points	1 year OS 88.1%
	AFP	Chua DW et al	79/Cox regression analysis	AFP=200 ng/mL		1 year OS 33.3%
				Tumor size=10 cm		1year recurrent rate 90.9%
		She WH et al.	114/Log-rank test	AFP≥256 ng/mL		mDFS 5.9 months
				AFP<256 ng/ml		mDFS 10.7 months

TAE, transcatheter artery embolization; rHCC, ruptured hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; mOS, median overall survival; TAA, tumor-associated antigen; AFP, alpha-fetoprotein; mDFS, median disease-free survival.

day fatality. Patients with rHCC have poor liver function, and underlying cirrhosis and liver dysfunction in most cases, which respond poorly to conservative treatment alone. Fan WZ et al. (26) consider emergency TAE to be an effective intervention in patients with Child-Pugh C grade rHCC with hepatic shock, particularly in those with shock index ≥1, Child-Pugh score 10/11 and grade 1 or lower branch portal vein cancer suppository. In contrast, the efficacy of TAE and conservative medical treatment were similar in patients with Child-Pugh score 12/13 tumors and portal vein trunk carcinoma suppositories.

4.4.1.2 Model for End-Stage Liver Disease (MELD) predicts prognosis for TAE treatment of rHCC

MELD scores are based on total serum bilirubin concentration, international normalized ratio of prothrombin time, and serum creatinine concentration (27). In addition, serum sodium concentration has been recognized as an important prognostic factor in patients with cirrhosis, and hyponatremia is associated with ascites (28), hepatorenal syndrome (29), and liver disease death (30). The combination of MELD score and serum sodium concentration (MELD-Na) can predict the case fatality rate of liver transplants with greater accuracy. Jundt MC et al. (31) used the MELD-Na score to evaluate the perioperative and short-term case fatality rates of rHCC patients undergoing TAE, and found that MELD-Na was an independent risk factor of post-TAE survival. Higher MELD-Na scores were associated with worse baseline liver function and tumor prognosis, and the 30-day and 90-day case fatality rates of patients with MELD-Na score >16 were respectively 67% and 89% after TAE. Thus, rHCC patients with a Child-Pugh score

>11, MELD-Na score >16 and portal vein main trunk carcinoma suppositories have extremely poor short- and long-term prognosis, and emergency intervention does not improve their chances of survival compared to conservative treatment.

4.4.2 Partial liver resection for rHCC

Most rHCC patients have underlying cirrhosis and decompensated liver function, which can be aggravated due to surgery. Furthermore, surgery also increases the risk of jaundice and refractory ascites, eventually leading to liver and kidney failure. Therefore, it is crucial to screen for the suitable patients.

4.4.2.1 Predictive model for partial hepatic resection of rHCC

Wu JJ et al. (32) conducted an univariate and multivariate analysis of 139 patients with rHCC, and established a new tumor-associated antigen (TAA) scoring model based on tumor diameter, alkaline phosphatase (ALP), and alpha-fetoprotein (AFP). Approximately 88.1% of the low-risk patients survived for more than 1 year compared to only 43.2% and 30.2% of the intermediate-risk and high-risk patients respectively (P<0.001). The 2-, 3-, and 5-year OS rates were 73.8%, 64.1%, and 44.2% respectively in the low-risk group, 27.3%, 24.8%, and 15.5% in the moderate-risk group, and 9.3%, 4.7%, and 0 in the high-risk group. The DFS rates also showed significant differences with the new staging model (32).

Compared to the Barcelona Clinic Liver Cancer (BCLC) and the Cancer of the Liver Italian Program (CLIP) classification models, the TAA model showed a higher Harrell's C statistic, indicating greater predictive accuracy for the postoperative prognosis of rHCC. In addition, the TAA model has lower Akaike Information Criterion (AIC) compared to BCLC and CLIP, indicating that the model fits well and loses less information when predicting OS (relative probability <0.001). Thus, the TAA model has better discrimination power and homogeneity than the BCLC and CLIP systems for predicting the OS and DFS of rHCC patients after surgical resection (32).

4.4.2.2 AFP predicts prognosis after rHCC resection

AFP is an important diagnostic and prognostic marker of HCC, and studies increasingly show that elevated AFP is associated with increased tumor burden (33, 34) and poor prognosis (21). However, it is unclear whether AFP levels can predict the survival in patients with rHCC. AFP > 200 ng/mL (35) or >1000 ng/ml (21) have been identified as independent risk factors for the overall survival of rHCC patients. In addition, tumor size > 10 cm and AFP > 200 ng/mL are associated with early postoperative recurrence rates of 54.5%-90.9% and perioperative case fatality rate of 66.7% in patients with rHCC, and are thus useful indicators for avoiding futile surgery (36). She WH et al. (37) showed that AFP ≥ 256 ng/mL is an independent risk factor of OS in rHCC patients, and portends worse survival regardless of tumor size. Thus, surgical intervention (ER or SH) is recommended for rHCC patients with low TAA score and AFP < 256 ng/mL. Although surgical resection is still the first choice for increasing the chances of survival in patients with higher TAA scores (6 to 9) and AFP ≥ 256 ng/mL, postoperative adjuvant therapy should be considered for lowering the risk of tumor recurrence.

4.5 Treatment of rHCC survivors

Adjuvant treatment after curative hepatectomy is a crucial factor influencing patient survival. However, data regarding the safety and efficacy of sorafenib in rHCC patients is limited. One single-center study showed that the cumulative survival rates in an rHCC cohort (38) after 4, 8, and 12 months of surgery were higher for the patients that received sorafenib as an adjuvant treatment. Postoperative TACE can also be used as adjuvant therapy to prevent recurrence after hepatectomy (39), although perioperative TACE decreases intrahepatic metastasis but increases peritoneal dissemination in rHCC patients. Recently, Huang A et al. (40) found that adjuvant TACE conferred a survival benefit in patients with a high risk of recurrence (multiple tumors, as well as micro- and macro-vascular invasion). However, these results should be interpreted with caution since their sample size was limited (38–41). Few studies have focused on the treatment of rHCC survivors, and the strategies are mainly determined based on the tumor burden after recurrence. Targeted therapies and immunotherapy are increasingly being considered for the management of advanced HCC (42).

In 2014, Zheng SZ et al. (38) conducted a retrospective study on a cohort of 32 rHCC patients to determine the efficacy and safety of sorafenib. Twenty-two patients in the cohort had undergone surgery (ER or SH), 10 received TAE or TACE, and 12 received sorafenib postoperatively. The initial dose of sorafenib was 200 mg bid, and increased to the full dose of 400 mg bid after 5 to 7 days in case there was no toxicity. The median survival duration of the surgery group (n=12) was 11.41 months, and that of the surgery + sorafenib group (n= 10) was 16.47 months. In contrast, the median survival duration in the surgery/TAE/TACE group (n=20) was only 8.32 months, compared to 16.41 months in the surgery/TAE/TACE+sorafenib group (n=12) (P=0.04). In addition, 2 patients achieved complete radiological remission, 3 patients were stable, and 7 patients developed tumors. Three patients were temporarily administered with a reduced dose of sorafenib due to toxicity,

and the main side effects were hand-foot skin reactions and diarrhea rather than any serious adverse reactions.

Thus, survivors of radical surgical resection (ER or SH) can be treated with adjuvant TACE, targeted drugs, immune checkpoint inhibitors, or hepatic artery perfusion chemotherapy based on locally advanced or advanced HCC.

5 Summary

It is often difficult to stratify rHCC patients based on clinical presentation and biochemical data to determine appropriate treatment strategies. There was no significant difference in the short-term efficacy of ER or SH in the treatment of ruptured HCC, and SH was superior to ER in the long-term survival. Identification of novel prognostic indicators or models of rHCC may help guide treatment decisions and improve outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

All authors contributed to the study concept, design, data interpretation, and discussion. YR and SY contributed to the screening and data collection. XB and DL contributed to the assessment of the included article. ZH and XL contributed to the data analysis. XH and CW contributed to the writing of the manuscript. JZ and XC contributed to provide expert insight into the revision of the manuscript and being as corresponding author. All authors approved the final version of the reports.

Funding

This research was supported by Sanming Project of Medicine in Shenzhen (No.SZSM202011010) and Shenzhen High-level Hospital Construction Fund.

Acknowledgments

The authors acknowledge Zhen Huang, MD, Ph.D., Hong Zhao, MD, Ph.D. work in National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, for the writing assistance and critical revision of the manuscript for important intellectual content.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.973857/full#supplementary-material

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet (London England)* (2018) 391(10127):1301–14. doi: 10.1016/s0140-6736(18)30010-2

2. Ren A, Luo S, Ji L, Yi X, Liang J, Wang J, et al. Peritoneal metastasis after emergency hepatectomy and delayed hepatectomy for spontaneous rupture of hepatocellular carcinoma. *Asian J Surg* (2019) 42(2):464–9. doi: 10.1016/j.asjsur.2018.09.006

3. Zhou C, Zhang C, Zu QQ, Wang B, Zhou CG, Shi HB, et al. Emergency transarterial embolization followed by staged hepatectomy versus emergency hepatectomy for ruptured hepatocellular carcinoma: A single-center, propensity score matched analysis. *Jpn J Radiol* (2020) 38(11):1090–8. doi: 10.1007/s11604-020-01007-2

4. Ou D, Yang H, Zeng Z, Luo Y, Yang L. Comparison of the prognostic influence of emergency hepatectomy and staged hepatectomy in patients with ruptured hepatocellular carcinoma. *Dig Liver Dis* (2016) 48(8):934–9. doi: 10.1016/j.dld.2016.04.016

5. Subramaniam S, Kelley RK, Venook AP. A review of hepatocellular carcinoma (HCC) staging systems. *Chin Clin Oncol* (2013) 2(4):33. doi: 10.3978/j.issn.2304-3865.2013.07.05

6. Nuño-Guzmán CM, Marín-Contreras ME. Ruptured hepatocellular carcinoma and non-alcoholic fatty liver disease, a potentially life-threatening complication in a population at increased risk. *Ann Hepatol* (2020) 19(1):3–4. doi: 10.1016/j.aohep.2019.11.001

7. Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, Kudo M, et al. Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: An analysis of 1160 cases from a nationwide survey. *Ann Surg* (2014) 259(3):532–42. doi: 10.1097/SLA.0b013e31828846de

8. Hiraoka A, Kawamura T, Aibiki T, Okudaira T, Toshimori A, Yamago H, et al. Prognosis and therapy for ruptured hepatocellular carcinoma: Problems with staging and treatment strategy. *Eur J Radiol* (2015) 84(3):366–71. doi: 10.1016/j.ejrad.2014.11.038

9. Chan AC, Dai JW, Chok KS, Cheung TT, Lo CM. Prognostic influence of spontaneous tumor rupture on hepatocellular carcinoma after interval hepatectomy. *Surgery* (2016) 159(2):409–17. doi: 10.1016/j.surg.2015.07.020

10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339: b2535. doi: 10.1136/bmj.b2535

11. Wu JJ, Zhu P, Zhang ZG, Zhang BX, Shu C, Mba'nbo-Koumpa AA, et al. Spontaneous rupture of hepatocellular carcinoma: Optimal timing of partial hepatectomy. *Eur J Surg Oncol* (2019) 45(10):1887–94. doi: 10.1016/j.ejso.2019.02.033

12. Zhong F, Cheng XS, He K, Sun SB, Zhou J, Chen HM. Treatment outcomes of spontaneous rupture of hepatocellular carcinoma with hemorrhagic shock: A multicenter study. *SpringerPlus* (2016) 5(1):1101. doi: 10.1186/s40064-016-2762-8

13. Yang H, Chen K, Wei Y, Liu F, Li H, Zhou Z, et al. Treatment of spontaneous ruptured hepatocellular carcinoma: A single-center study. *Pak J Med Sci* (2014) 30(3):472–6. doi: 10.12669/pjms.303.4001

14. Hsueh KC, Fan HL, Chen TW, Chan DC, Yu JC, Tsou SS, et al. Management of spontaneously ruptured hepatocellular carcinoma and hemoperitoneum manifested as acute abdomen in the emergency room. *World J Surg* (2012) 36 (11):2670–6. doi: 10.1007/s00268-012-1734-6

15. Buczkowski AK, Kim PT, Ho SG, Schaeffer DF, Lee SI, Owen DA, et al. Multidisciplinary management of ruptured hepatocellular carcinoma. *J Gastrointest Surg* (2006) 10(3):379–86. doi: 10.1016/j.gassur.2005.10.012

16. Zhu LX, Wang GS, Fan ST. Spontaneous rupture of hepatocellular carcinoma. *Br J Surg* (1996) 83(5):602–7. doi: 10.1002/bjs.1800830507

17. Rossetto A R, Adani GL, Risaliti A, Baccarani U, Bresadola V, Lorenzin D, et al. Combined approach for spontaneous rupture of hepatocellular carcinoma. *World J Hepatol* (2010) 2(1):49–51. doi: 10.4254/wjh.v2.i1.49

18. Xia F, Ndhlovu E, Zhang M, Chen X, Zhang B, Zhu P. Ruptured hepatocellular carcinoma: Current status of research. *Front Oncol* (2022) 12:848903. doi: 10.3389/fonc.2022.848903

19. Zhu Q, Li J, Yan JJ, Huang L, Wu MC, Yan YQ. Predictors and clinical outcomes for spontaneous rupture of hepatocellular carcinoma. *World J Gastroenterol* (2012) 18(48):7302–7. doi: 10.3748/wjg.v18.i48.7302

20. Moris D, Chakedis J, Sun SH, Spolverato G, Tsilimigras DI, Ntanasis-Stathopoulos I, et al. Management, outcomes, and prognostic factors of ruptured hepatocellular carcinoma: A systematic review. *J Surg Oncol* (2018) 117(3):341–53. doi: 10.1002/jso.24869

21. Zhang W, Zhang ZW, Zhang BX, Huang ZY, Zhang WG, Liang HF, et al. Outcomes and prognostic factors of spontaneously ruptured hepatocellular carcinoma. *J Gastrointest Surg* (2019) 23(9):1788–800. doi: 10.1007/s11605-018-3930-7

22. Zheng YJ Z, Li DL, Luo D, Chen XP, Zhang B, Fang C, et al. Early versus delayed hepatectomy for spontaneously ruptured hepatocellular carcinoma: A systematic review and meta-analysis. *J Invest Surg* (2021) 34(11):1214–22. doi: 10.1080/08941939.2020.1792009

23. Ngan H, Tso WK, Lai CL, Fan ST. The role of hepatic arterial embolization in the treatment of spontaneous rupture of hepatocellular carcinoma. *Clin Radiol* (1998) 53(5):338–41. doi: 10.1016/s0009-9260(98)80004-4

24. Okazaki M, Higashihara H, Koganemaru F, Nakamura T, Kitsuki H, Hoashi T, et al. Intraperitoneal hemorrhage from hepatocellular carcinoma: emergency chemoembolization or embolization. *Radiology* (1991) 180(3):647–51. doi: 10.1148/radiology.180.3.1651524

25. Lee KH, Tse MD, Law M, Cheng AK, Wong HF, Yu ML, et al. Development and validation of an imaging and clinical scoring system to predict early mortality in spontaneous ruptured hepatocellular carcinoma treated with transarterial embolization. *Abdom Radiol (NY)* (2019) 44(3):903–11. doi: 10.1007/s00261-019-01895-7

26. Fan WZ, Zhang YQ, Yao W, Wang Y, Tan GS, Huang YH, et al. Is emergency transcatheter hepatic arterial embolization suitable for spontaneously ruptured hepatocellular carcinoma in child-pugh c cirrhosis? *J Vasc Interv Radiol* (2018) 29(3):404–12.e3. doi: 10.1016/j.jvir.2017.09.022

27. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* (2001) 33(2):464–70. doi: 10.1053/jhep.2001.22172

28. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: Pathophysiological basis of therapy and current management. *J Hepatol* (2003) 38:69–89. doi: 10.1016/S0168-8278(03)00007-2

29. Porcel A, Díaz F, Rendón P, Macías M, Martín-Herrera L, Girón-González JA. Dilutional hyponatremia in patients with cirrhosis and ascites. *Arch Intern Med* (2002) 162(3):323–8. doi: 10.1001/archinte.162.3.323

30. Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P, Uriz J, Quintó L, Ventura P-J, et al. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol* (2001) 34(1):46–52. doi: 10.1016/S0168-8278(00)00011-8

31. Jundt MC, Owen RL, Thompson SM, Fleming CJ, Stockland AH, Andrews JC. MELD-Na > 16 is associated with high peri-procedural and short-term mortality in patients with ruptured hepatocellular carcinoma treated with emergent transarterial embolization. *Abdom Radiol (NY)* (2022) 47(1):416–22. doi: 10.1007/s00261-021-03306-2

32. Wu J, Zhu P, Zhang Z, Zhang B, Shu C, Chen L, et al. A new tumor-associated antigen prognostic scoring system for spontaneous ruptured hepatocellular carcinoma after partial hepatectomy. *Cancer Biol Med* (2018) 15 (4):415–24. doi: 10.20892/j.issn.2095-3941.2018.0095

33. She WH, Chan ACY, Cheung TT, Lo CM, Chok KSH. Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels. *World J Hepatol* (2018) 10 (2):308–18. doi: 10.4254/wjh.v10.i2.308

34. Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl* (2014) 20 (8):945–51. doi: 10.1002/lt.23904

35. Kerdsuknirun J, Vilaichone V, Vilaichone RK. Risk factors and prognosis of spontaneously ruptured hepatocellular carcinoma in Thailand. *Asian Pac J Cancer Prev* (2018) 19(12):3629–34. doi: 10.31557/apjcp.2018.19.12.3629

36. Chua DW, Koh YX, Liew YX, Chan CY, Lee SY, Cheow PC, et al. Pre-operative predictors of early recurrence/mortality including the role of inflammatory indices in patients undergoing partial hepatectomy for spontaneously ruptured hepatocellular carcinoma. *J Surg Oncol* (2018) 118 (8):1227–36. doi: 10.1002/jso.25281

37. She WH, Chan MY, Ma KW, Tsang SHY, Dai WC, Chan ACY, et al. Alpha-fetoprotein in predicting survival of patients with ruptured hepatocellular carcinoma after resection. *J Invest Surg* (2022) 35(5):1–7. doi: 10.1080/08941939.2021.2012615

38. Zheng SZ, Liu DJ, Sun P, Yu GS, Xu YT, Gong W, et al. Feasibility and safety of sorafenib treatment in hepatocellular carcinoma patients with spontaneous rupture. *World J Gastroenterol* (2014) 20(43):16275–81. doi: 10.3748/wjg.v20.i43.16275

39. Wang Z, Ren Z, Chen Y, Hu J, Yang G, Yu L, et al. Adjuvant transarterial chemoembolization for HBV-related hepatocellular carcinoma after resection: A randomized controlled study. *Clin Cancer Res* (2018) 24(9):2074–81. doi: 10.1158/1078-0432.ccr-17-2899

40. Huang A, Guo DZ, Wang YP, Fan J, Yang XR, Zhou J. The treatment strategy and outcome for spontaneously ruptured hepatocellular carcinoma: A single-center experience in 239 patients. *J Cancer Res Clin Oncol* (2022). doi: 10.1007/s00432-022-03916-3

41. Roussel E, Bubenheim M, Le Treut YP, Laurent A, Herrero A, Muscari F, et al. Peritoneal carcinomatosis risk and long-term survival following hepatectomy for spontaneous hepatocellular carcinoma rupture: Results of a multicenter French study (FRENCH-AFC). *Ann Surg Oncol* (2020) 27(9):3383–92. doi: 10.1245/s10434-020-08442-5

42. Huang X, Xu L, Ma T, Yin X, Huang Z, Ran Y, et al. Lenvatinib plus immune checkpoint inhibitors improve survival in advanced hepatocellular carcinoma: A retrospective study. *Front Oncol* (2021) 11:751159. doi: 10.3389/fonc.2021.751159

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 03 October 2022
DOI 10.3389/fsurg.2022.945126

OPEN ACCESS

EDITED BY
Veronica De Simone,
Agostino Gemelli University Polyclinic (IRCCS), Italy

REVIEWED BY
Vincenzo Lizzi,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy
Giulia Turri,
University of Verona, Italy
Simona Ascanelli,
University Hospital of Ferrara, Italy

*CORRESPONDENCE
Da-Chun Xiao
dachunxiao0011@163.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 16 May 2022
ACCEPTED 16 September 2022
PUBLISHED 03 October 2022

CITATION
Wen Z-L, Zhou X and Xiao D-C (2022) Is red blood cell distribution width a prognostic factor for colorectal cancer? A meta-analysis. Front. Surg. 9:945126. doi: 10.3389/fsurg.2022.945126

Is red blood cell distribution width a prognostic factor for colorectal cancer? A meta-analysis

Ze-Lin Wen, Xiong Zhou and Da-Chun Xiao*

Department of Gastrointestinal Surgery, Chongqing Medical University, Yongchuan Hospital, Chongqing, China

Background: RDW might be an easy and cost-effective pre-operative prognostic factor for cancer patients. The aim of the current study was to analyze whether red blood cell distribution width (RDW) was a prognostic factor for colorectal cancer (CRC) patients who underwent radical surgery.
Methods: We conducted the searching strategy in three databases including the PubMed, Embase and Cochrane Library from the inception to May 07, 2022, to find eligible studies. In this meta-analysis, we focused on the prognosis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS).
Results: A total of seven studies involving 7,541 patients were included in this meta-analysis. After pooling up the HRs, red blood cell distribution width-coefficient of variation (RDW-CV) was not an independent prognostic factor of OS (HR = 1.48, I^2 = 90%, 95% CI = 0.93 to 2.36, P = 0.10), however, red blood cell distribution width-standard deviation (RDW-SD) was an independent prognostic factor of OS (HR = 1.99, I^2 = 0%, 95% CI = 1.59 to 2.49, P < 0.01). As for DFS, we found that RDW-CV (HR = 1.51, I^2 = 83%, 95% CI = 0.94 to 2.43, P = 0.09 < 0.10) and RDW-SD (HR = 1.77, I^2 = 56%, 95% CI = 0.91 to 3.43, P = 0.09 < 0.10) were both the independent prognostic factors. In terms of CSS, we found that RDW-CV was not an independent prognostic factor (HR = 1.23, I^2 = 95%, 95% CI = 0.72 to 2.10, P = 0.46).
Conclusion: RDW-SD was an independent prognostic factor of OS and DFS, and RDW-CV was an independent prognostic factor of DFS.

KEYWORDS
red blood cell distribution width, colorectal cancer, meta-analysis, surgery, survival

Introduction

The incidence of colorectal cancer (CRC) was 38.7 per 100,000 and the mortality rate was 13.9 per 100,000% (1). Among them, CRC was the third most common cancer in males and the second in females (2). The treatments of CRC include surgery, chemotherapy, radiotherapy, surgery, targeted therapy and immunotherapy (3–8). Nowadays, radical surgery is the cornerstone treatment of CRC (9, 10), which not only can treat cancer, but also help in the improvement of some comorbidities (11, 12).

Red blood cell distribution width (RDW) is a hematological parameter which can be divided into two types as follows: RDW standard deviation (RDW-SD) and RDW

coefficient of variation (RDW-CV), whose unit was FL and %, respectively (13). RDW can reflect the heterogeneity of red blood cell size (14), and it has been applied to predict anemia, chronic inflammation and cardiovascular disease (15–18). Recent studies reported that RDW could predict the prognosis of patients with esophageal cancer, gastric cancer and liver cancer (19–22).

Some studies reported the relationship between RDW and CRC patients as well, however, whether RDW could affect the prognosis of CRC was controversial (13–26). Furthermore, the prognostic value of RDW-SD and RDW-CV might be inconsistent. Thus, it is necessary to analyze the exact impact of RDW (RDW-SD and RDW-CV) on CRC.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (27).

Literature search strategy

Two authors conducted the searching strategy in three databases including the PubMed, Embase and Cochrane Library independently. The searching date was May 07, 2022. As for RDW, the searching strategy included: "red blood cell distribution width" OR "red cell distribution width" OR "RDW"; As for CRC, the searching strategy included: "colorectal cancer" OR "colon cancer" OR "rectal cancer" OR "colorectal neoplasm" OR "colon neoplasm" OR "rectal neoplasm" OR "colorectal tumor" OR "colon tumor" OR "rectal tumor". The language was limited to English and the searching scope was limited to titles and abstracts.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1, CRC patients who underwent primary and radical surgery; 2, Pre-operative RDW (RDW-CV or RDW-SD) was tested; and 3, Overall survival (OS), disease-free survival (DFS) or cancer-specific survival (CSS) was reported. The exclusion criteria were as follows: 1, The type of article was letters, case reports, comments, reviews, or conference; 2, Repeated or overlapped data; and 3, Insufficient data reporting the prognosis including OS, DFS or CSS.

Study selection

Two authors conducted the study selection independently. Firstly, the titles and abstracts were looked through by authors to find potentially relevant studies; Secondly, the full texts were read and discussed by the two authors based on the inclusion and exclusion criteria. If there was a disagreement, another author was due to make a final judgment.

Data extraction

The data were extracted by two authors. The extracted article information included the first author, publishing country and publishing year. The extracted patients' data included RDW type, sample size, cut-off value of RDW, OS, DFS and CSS.

Clinical characteristics

As for clinical-pathological characteristics, two authors collected the data independently. The third author was responsible for checking the information to ensure their accuracy and completeness. Only variables which were reported by more than two studies were allowed. The baseline characteristics included age, gender, carcinoembryonic antigen (CEA), tumor location, histological differentiation, Tumor Node Metastasis (TNM) stage, vascular invasion, and adjuvant chemotherapy.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies (28). The score equaled 9 points represented high quality, the score equaled 7 or 8 points represented medium-quality and the score which was less than 7 points represented low quality.

Statistical analysis

In this meta-analysis, we focused on the prognosis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for OS, DFS and CSS. The I^2 value and the results of the chi-squared test were used to assess the statistical heterogeneity (29, 30). High heterogeneity was considered when I^2>50%; in such cases, the random effects model was used, and $P < 0.1$ was considered statistically significant. The fixed effects model was used when $I^2 \leq 50\%$, and $P < 0.05$ was considered statistically significant. This meta-analysis was performed with RevMan 5.3 (The Cochrane Collaboration, London, United Kingdom).

Results

Study selection

A total of 76 studies were found in the databases, including 25 studies in the PubMed, 50 studies in the Embase and 1 study in the Cochrane Library. Finally, seven studies (23–26, 31–33) were included for final analysis. The flow chart of the study selection was shown in **Figure 1**.

Baseline characteristics

Seven studies included 7,541 patients were included in this meta-analysis. The publication year ranged from 2018 to 2022. Two studies were from China, two studies were from Japan, one study was from Italy, one study was from United Kingdom and one study was from Switzerland. The study date was from 2001 to 2020. Three studies reported RDW-SD and five studies reported RDW-CV. The cut-off values and NOS were shown in **Table 1**.

Clinical characteristics

After pooling up the odds ratio and 95% CI, there were more older patients, higher CEA level, and more TNM stage II in the high RDW group than in the low RDW group. Other characteristics including gender, tumor location, histological differentiation, TNM stage III, vascular invasion, and adjuvant chemotherapy were not significantly different between the two groups (**Table 2**).

OS of RDW

Four studies reported OS of RDW-CV, after pooling up the HRs, RDW-CV was not an independent prognostic factor of OS

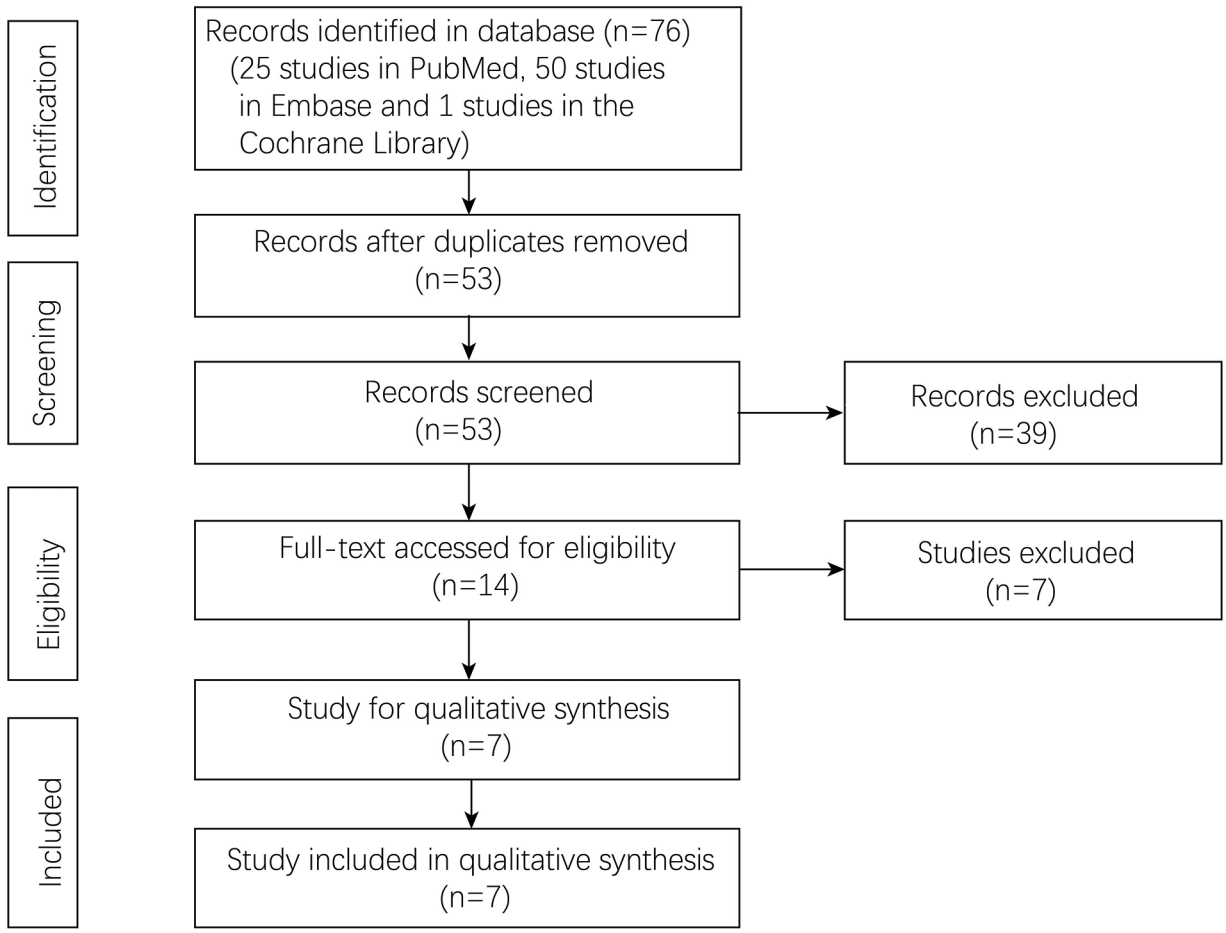

FIGURE 1
Flowchart of study selection.

TABLE 1 Baseline characteristics of included studies.

Author	Year	Country	Study date	Patients	RDW type	Sample size	Cut-off volume	NOS
Ide S	2020	Japan	2001–2017	RC	RDW-SD	120	47.1 fl	7
Pedrazzani C	2020	Italy	2005–2016	CRC	RDW-CV	591	14.1%	8
McSorley ST	2019	United Kingdom	2008–2017	CRC	RDW-CV	824	NA	8
Chen WC	2022	China	2016–2019	CRC	RDW-SD	143	12.6 fl	7
Sato R	2022	Japan	2013–2020	CRC	RDW-CV	85	13.8%	7
Cheng KC	2022	Switzerland	2004–2018	CRC	RDW-CV	5153	13.8%	8
Zhang XB	2018	China	2009–2014	RC	RDW-CV/RDW-SD	625	14.1%/48.2 fl	8

Abbreviations: RDW, red blood cell distribution width; NA, not applicable; NOS, Newcastle-Ottawa Scales; RC, rectal cancer; CRC, colorectal cancer.

TABLE 2 Summary of characteristics between high RDW group and Low RDW group.

Characteristics	Studies	Participants (High RDW/Low RDW)	Odds Ratio [95% CI]	Model	Heterogeneity
Age					
Younger	2	312/398	Reference	Reference	Reference
Older	2	312/398	2.13 [1.57, 2.90]; $P = 0.00$	FE	$I^2 = 0.00\%$; $P = 0.93$
Gender					
Female	3	2496/3367	Reference	Reference	Reference
Male	3	2496/3367	1.02 [0.42, 2.51]; $P = 0.96$	RE	$I^2 = 95.38\%$; $P = 0.00$
CEA					
<5	3	1755/2300	Reference	Reference	Reference
≥5	3	1755/2300	1.60 [1.39, 1.85]; $P = 0.00$	FE	$I^2 = 0.00\%$; $P = 0.90$
Tumor location					
Right colon	2	1201/2988	Reference	Reference	Reference
Left colon	2	1201/2988	0.56 [0.31, 1.02]; $P = 0.06$	FE	$I^2 = 47.80\%$; $P = 0.17$
Histological differentiation					
Well or moderate	3	2244/2988	Reference	Reference	Reference
*P*oor	3	2244/2988	1.37 [0.83, 2.26]; $P = 0.22$	FE	$I^2 = 12.59\%$; $P = 0.32$
TNM stage					
I	2	2449/3329	Reference	Reference	Reference
II	2	2449/3329	2.20 [1.68, 2.87]; $P = 0.00$	FE	$I^2 = 47.82\%$; $P = 0.17$
III	2	2449/3329	1.39 [0.94, 2.07]; $P = 0.10$	FE	$I^2 = 0.00\%$; $P = 0.80$
Vascular invasion	2	312/398	0.71 [0.28, 1.78]; $P = 0.47$	RE	$I^2 = 60.80\%$; $P = 0.11$
Adjuvant chemotherapy	2	312/398	2.10 [0.74, 6.01]; $P = 0.17$	RE	$I^2 = 81.24\%$; $P = 0.02$

Abbreviations: RDW, red blood cell distribution width; CI, confidence intervals; CEA, carcinoembryonic antigen; TNM, Tumor Node Metastasis.

(HR = 1.48, $I^2 = 90\%$, 95% CI = 0.93 to 2.36, $P = 0.10$) (Figure 2a).

Three studies reported OS of RDW-SD, after pooling up the HRs, RDW-CV was an independent prognostic factor of OS (HR = 1.99, $I^2 = 0\%$, 95% CI = 1.59 to 2.49, $P < 0.01$) (Figure 2b).

DFS of RDW

Then, we conducted meta-analysis of RDW (RDW-CV/RDW-SD) on DFS. We found that RDW-CV (HR = 1.51, $I^2 = 83\%$, 95% CI = 0.94 to 2.43, $P = 0.09 < 0.10$) and RDW-SD (HR = 1.77, $I^2 = 56\%$, 95% CI = 0.91 to 3.43, $P = 0.09 < 0.10$) were both independent prognostic factors of DFS (Figures 3A,B).

CSS of RDW

Four studies reported RDW-CV on the prognostic roles on CSS, and we found that RDW-CV was not an independent prognostic factor (HR = 1.23, $I^2 = 95\%$, 95% CI = 0.72 to 2.10, $P = 0.46$) (Figure 4). However, no information was found about RDW-SD on the prognostic roles on CSS.

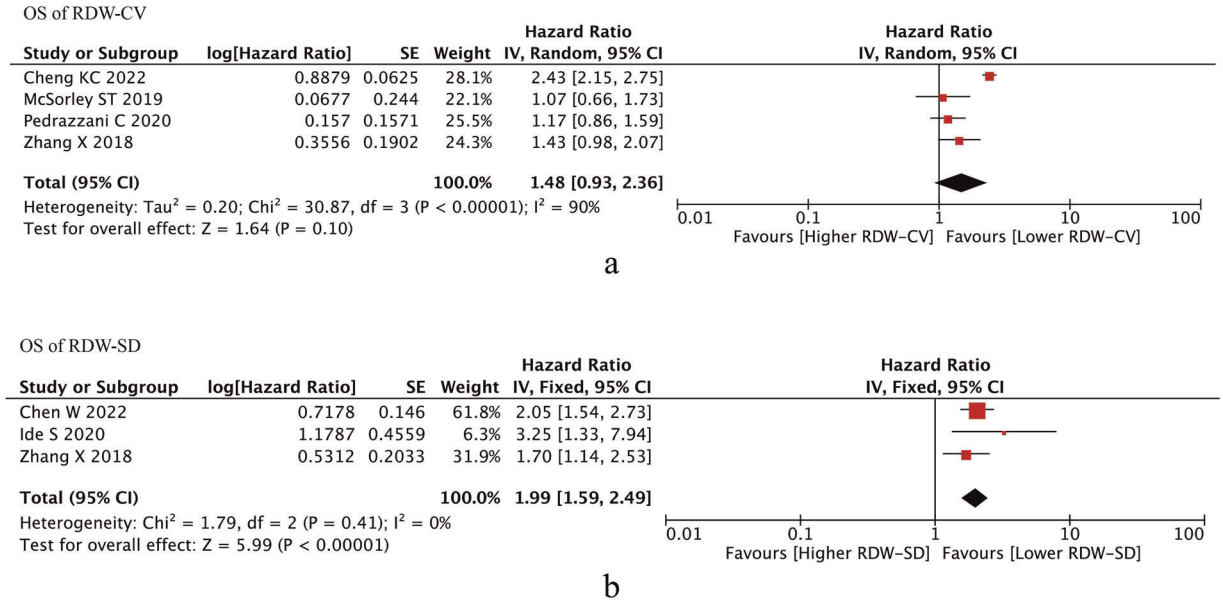

FIGURE 2
Os of RDW. (A) OS of RDW-CV; (B) OS od RDW-SD. Abbreviations: OS, overall survival; RDW, red blood cell distribution width.

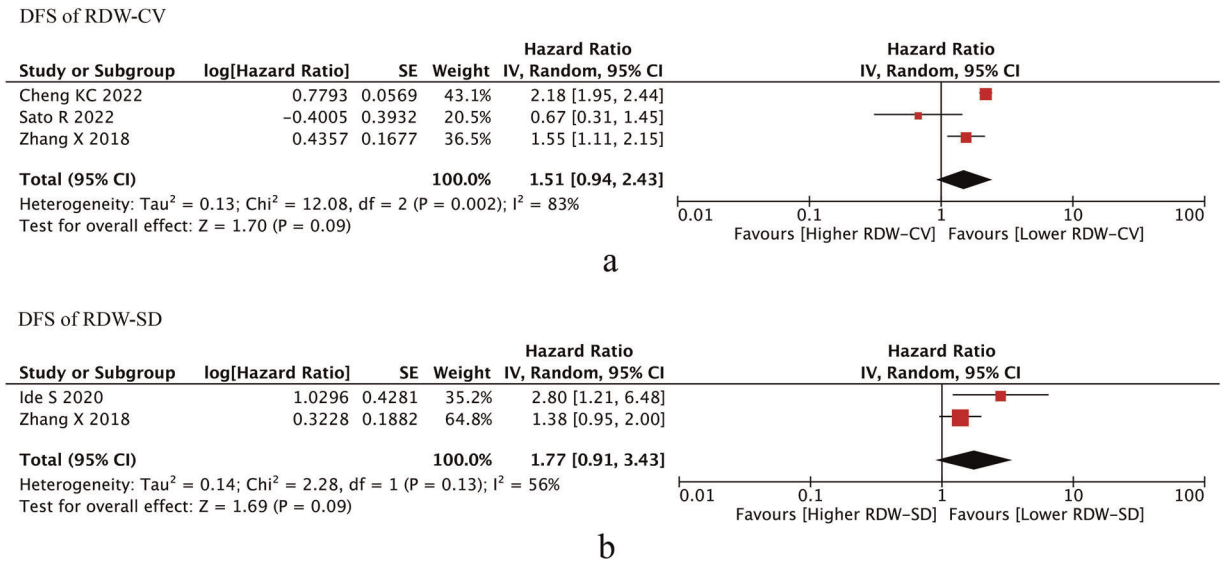

FIGURE 3
DFS of RDW. (A) DFS of RDW-CV; (B) DFS od RDW-SD. Abbreviations: DFS, disease-free survival; RDW, red blood cell distribution width.

Sensitivity analysis

Repeated meta-analysis was performed by excluding one study at a time, and the exclusion of any one study did not significantly alter the results.

Discussion

A total of seven studies involving 7541 patients were included in this meta-analysis. After pooling up the HRs, RDW-CV was not an independent prognostic factor of OS,

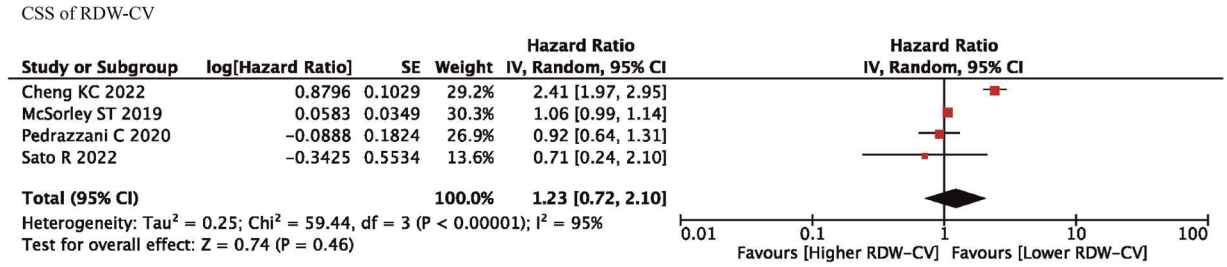

FIGURE 4
CSS of RDW-CV. Abbreviations: CSS, cancer-specific survival; RDW, red blood cell distribution width.

however, RDW-SD was an independent prognostic factor of OS. As for DFS, we found that RDW-CV and RDW-SD were both independent prognostic factors. In terms of CSS, we found that RDW-CV was not an independent prognostic factor. As for clinical characteristics, the high RDW group had more older patients, higher CEA level, and more TNM stage II than the low RDW group.

RDW can reflect the heterogeneity of red blood cell size (14), and the primary role of RDW is to diagnose anemia (13). The increase of RDW could accompanied by other cancer prognostic risk factors including age, later TNM stage and higher tumor markers level (34, 35). Furthermore, RDW is also associated with various diseases such as heart disease, lung disease, and even trauma (14, 36). In addition, RDW is also considered as an indicator for some inflammatory diseases including pancreatitis and hepatitis (35, 36). However, the mechanism has not been clearly demonstrated.

Previous studies had reported the relationship between RDW and the prognosis of CRC (23–26, 31–33). Zhang X et al. (23) reported that elevated RDW could be an independent factor for non-metastatic rectal cancer; Cheng KC et al. (37) analyzed 5,315 CRC patients and did propensity score matching analysis, they found that RDW was a predictor of OS, DFS and CSS. However, Pedrazzani C et al. (25) reported that RDW did not seem to influence OS or CSS, independently. Moreover, McSorley ST et al. (26) reported the same results that RDW was not a predictor of prognosis. Therefore, it is necessary to analyze the exact impact of RDW on CRC (38).

There were many factors which could affect the prognosis of CRC, including tumor stage, tumor size, age, body mass index (BMI), type 2 diabetes mellitus and so on (39–44). Prognostic indicators related to blood examination included lymphocyte count ratio (NLR), platelet count and lymphocyte count ratio (PLR), etc (31, 45, 46). The main reason that NLR and PLR could affect the prognosis was that they were important markers of systemic inflammation (23,24). Furthermore, PLR and NLR levels increased the body's inflammatory response, promoted tissue infiltration and angiogenesis (47). Similarly, in our meta-analysis, RDW could also affect the prognosis of CRC, the mechanism might be that RDW was another important marker of systemic inflammation as well.

Besides the systemic inflammation mechanism, RDW was thought to reflect oxidative stress, malnutrition, dyslipidemia, hypertension, erythrocyte fragmentation and erythropoietin alterations (48). Furthermore, RDW correlated with plasma markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP) values and erythrocyte sedimentation rate (ESR) (49). RDW was shown to reflect increased levels of circulating cytokines, including interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (50). Thus, these findings suggested that increased RDW might reflect inflammatory responses, malnutrition status and elevated oxidative stress, leading to the hypothesis that RDW was associated with poorer prognosis.

To our knowledge, previous studies had controversy about the effect of RDW on the prognosis of CRC, and this is the first study pooling up all the data to identify the accurate prognostic roles of RDW on CRC patients. Some limitations existed in this study. First, we included seven studies whose sample size was relatively small; Second, the cut-off of RDW-CV and RDW-SD was inconstant, which might cause inaccuracy; Third, small number of studies reporting OS, DFS and CSS, therefore, heterogeneity occurred, random-effects test was adopted.

In conclusion, RDW-SD was an independent prognostic factor of OS and DFS, and RDW-CV was an independent prognostic factor of DFS.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

Data extraction, Z-LW, D-CX and XZ; quality assessments, XZ; data analysis, XZ and Z-LW; writing-origin draft, Z-LW and D-CX; writing-review and editing, XZ, Z-LW and D-CX.

All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. (2020) 70(3):145–64. doi: 10.3322/caac.21601

2. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol*. (2019) 14(2):89–103. doi: 10.5114/pg.2018.81072

3. Peng D, Cheng YX, Cheng Y. Improved overall survival of colorectal cancer under multidisciplinary team: a meta-analysis. *Biomed Res Int*. (2021) 2021:5541613. doi: 10.1155/2021/5541613

4. Cheng YX, Tao W, Zhang H, Peng D, Wei ZQ. Does liver cirrhosis affect the surgical outcome of primary colorectal cancer surgery? A meta-analysis. *World J Surg Oncol*. (2021) 19(1):167. doi: 10.1186/s12957-021-02267-6

5. Ba L, Wang Q, Wang H, Zhu L, Zhang T, Ren J, et al. Survival analysis and prognostic factors of palliative radiotherapy in patients with metastatic colorectal cancer: a propensity score analysis. *J Gastrointest Oncol*. (2021) 12(5):2211–22. doi: 10.21037/jgo-21-540

6. Lin Y, Kong DX, Zhang YN. Does the microbiota composition influence the efficacy of colorectal cancer immunotherapy? *Front Oncol*. (2022) 12:852194. doi: 10.3389/fonc.2022.852194

7. Janani B, Vijayakumar M, Priya K, Kim JH, Prabakaran DS, Shahid M, et al. EGFR-Based Targeted therapy for colorectal cancer-promises and challenges. *Vaccines (Basel)*. (2022) 10(4):499. doi: 10.3390/vaccines10040499

8. Liu XY, Yuan C, Kang B, Cheng YX, Tao W, Zhang B, et al. Predictors associated with planned and unplanned admission to intensive care units after colorectal cancer surgery: a retrospective study. *Support Care Cancer*. (2022) 30 (6):5099–105. doi: 10.1007/s00520-022-06939-1

9. Ji X, Zhao Y, Zhu X, Shen Z, Li A, Chen C, et al. Outcomes of stereotactic body radiotherapy for metastatic colorectal cancer with oligometastases, oligoprogression, or local control of dominant tumors. *Front Oncol*. (2021) 10:595781. doi: 10.3389/fonc.2020.595781

10. Tharin Z, Blanc J, Alaoui IC, Bertaut A, Ghiringhelli F. Influence of first line chemotherapy strategy depending on primary tumor location in metastatic colorectal cancer. *J Gastrointest Oncol*. (2021) 12(4):1509–17. doi: 10.21037/jgo-20-593

11. Liu XY, Kang B, Cheng YX, Yuan C, Tao W, Zhang B, et al. Higher body mass index was associated with better prognosis in diabetic patients with stage II colorectal cancer. *BMC Cancer*. (2022) 22(1):596. doi: 10.1186/s12885-022-09691-1

12. Cheng YX, Tao W, Liu XY, Yuan C, Zhang B, Wei ZQ, et al. Hypertension remission after colorectal cancer surgery: a single-center retrospective study. *Nutr Cancer*. (2022) 74(8):2789–95. doi: 10.1080/01635581.2021.2025256

13. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci*. (2015) 52(2):86–105. doi: 10.3109/10408363.2014.992064

14. Miyamoto K, Inai K, Takeuchi D, Shinohara T, Nakanishi T. Relationships among red cell distribution width, anemia, and interleukin-6 in adult congenital heart disease. *Circ J*. (2015) 79(5):1100–6. doi: 10.1253/circj.CJ-14-1296

15. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. *Dis Markers*. (2017) 2017:7089493. doi: 10.1155/2017/7089493

16. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med*. (2009) 169(5):515–23. doi: 10.1001/archinternmed.2009.11

17. Lee WS, Kim TY. Relation between red blood cell distribution width and inflammatory biomarkers in rheumatoid arthritis. *Arch Pathol Lab Med*. (2010) 134(4):505–6. doi: 10.5858/134.4.505.c

18. Song CS, Park DI, Yoon MY, Seok HS, Park JH, Kim HJ, et al. Association between red cell distribution width and disease activity in patients with inflammatory bowel disease. *Dig Dis Sci*. (2012) 57(4):1033–8. doi: 10.1007/s10620-011-1978-2

19. Chen GP, Huang Y, Yang X, Feng JF. A nomogram to predict prognostic value of red cell distribution width in patients with esophageal cancer. *Mediators Inflamm*. (2015) 2015:854670. doi: 10.1155/2015/854670

20. Saito H, Shimizu S, Shishido Y, Miyatani K, Matsunaga T, Fujiwara Y. Prognostic significance of the combination of preoperative red cell distribution width and platelet distribution width in patients with gastric cancer. *BMC Cancer*. (2021) 21(1):1317. doi: 10.1186/s12885-021-09043-5

21. Fu L, Li Q, Fan Q. Combination of preoperative red cell distribution width and neutrophil to lymphocyte ratio as a prognostic marker for gastric cancer patients. *J Gastrointest Oncol*. (2021) 12(3):1049–57. doi: 10.21037/jgo-21-271

22. Jing JS, Fu XL, Zhao W, Kong LB. Red cell distribution width as a prognostic factor in patients with hepatocellular carcinoma. *Clin Lab*. (2020) 66(7). doi: 10.7754/Clin.Lab.2019.191027

23. Zhang X, Wu Q, Hu T, Gu C, Bi L, Wang Z. Elevated red blood cell distribution width contributes to poor prognosis in patients undergoing resection for nonmetastatic rectal cancer. *Med (Baltimore)*. (2018) 97(3):e9641. doi: 10.1097/MD.0000000000009641

24. Ide S, Toiyama Y, Okugawa Y, Omura Y, Kitajima T, Fujikawa H, et al. Clinical significance of an increased red blood cell distribution width in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. *Surg Today*. (2020) 50(6):551–9. doi: 10.1007/s00595-019-01933-3

25. Pedrazzani C, Tripepi M, Turri G, Fernandes E, Scotton G, Conci S, et al. Prognostic value of red cell distribution width (RDW) in colorectal cancer. Results from a single-center cohort on 591 patients. *Sci Rep*. (2020) 10(1):1072. doi: 10.1038/s41598-020-57721-4

26. McSorley ST, Tham A, Steele CW, Dolan RD, Roxburgh CS, Horgan PG, et al. Quantitative data on red cell measures of iron status and their relation to the magnitude of the systemic inflammatory response and survival in patients with colorectal cancer. *Eur J Surg Oncol*. (2019) 45(7):1205–11. doi: 10.1016/j.ejso.2019.02.027

27. Moher D, Liberati A, Tetzlaff J. Altman DG; PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097

28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–e5. doi: 10.1007/s10654-010-9491-z

29. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract*. (2008) 14(5):951–7. doi: 10.1111/j.1365-2753.2008.00986.x

30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

31. Chen W, Xin S, Xu B. Value research of NLR, PLR, and RDW in prognostic assessment of patients with colorectal cancer. *J Healthc Eng*. (2022) 2022:7971415. doi: 10.1155/2022/7971415

32. Sato R, Oikawa M, Kakita T, Okada T, Abe T, Yazawa T, et al. Prognostic significance of the mean corpuscular volume (MCV) and red cell distribution

width (RDW) in obstructive colorectal cancer patients with a stent inserted as a bridge to curative surgery. *Surg Today*. (2022). doi: 10.1007/s00595-022-02504-9

33. Cheng KC, Lin YM, Liu CC, Wu KL, Lee KC. High red cell distribution width is associated with worse prognosis in early colorectal cancer after curative resection: a propensity-matched analysis. *Cancers (Basel)*. (2022) 14(4):945. doi: 10.3390/cancers14040945

34. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al. Red cell distribution width and mortality in older adults: a meta-analysis. *J Gerontol A Biol Sci Med Sci*. (2010) 65(3):258–65. doi: 10.1093/gerona/glp163

35. Patel R, English L, Liu WK, Tree AC, Ayres B, Watkin N, et al. Red cell differential width (RDW) as a predictor of survival outcomes with palliative and adjuvant chemotherapy for metastatic penile cancer. *Int Urol Nephrol*. (2020) 52(12):2301–6. doi: 10.1007/s11255-020-02565-0

36. Liu Q, Dang AM, Chen BW, Lv NQ, Wang X, Zheng DY. The association of red blood cell distribution width with anemia and inflammation in patients with takayasu arteritis. *Clin Chim Acta*. (2015) 438:205–9. doi: 10.1016/j.cca.2014.08.025

37. Fu Y, Mao Y, Chen S, Yang A, Zhang Q. A novel inflammation- and nutrition-based prognostic system for patients with laryngeal squamous cell carcinoma: combination of red blood cell distribution width and body mass Index (COR-BMI). *PLoS One*. (2016) 11(9):e0163282. doi: 10.1371/journal.pone.0163282

38. Li Z, Hong N, Robertson M, Wang C, Jiang G. Preoperative red cell distribution width and neutrophil-to-lymphocyte ratio predict survival in patients with epithelial ovarian cancer. *Sci Rep*. (2017) 7:43001. doi: 10.1038/srep43001

39. Cheng Y, Cheng YX, Liu XY, Kang B, Tao W, Peng D. The effect of type 2 diabetes Mellitus on the short-term outcomes and prognosis of stage I-III colorectal cancer: a propensity score matching analysis. *Cancer Manag Res*. (2022) 14:205–14. doi: 10.2147/CMAR.S347242

40. Dell'Aquila E, Rossini D, Galletti A, Stellato M, Boccaccino A, Conca V, et al. Prognostic and predictive role of body mass Index (BMI) in metastatic colorectal cancer (mCRC): a pooled analisys of tribe and tribe-2 studies by GONO. *Clin Colorectal Cancer*. (2022) 21(3):220–28. doi: 10.1016/j.clcc.2022.02.003

41. Lv MY, Wang W, Zhong ME, Cai D, Fan D, Li CH, et al. DNA Repair-Related gene signature in predicting prognosis of colorectal cancer patients. *Front Genet*. (2022) 13:872238. doi: 10.3389/fgene.2022.872238

42. Alese OB, Zhou W, Jiang R, Zakka K, Huang Z, Okoli C, et al. Predictive and prognostic effects of primary tumor size on colorectal cancer survival. *Front Oncol*. (2021) 11:728076. doi: 10.3389/fonc.2021.728076

43. Cheng YX, Liu XY, Kang B, Tao W, Wei ZQ, Peng D. Comparison of surgical and oncologic outcomes in very elderly patients (≥ 80 years old) and elderly (65–79 years old) colorectal cancer patients: a propensity score matching. *BMC Gastroenterol*. (2022) 22(1):205. doi: 10.1186/s12876-022-02277-y

44. Li N, Lu B, Luo C, Cai J, Lu M, Zhang Y, et al. Incidence, mortality, survival, risk factor and screening of colorectal cancer: a comparison among China, Europe, and northern America. *Cancer Lett*. (2021) 522:255–68. doi: 10.1016/j.canlet.2021.09.034

45. Naszai M, Kurjan A, Maughan TS. The prognostic utility of pre-treatment neutrophil-to-lymphocyte-ratio (NLR) in colorectal cancer: a systematic review and meta-analysis. *Cancer Med*. (2021) 10(17):5983–97. doi: 10.1002/cam4.4143

46. Ying HQ, Deng QW, He BS, Pan YQ, Wang F, Sun HL, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. *Med Oncol*. (2014) 31(12):305. doi: 10.1007/s12032-014-0305-0

47. Varkaris A, Katsiampoura A, Davis JS, Shah N, Lam M, Frias RL, et al. Circulating inflammation signature predicts overall survival and relapse-free survival in metastatic colorectal cancer. *Br J Cancer*. (2019) 120(3):340–5. doi: 10.1038/s41416-018-0360-y

48. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. *Crit Care Med*. (2011) 39(8):1913–21. doi: 10.1097/CCM.0b013e31821b85c6

49. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med*. (2009) 133(4):628–32. doi: 10.5858/133.4.628

50. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J*. (2009) 158(4):659–66. doi: 10.1016/j.ahj.2009.07.024

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 11 October 2022
DOI 10.3389/fsurg.2022.989065

OPEN ACCESS

EDITED BY
Andrew Gumbs,
Centre Hospitalier Intercommunal de Poissy, France

REVIEWED BY
Xiaohang Li,
The First Affiliated Hospital of China Medical University, China
Xu Che,
Cancer Hospital Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

*CORRESPONDENCE
Taiping Zhang
tpingzhang@yahoo.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 08 July 2022
ACCEPTED 20 September 2022
PUBLISHED 11 October 2022

CITATION
Fu Y, Qiu J, Yu Y, Wu D and Zhang T (2022) Meta-analysis of robotic versus open pancreaticoduodenectomy in all patients and pancreatic cancer patients.
Front. Surg. 9:989065.
doi: 10.3389/fsurg.2022.989065

Meta-analysis of robotic versus open pancreaticoduodenectomy in all patients and pancreatic cancer patients

Yibo Fu[1†], Jiangdong Qiu[1†], Yiqi Yu[1], Danning Wu[1] and Taiping Zhang[1,2*]

[1]Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2]Clinical Immunology Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Purposes: To compare perioperative outcomes of robotic pancreaticoduodenectomy (RPD) to open pancreaticoduodenectomy (OPD) using evidence from cohort studies.
Methods: Outcomes of interest include operative time, blood loss, R0 resection rate, lymph nodes harvested, overall complication rate, pancreatic fistula rate, delayed gastric emptying rate and 90-day mortality.
Results: 6 prospective studies and 15 retrospective studies were included. Five of these studies were limited to patients with pancreatic cancer. Operative time was significantly longer in RPD (WMD: 64.60 min; 95% CI: 26.89 to 102.21; $p = 0.001$). Estimated blood loss was lower in RPD (WMD: −185.44 ml; 95% CI: −239.66 to −131.21; $p < 0.001$). Overall complication rates (OR: 0.66; 95% CI: 0.44 to 0.97; $p < 0.001$) and pancreatic fistula rate (OR: 0.67; 95% CI: 0.55 to 0.82; $p < 0.001$) were both lower in RPD. Length of hospital stay was longer in OPD (WMD: −1.90; 95% CI: −2.47 to −1.33). 90-day mortality was lower in RPD [odds ratio (OR): 0.77; 95% CI: 0.45 to 0.95; $p = 0.025$].
Conclusion: At current level of evidence, RPD is a safer alternative than OPD with regard to post-operative outcomes and blood loss. However, in terms of oncological outcomes RPD show no advantage over OPD, and the cost of RPD was higher. In general, RPD is now considered a reliable technology, but high-quality randomized controlled trial (RCT) studies are still needed to support this conclusion.

KEYWORDS
robotic pancreaticoduodenectomy, open pancreaticoduodenectomy, pancreatic cancer, outcome, meta-analysis

1. Introduction

Pancreaticoduodenectomy (PD) has been universally accepted to be indicated in benign or malignant lesions of the pancreatic head, duodenum, and distal common bile duct. In 1994, Gagner reported the first laparoscopic pancreaticoduodenectomy, since when minimally invasive pancreaticoduodenectomy (MIPD) are increasingly being performed over the world (1). The development of the Da Vinci robotic platform takes MIPD a step further. Laparoscopic surgery has some shortcomings

compared to robotic surgery, including limited vision and flexibility. And this contributed to the popularity of robotic surgery over the world (2). The first case of robotic-assistant pancreaticoduodenectomy (RAPD) was reported in 2007, and since then many studies have compared the safety and efficacy between open pancreaticoduodenectomy (OPD) and robotic pancreaticoduodenectomy (RPD). There have been several meta-analyses evaluating the effect between OPD and RPD. However, robotic surgery technology developed rapidly in these years, and the studies used in the existing meta-analyses are not new enough. Therefore, we focused on those studies published in the last 5 years (in or after 2016) to provide high-quality evidence for further clinical practice.

2. Methods

2.1. Literature-search strategy

A systematic review of the literature was performed in PubMed and Web of Science from January 2016 to October 2021. These key words were used: robot, robotic, robotic-assisted, open, and pancreaticoduodenectomy. Studies included should fulfill the following PICOS criteria in our meta-analyses. P (patients): Male or female patients with a benign or malignant disease that requires elective PD; I (intervention): RPD; C (control): OPD; O (outcome): At least 1 of the interested outcomes; S (study design): randomized controlled trials (RCTs) and observative studies.

References of the acquired articles were manually searched to broaden the search. When multiple researches describing the same population were published, the most complete or recent research was used.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as followed: (1) comparative study of RPD and OPD; (2) papers written in English; (3) papers published in or after 2016. Abstracts, case reports, reviews, letters to the editor, non-comparative studies, and articles without available data were excluded.

2.3. Data extraction and outcome of interest

All references were reviewed and evaluated by two researchers independently. Only full-length articles were eligible for extraction. The following data of included articles were extracted: first author, year of publication, study design, number of operated subjects, operative time, blood loss, R0 resection rate, lymph nodes harvested, overall complication rate, pancreatic fistula rate, delayed gastric emptying and 90-day mortality.

2.4. Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of non-randomized studies. Scores of each observational study range from 0 to 9, and studies having six or more stars were considered to be high-quality studies.

2.5. Statistical analysis

This meta-analysis was performed using Stata MP 16.0 software. The odds ratios (OR) and the weighted mean difference (WMD) with a 95% confidence interval (95% CI) were used to estimate dichotomous and continuous variables, respectively. $p < 0.05$ was considered statistically significant. For studies that reported continuous data as median and range values (or quartile and median), the standard deviations were calculated using the method described by Luo et al. (3). Heterogeneity was evaluated by the Chi-square test, and $p < 0.100$ was considered significant. I^2 values were used for the evaluation of statistical heterogeneity. An I^2 value of 50% or more indicated the presence of heterogeneity. The fixed effect model (FEM) and random effect model (REM) were used based on the value of I^2. FEM was used in the case of $I^2 < 50\%$ while REM was adopted in the case of $I^2 > 50\%$.

3. Result

3.1. Literature-search results

The first search strategy generated 518 studies. 21 articles including 5,756 patients (2,561 cases for RPD and 3,285 cases for OPD) fulfilled the predefined inclusion criteria and were included in this meta-analysis (4–24). All studies were non-RCTs, of which 6 studies were prospective while 15 studies were retrospective. The selection process is shown in **Figure 1**.

3.2. Study characteristics and quality assessment

The study characteristics and study quality are shown in **Table 1**. We screened articles published in 2016 and beyond. This is a worldwide meta-analysis, in which eight articles are from America, six articles are from China, four articles are from Italy, two articles are from Korea, and one article is from Spain. In most studies the robotic surgery group carried out RPD,

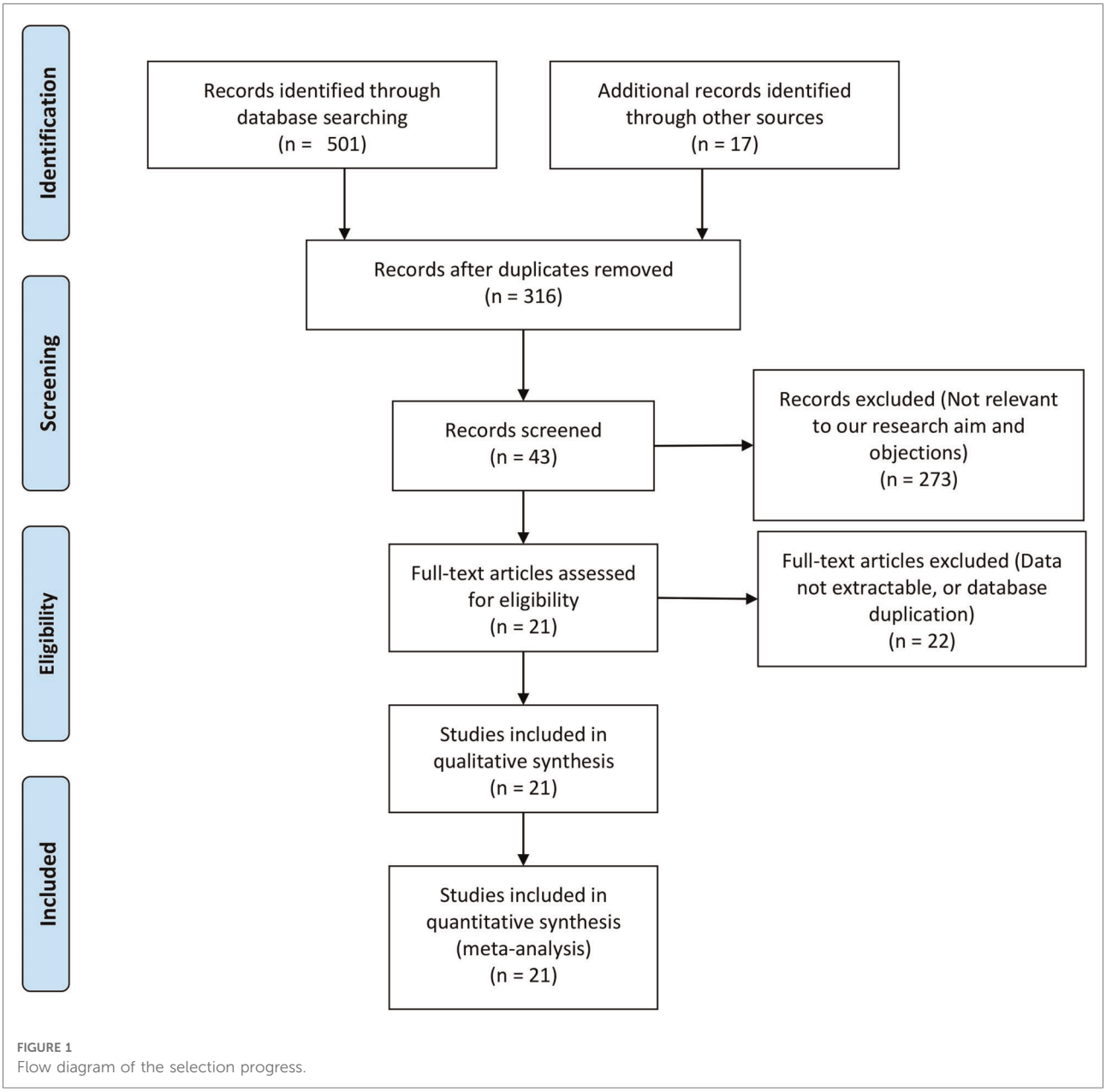

FIGURE 1
Flow diagram of the selection progress.

while in four studies RAPD were used, where robots were only involved in some parts of the surgery. In five studies patients were limited to pancreatic cancer, while in other studies the indication for surgery were wide, including benign and malignant disease. All the studies were of high quality according to the Newcastle–Ottawa Scale (NOS) (Supplementary Table S1).

Patients' baseline characteristics are summarized in Table 2.

3.3. Meta-analysis results

All 21 studies were included in this meta-analysis. The summarized result of meta-analysis is shown in Table 3.

3.3.1. Intraoperative outcomes

3.3.1.1. Operative time

Operative time was reported in 17 studies (1,924 RPD vs. 2,690 OPD). According to the results of this meta-analysis, operative time was significantly longer in RPD group (WMD: 64.60 min; 95% CI: 26.89 to 102.21; $p = 0.001$), with high heterogeneity ($I^2 = 97.8\%$; $\text{Tau}^2 = 2133.45$) in the REM (Figure 2A).

3.3.1.2. Estimated blood loss

Estimated blood loss was reported in 14 studies (1,604 RPD vs. 1,583 OPD) and was significantly lower in RPD (WMD: −185.44 ml; 95% CI: −239.66 to −131.21; $p < 0.001$) with high

TABLE 1 Characteristics of the included studies and quality assessment.

Article	Country	Design	Number of patients (robotic)	Number of patients (open)	Quality score	Robotic technique	Indication for surgery (benign or malignant disease)
Emanuele 2018	Italy	Retrospective	24	26	6	RPD	M
Hassan 2021	America	Retrospective	310	310	8	RPD	M
Shyr 2021	China	Prospective	65	65	6	RPD	M
Maria 2020	America	Retrospective	38	38	7	RPD	M
Weng 2020	China	Retrospective	105	210	8	RAPD	M
Amer 2016	America	Retrospective	211	817	6	RPD	B&M
Matthew 2016	America	Retrospective	152	152	7	RPD	B&M
Mejia 2020	America	Retrospective	102	54	6	RPD	B&M
Wang 2018	China	Prospective	87	87	8	RPD	B&M
Kim 2018	Korea	Retrospective	51	186	7	RPD	B&M
Varley 2018	America	Retrospective	133	149	7	RPD	B&M
Cai 2019	America	Prospective	460	405	8	RPD	B&M
Paolini 2021	Italy	Retrospective	65	53	6	RPD	B&M
Benedetto 2018	Spain	Prospective	17	17	7	RPD	B&M
Marino 2019	Italy	Prospective	35	35	8	RAPD	B&M
Shi 2021	China	Retrospective	187	187	8	RAPD	B&M
Bencini 2020	Italy	Retrospective	35	35	8	RPD	B&M
Hyeyeon 2020	Korea	Retrospective	55	55	7	RAPD	B&M
Oosten 2020	America	Retrospective	96	192	8	RPD	B&M
Shyr 2020	China	Retrospective	284	169	6	RPD	B&M
Wang 2021	China	Prospective	49	43	7	RPD	B&M

among-study statistical heterogeneity ($I^2 = 92.7\%$; $Tau^2 = 3152.37$) (Figure 2B).

3.3.2. Oncological outcomes

3.3.2.1. Lymph nodes harvested

13 studies reported the results of lymph nodes harvested (1,337 RPD vs. 1,699 OPD). No statistically significant differences were found between the two groups (WMD: 1.13; 95% CI: −0.27 to 2.54; $p = 0.115$), with a high heterogeneity ($I^2 = 82.8\%$, $Tau^2 = 4.69$) in the REM (Figure 3A).

3.3.2.2. Lymph nodes harvested (in pancreatic cancer)

Four studies reporting the results of lymph nodes harvested are limited in pancreatic cancer patients (518 RPD vs. 623 OPD). No statistically significant differences were found between the two groups (WMD: 0.4; 95% CI: −0.59 to 1.40; $p = 0.425$), with a low heterogeneity ($I^2 = 0\%$) in the FEM (Figure 3B).

3.3.2.3. R0 resection

Ten studies reported the results of lymph nodes harvested (955 RPD vs. 1,026 OPD). No statistically significant differences were found between the two groups (OR: 1.02; 95% CI: 0.79 to 1.30; $p = 0.889$), with a low heterogeneity ($I^2 = 0\%$) in the FEM (Figure 3C).

3.3.3. Post-operative outcomes

3.3.3.1. Overall complication rates

Overall complication rate was reported in 13 studies (1,192 RPD vs. 1,856 OPD) and was significantly lower in RPD (OR: 0.66; 95% CI: 0.44 to 0.97; $p < 0.001$) with high among-study statistical heterogeneity ($I^2 = 76.2\%$; $Tau^2 = 0.3524$) in the REM (Figure 4A).

3.3.3.2. Pancreatic fistula

Pancreatic fistula was reported in 13 studies (1,938 RPD vs. 2,104 OPD) and was significantly lower in RPD (OR: 0.67; 95% CI: 0.55 to 0.82; $p < 0.001$) with low among-study statistical heterogeneity ($I^2 = 26.9\%$) in the FEM (Figure 4B).

3.3.3.3. Delayed gastric emptying

Thirteen studies reported the results of delayed gastric emptying (1,055 RPD vs. 1,257 OPD). No statistically significant

TABLE 2 Comparison of patients' baseline characteristics in robotic vs. open pancreaticoduodenectomy.

Article	Age (years)		Gender (male) (%)		BMI		Tumor diameter (cm)		Preoperative CA 199	
	RPD	OPD	RPD	OPD	RPD	OPD	RPD	OPD	RPD	OPD
Emanuele 2018	65 (58.5–74.75)	72.5 (59.75–78.75)	50.0	54.1	23.1 ± 3.2	24.1 ± 3.1	2.7 ± 0.6	2.7 ± 0.9	353.3 ± 528.6	1362.7 ± 4497
Hassan 2021	66 ± 21.3	68.1 ± 19.3	50.1	51.1	NM	NM	NM	NM	NM	NM
Shyr 2021	66 ± 13	66 ± 11	52.3	40.0	24 ± 4	22 ± 3	3.1 ± 0.8	3.1 ± 0.7	NM	NM
Maria 2020	66 (38–84)[a]	68 (42–81)[a]	42.1	42.1	24.7 (19.6–39.1)[a]	25.7 (15.8–44.8)[a]	3 (0.5–6)[a]	2.9 (0.9–7)[a]	NM	NM
Weng 2020	63 (57–68)	64 (58–70)	61.7	65.9	22.8 ± 2.8	22.6 ± 3.1	3 (2.2–3.5)	3.0 (2.3–3.8)	144.4 (40.1–375.4)	153.4 (46.0–505.2)
Amer 2016	67 (15–86)[a]	65 (15–93)[a]	52.9	55.5	27.5 (18.1–47.6)[a]	26.1 (14.7–85.5)[a]	2.5 (0.1–26.0)[a]	2.9 (0–5.0)[a]	NM	NM
Matthew 2016	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mejia 2020	66 ± 10.6	61.7 ± 14.1	52	55.6	NM	NM	3.4 ± 1.6	3.7 ± 2.1	NM	NM
Wang 2018	NM	NM	50	56.7	NM	NM	NM	NM	NM	NM
Kim 2018	60.7 ± 11.9	65.4 ± 10.1	47.1	58.1	22.7 ± 2.5	24.0 ± 3.1	NM	NM	NM	NM
Varley 2018	66.3 ± 10.6	67.0 ± 10.5	48	53	27.5 ± 6.1	26.7 ± 5.6	NM	NM	NM	NM
Cai 2019	66.5 ± 11.0	67.5 ± 10.7	55	52.1	27.8 ± 5.8	27.2 ± 5.9	NM	NM	NM	NM
Paolini 2021	70 (42–85)[a]	73 (45–91)[a]	50.9	53.8	26 (17–33)[a]	23 (14–33)[a]	2.3 (0.7–6)[a]	2.5 (0.6–8.2)[a]	85.0 (1.6–1,617.0)[a]	132.3 (1.6–91,000.0)[a]
Benedetto 2018	66.8 ± 9.5	61.4 ± 11.9	47.1	58.8	23.8 ± 4.1	24.6 ± 3.36	24.1 ± 5.4	24.8 ± 6.1	NM	NM
Marino 2019	60.4 (43–72)[a]	62.3 (45–73)[a]	54.3	42.9	23.8 (19.4–30.9)[a]	23.5 (18.8–28.1)[a]	2.35 (1.6–3.4)[a]	2.22 (1.2–3.5)[a]	NM	NM
Shi 2021	60.9 ± 11.4	60.1 ± 10.8	58.3	57.2	NM	NM	2.7 ± 1.1	2.7 ± 1.3	NM	NM
Bencini 2020	70.5 (42–85)[a]	69 (50–88)[a]	56.3	45.7	26 (18–32)[a]	24 (18–38)[a]	30 (18–40)[a]	37 (2–51)[a]	143 (2–1,617)[a]	70 (2–2,617)[a]
Hyeyeon 2020	58.6 ± 8.3	59.9 ± 13.4	47.3	54.5	23.7 ± 2.8	23.9 ± 3.6	2.6 ± 1.2	2.6 ± 1.8	NM	NM
Oosten 2020	67 (60–73)	67 (58–73)	NM	NM	26 (23–30)	27 (23–29)	NM	NM	NM	NM
Shyr 2020	65 ± 12	64 ± 11	53.3	53.5	24 ± 4	23 ± 3	3.2 ± 1.5	3.7 ± 2.5	NM	NM
Wang 2021	64.7 ± 11.8	64.8 ± 11.6	51.9	53.4	27.7 ± 5.6	27.4 ± 5.8	NM	NM	NM	NM

BMI, body mass index; expressed in mean ± SD and median (IQR).
[a]Expressed in median (range).

TABLE 3 Outcomes of the included studies.

Outcomes	Studies, *n*	RPD	OPD	WMD/OR (95% CI)	*p* value	Heterogeneity	
						I^2	Tau^2
Intraoperative outcomes							
Operative time	17	1,924	2,690	64.60 (26.89 to 102.21)	0.001	0.978	
Estimated blood loss	14	1,604	1,583	−185.44 (−239.66 to −131.21)	<0.001	0.927	
Oncological outcomes							
Lymph nodes harvested	13	1,337	1,699	1.13 (−0.27 to 2.54)	0.115	0.828	4.69
R0 resection	10	955	1,026	1.02 (0.79 to 1.30)	0.889	0	*n*
Post-operative outcomes							
Overall complication rates	13	1,192	1,856	0.66 (0.44 to 0.97)	<0.001	0.762	0.3524
Pancreatic fistula	13	1,938	2,104	0.67 (0.55 to 0.82)	<0.001	0.269	*n*
Length of stay	20	2,496	3,220	−1.90 (−2.47 to −1.33)	<0.001	0.685	0.6432
90-day mortality	12	1,841	2,591	0.77 (0.45 to 0.95)	0.025	0.038	*n*

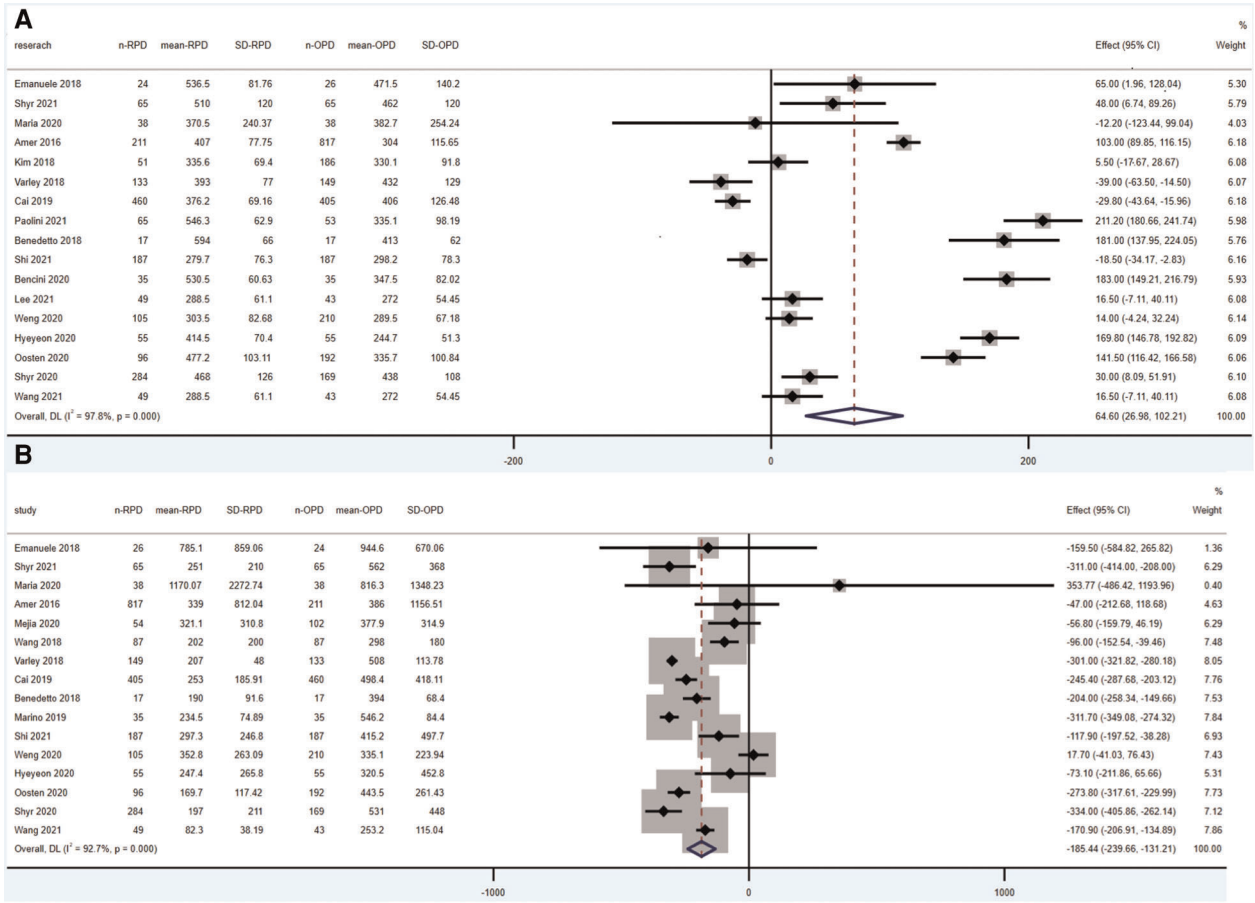

FIGURE 2
Meta-analysis of intraoperative outcomes: (A) operative time. (B) Estimated blood loss.

differences were found between the two groups (OR: 0.67; 95% CI: 0.38 to 1.18; $p = 0.165$), with a high heterogeneity ($I^2 = 51.3\%$, $\text{Tau}^2 = 0.4918$) in the REM (Figure 4C).

3.3.3.4. Length of stay

20 studies reported the data of length of stay (2,496 RPD vs. 3,220 OPD). The meta-analysis showed OPD has significant longer length of stay than RPD (WMD: −1.90; 95% CI: −2.47 to −1.33; $p < 0.001$), with a high heterogeneity ($I^2 = 68.5\%$, $\text{Tau}^2 = 0.6432$) in the REM (Figure 4D).

3.3.3.5. 90-day Mortality

12 studies reported the data of 90-day mortality (1,841 RPD vs. 2,591 OPD). The meta-analysis showed RPD has significant lower 90-day mortality than OPD (OR: 0.65; 95% CI: 0.45 to 0.95; $p = 0.025$), with a low heterogeneity ($I^2 = 3.8\%$) in the FEM (Figure 4E).

4. Discussion

Since first RAPD was reported in 2007, RPD technology has developed rapidly. With the improvement of equipment and doctors gradually through the learning curve, the safety and efficiency of RPD comparing to OPD is gradually improved. Hence, the relevant research results have timeliness. Therefore, although there have been previous meta-analyses comparing clinical outcomes between OPD and RPD, these meta-analyses contained some former studies and can't sufficiently represent current situation. So, we screened articles published after 2016 in our meta-analyses and contained several new studies in this year in order to show the latest RPD development as far as possible.

4.1. Findings in our meta-analyses

According to the result of our meta-analysis, RPD has a longer operative time and lower blood loss comparing to

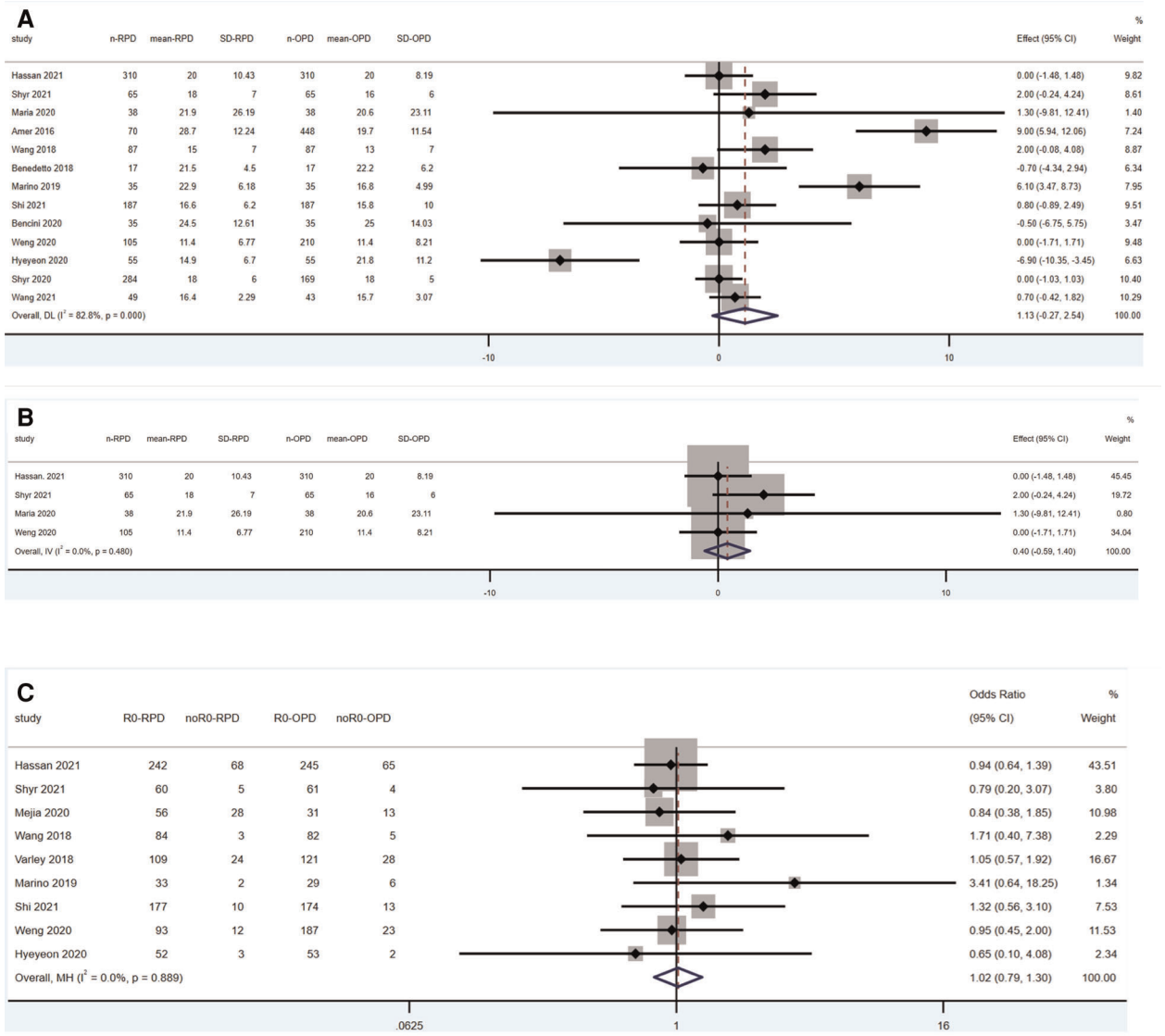

FIGURE 3
Meta-analysis of oncological outcomes: (A) lymph nodes harvested. (B) Lymph nodes harvested (in pancreatic cancer). (C) R0 resection.

OPD, which is also supported by previous researches. As a significant advantage of robotic surgery, RPD showed a lower blood loss. And it may be explained by high-quality three-dimensional (3-D), optical 10–15 magnification vision, and greater precision (25). Multiple factors may lead to the longer operative time in RPD. On one hand, the long time for preparation of machine before operation resulted in a longer operative time. On the other hand, surgeons in these studies not passing through the learning curve may also contribute to longer operative time. What deserve attention is that the result of operative time and estimated blood loss showed high heterogeneity. According to the forest plot of operative time (**Figure 2A**), most studies raised up that operative time was higher in RPD group, but four studies reached the opposite conclusion (7, 14, 15, 19). Many factors can affect the operation time, of which the most important factor is the proficiency of the surgeon. In addition, the equipment of the center and the surgery team also influence the operative time. The heterogeneity of estimated blood loss was also high ($I^2 = 0.927$). One study showed obvious different conclusion comparing with other studies (7). It's obvious that the exclusion of this study will not influence the conclusion of our article. Blood loss can be affected by the proficiency of the surgeon and the condition of the patients (e.g., the location and kind of cancer).

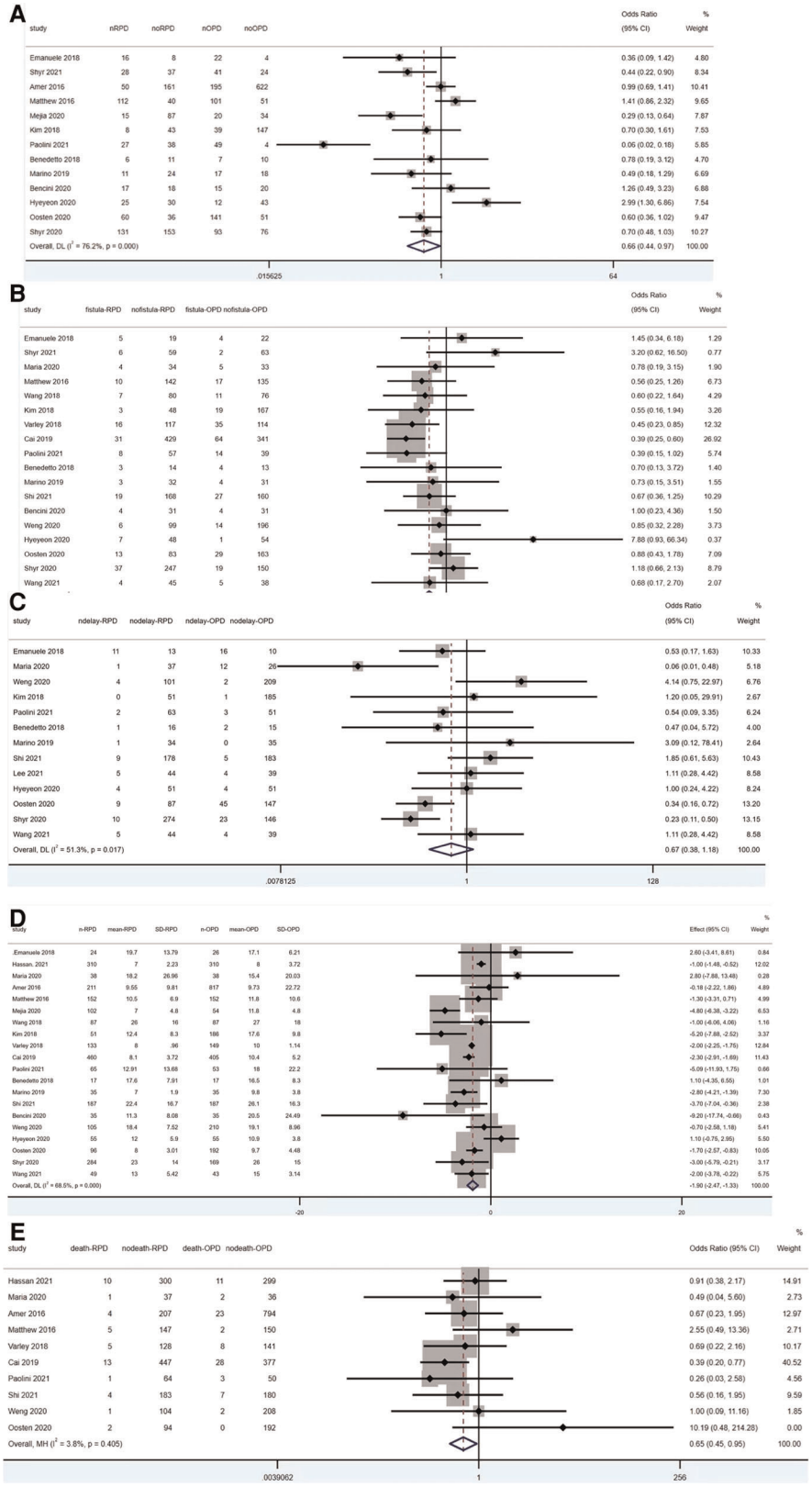

FIGURE 4
Meta-analysis of post-operative outcomes: (A) overall complication rates. (B) Pancreatic fistula. (C) Delayed gastric emptying. (D) Length of stay. (E) 90-day mortality.

Lymph nodes harvested and margin status are considered to be consistent with prognosis of pancreatic cancer. Although various methods of margin quantification in different studies increase the complexity to assessment, margin status is still recognized to have prognostic significance for overall survival of pancreatic ductal adenocarcinoma (PDAC) in PD (26). Similarly, the number of lymph nodes harvested also plays a role in the reveal of prognostic performance (27). Historically, a mass of researches on OPD and RPD compared their differences in margin status, and previous meta-analysis also counted the oncological outcomes of the two groups. Except the meta-analysis of Dong et al. demonstrated that the RPD group has a larger number of lymph nodes harvested and a lower resection margin involvement rate, another two meta-analyses early and this meta-analysis all reveal that there is no difference of those oncological outcomes in the two groups (28–30). The heterogeneity of lymph nodes harvested and overall complication rate is high. The composition of patients' tumor varies in different studies, which may lead to the heterogeneity of lymph nodes harvested. Besides, different operation centers may have different diagnostic criteria and definition for post-operative complications, causing the heterogeneity of overall complication rate.

Furthermore, we analyzed the oncological outcomes in studies limited to pancreatic cancer. Five studies analyzed patients with only pancreatic cancer, and other studies contained patients with kinds of disease which accepted RPD or OPD. In most studies, patients accepted PD because of different diseases, including pancreatic cancer, ampullary adenocarcinoma, and neuroendocrine tumor. Obviously, the malignancy of these tumors is different, reducing the credibility of the comparison of the prognosis indicator between OPD and RPD.

Of the five studies limited to pancreatic cancer, four involved lymph nodes harvested, and analysis of these four articles also showed no difference in RPD and OPD groups. Only two articles limited in pancreatic cancer mentioned R0 resection which is too few to analyze. Comparing the results of the two meta-analyses, no different conclusions were reached.

The safety of RPD has been proved in previous studies. As expected, our meta-analysis revealed that clinical outcomes favor RPD, including overall complication rates, pancreatic fistula rate, and length of hospital stay. Besides, different from the previous meta-analysis, this meta-analysis demonstrated that 90-day mortality also favors RPD.

4.2. Strengths

The safety and efficiency of RPD comparing to OPD is gradually improved, owing to the improvement of equipment and doctors gradually through the learning curve. This is the latest meta-analyses that included all eligible studies published in these 5 years. The number of studies is one strength of our article. Furthermore, to our knowledge, this is the first meta-analyses and systematic review that included all studies limited to patients with pancreatic cancer.

4.3. Limitations

Although we found 5 studies researching RPD and OPD in pancreatic cancer patients, most studies mix patients with various diseases together for analysis, making it impossible to conduct subgroup analysis. Besides, lack of RCTs in our meta-analysis is another limitation.

4.4. Implications for clinical practice

This meta-analysis found that RPD showed lower blood loss, overall complication rates, pancreatic fistula, and 90-day mortality compared with OPD. Besides, length of hospital stay was shorter in RPD. Although the operative time is longer in RPD group, and there were no differences in R0 resection and lymph nodes harvested, RPD has shown benefits over OPD and seemed to be proposed as an equivalent alternative to OPD. However, all the current studies about OPD and RPD are not RCTs, and high-quality studies are still needed. In addition, centers with the ability to perform a sufficient number of surgeries and professional surgeons who have overcome the learning curve are essential for successful implementation of RPD. What's more, RPD costs much higher than OPD, which is also an important factor in the choice of surgical methods.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

Conception and design of the work: YF and JQ. Data acquisition and analysis: YF and YY. Interpretation of the data: YF and YY. Drafting the manuscript: YF and JQ. Critical revision of the manuscript: YY and DW. Agreement to be accountable for all aspects of the work: YF, JQ, YY, DW, and TZ. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by grants from the National Key R&D Program of China (2018YFE0118600); National Natural Science Foundation of China (No. 81972258); National Multidisciplinary Cooperative Diagnosis and Treatment Capacity Building Project for Major Diseases.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.989065/full#supplementary-material.

References

1. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. *Surg Endosc.* (1994) 8(5):408–10. doi: 10.1007/BF00642443

2. Kornaropoulos M, Moris D, Beal EW, Makris MC, Mitrousias A, Petrou A, et al. Total robotic pancreaticoduodenectomy: a systematic review of the literature. *Surg Endosc.* (2017) 31(11):4382–92. doi: 10.1007/s00464-017-5523-z

3. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res.* (2018) 27(6):1785–805. doi: 10.1177/0962280216669183

4. Kauffmann EF, Napoli N, Menonna F, Iacopi S, Lombardo C, Bernardini J, et al. A propensity score-matched analysis of robotic versus open pancreatoduodenectomy for pancreatic cancer based on margin status. *Surg Endosc.* (2019) 33(1):234–42. doi: 10.1007/s00464-018-6301-2

5. Aziz H, Khan M, Khan S, Serra GP, Goodman MD, Genyk Y, et al. Assessing the perioperative complications and outcomes of robotic pancreaticoduodenectomy using the national cancer database: is it ready for prime time? *J Robot Surg.* (2022) 16(3):687–94. doi: 10.1007/s11701-021-01296-3

6. Shyr BU, Shyr BS, Chen SC, Shyr YM, Wang SE. Propensity score-matched comparison of the oncological feasibility and survival outcomes for pancreatic adenocarcinoma with robotic and open pancreatoduodenectomy. *Surg Endosc.* (2022) 36(2):1507–14. doi: 10.1007/s00464-021-08437-7

7. Baimas-George M, Watson M, Murphy KJ, Iannitti D, Baker E, Ocuin L, et al. Robotic pancreaticoduodenectomy may offer improved oncologic outcomes over open surgery: a propensity-matched single-institution study. *Surg Endosc.* (2020) 34(8):3644–9. doi: 10.1007/s00464-020-07564-x

8. Weng Y, Jiang Y, Fu N, Jin J, Shi Y, Huo Z, et al. Oncological outcomes of robotic-assisted versus open pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a propensity score-matched analysis. *Surg Endosc.* (2021) 35(7):3437–48. doi: 10.1007/s00464-020-07791-2

9. Zureikat AH, Postlewait LM, Liu Y, Gillespie TW, Weber SM, Abbott DE, et al. A multi-institutional comparison of perioperative outcomes of robotic and open pancreaticoduodenectomy. *Ann Surg.* (2016) 264(4):640–9. doi: 10.1097/SLA.0000000000001869

10. McMillan MT, Zureikat AH, Hogg ME, Kowalsky SJ, Zeh HJ, Sprys MH, et al. A propensity score-matched analysis of robotic vs open pancreatoduodenectomy on incidence of pancreatic fistula. *JAMA Surg.* (2017) 152(4):327–35. doi: 10.1001/jamasurg.2016.4755

11. Mejia A, Shah J, Vivian E, Acharya P. Analysis of 102 fully robotic pancreaticoduodenectomies: clinical and financial outcomes. *Pancreas.* (2020) 49(5):668–74. doi: 10.1097/MPA.0000000000001545

12. Wang SE, Shyr BU, Chen SC, Shyr YM. Comparison between robotic and open pancreaticoduodenectomy with modified blumgart pancreaticojejunostomy: a propensity score-matched study. *Surgery.* (2018) 164(6):1162–7. doi: 10.1016/j.surg.2018.06.031

13. Kim HS, Han Y, Kang JS, Kim H, Kim JR, Kwon W, et al. Comparison of surgical outcomes between open and robot-assisted minimally invasive pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci.* (2018) 25(2):142–9. doi: 10.1002/jhbp.522

14. Varley PR, Zenati MS, Klobuka A, Tobler J, Hamad A, Hogg ME, et al. Does robotic pancreaticoduodenectomy improve outcomes in patients with high risk morphometric features compared to the open approach. *HPB.* (2019) 21(6):695–701. doi: 10.1016/j.hpb.2018.10.016

15. Cai J, Ramanathan R, Zenati MS, Al Abbas A, Hogg ME, Zeh HJ, et al. Robotic pancreaticoduodenectomy is associated with decreased clinically relevant pancreatic fistulas: a propensity-matched analysis. *J Gastrointest Surg.* (2020) 24(5):1111–8. doi: 10.1007/s11605-019-04274-1

16. Paolini C, Bencini L, Gabellini L, Urciuoli I, Pacciani S, Tribuzi A, et al. Robotic versus open pancreaticoduodenectomy: is there any difference for frail patients? *Surg Oncol.* (2021) 37:101515. doi: 10.1016/j.suronc.2020.12.009

17. Ielpo B, Caruso R, Duran H, Diaz E, Fabra I, Malavé L, et al. Robotic versus standard open pancreatectomy: a propensity score-matched analysis comparison. *Updates Surg.* (2019) 71(1):137–44. doi: 10.1007/s13304-018-0529-1

18. Marino MV, Podda M, Gomez Ruiz M, Fernandez CC, Guarrasi D, Gomez Fleitas M. Robotic-assisted versus open pancreaticoduodenectomy: the results of a case-matched comparison. *J Robot Surg.* (2020) 14(3):493–502. doi: 10.1007/s11701-019-01018-w

19. Shi Y, Jin J, Qiu W, Weng Y, Wang J, Zhao S, et al. Short-term outcomes after robot-assisted vs open pancreaticoduodenectomy after the learning curve. *JAMA Surg.* (2020) 155(5):389–94. doi: 10.1001/jamasurg.2020.0021

20. Bencini L, Tofani F, Paolini C, Vaccaro C, Checcacci P, Annecchiarico M, et al. Single-centre comparison of robotic and open pancreatoduodenectomy: a propensity score-matched study. *Surg Endosc.* (2020) 34(12):5402–12. doi: 10.1007/s00464-019-07335-3

21. Kim H, Park SY, Park Y, Kwon J, Lee W, Song KB, et al. Assessment of learning curve and oncologic feasibility of robotic pancreaticoduodenectomy: a propensity score-based comparison with open approach. *J Hepatobiliary Pancreat Sci.* (2022) 29(6):649–58. doi: 10.1002/jhbp.837

22. van Oosten AF, Ding D, Habib JR, Irfan A, Schmocker RK, Sereni E, et al. Perioperative outcomes of robotic pancreaticoduodenectomy: a propensity-matched analysis to open and laparoscopic pancreaticoduodenectomy. *J Gastrointest Surg.* (2021) 25(7):1795–804. doi: 10.1007/s11605-020-04869-z

23. Shyr BU, Shyr BS, Chen SC, Shyr YM, Wang SE. Robotic and open pancreaticoduodenectomy: results from Taipei veterans general hospital in Taiwan. *Updates Surg.* (2021) 73(3):939–46. doi: 10.1007/s13304-020-00899-z

24. Wang W, Liu Q, Zhao ZM, Tan XL, Wang ZZ, Zhang KD, et al. Comparison of robotic and open pancreaticoduodenectomy for primary nonampullary duodenal adenocarcinoma: a retrospective cohort study. *Langenbecks Arch Surg.* (2022) 407(1):167–73. doi: 10.1007/s00423-021-02303-9

25. Shyr YM, Wang SE, Chen SC, Shyr BU, Shyr BS. Robotic pancreaticoduodenectomy for pancreatic head cancer and periampullary lesions. *Ann Gastroenterol Surg*. (2021) 5(5):589–96. doi: 10.1002/ags3.12457

26. Pine JK, Haugk B, Robinson SM, Darne A, Wilson C, Sen G, et al. Prospective assessment of resection margin status following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma after standardisation of margin definitions. *Pancreatology*. (2020) 20(3):537–44. doi: 10.1016/j.pan.2020.01.004

27. You MS, Lee SH, Choi YH, Shin BS, Paik WH, Ryu JK, et al. Lymph node ratio as valuable predictor in pancreatic cancer treated with R0 resection and adjuvant treatment. *BMC Cancer*. (2019) 19(1):952. doi: 10.1186/s12885-019-6193-0

28. Da Dong X, Felsenreich DM, Gogna S, Rojas A, Zhang E, Dong M, et al. Robotic pancreaticoduodenectomy provides better histopathological outcomes as compared to its open counterpart: a meta-analysis. *Sci Rep*. (2021) 11(1):3774. doi: 10.1038/s41598-021-83391-x

29. Yan Q, Xu LB, Ren ZF, Liu C. Robotic versus open pancreaticoduodenectomy: a meta-analysis of short-term outcomes. *Surg Endosc*. (2020) 34(2):501–9. doi: 10.1007/s00464-019-07084-3

30. Peng L, Lin S, Li Y, Xiao W. Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy. *Surg Endosc*. (2017) 31(8):3085–97. doi: 10.1007/s00464-016-5371-2

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 14 October 2022
DOI 10.3389/fsurg.2022.988331

OPEN ACCESS

EDITED BY
Claudia Di Bella,
The University of Melbourne, Australia

REVIEWED BY
Caio Vinícius Suartz,
University of São Paulo, Brazil
Sarah O'Reilly-Harbidge,
St Vincent's Hospital (Melbourne), Australia

*CORRESPONDENCE
Wenli Zhang
zwlbox@163.com
Hong Duan
duanhong1970@126.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 07 July 2022
ACCEPTED 12 September 2022
PUBLISHED 14 October 2022

CITATION
Banskota N, Yang H, Fang X, Yuan D, Zhang W and Duan H (2022) Comparative study of pelvic sarcoma patients undergoing internal and external hemipelvectomy: A meta-analysis study.
Front. Surg. 9:988331.
doi: 10.3389/fsurg.2022.988331

Comparative study of pelvic sarcoma patients undergoing internal and external hemipelvectomy: A meta-analysis study

Nishant Banskota†, Hongsheng Yang†, Xiang Fang, Dechao Yuan, Wenli Zhang* and Hong Duan*

Department of Orthopedics, West China School of Medicine/West China Hospital, Sichuan University, Chengdu, China

Introduction: Malignant and giant pelvic tumors are complex and rare, and hemipelvectomies are complex procedures performed for this malignant lesion. Only a few studies had been conducted on the survival and recurrence of pelvic sarcomas patients undergoing internal or external hemipelvectomy. In the present study, we compared internal with external hemipelvectomy in pelvic sarcomas on clinical outcomes by a meta-analysis.
Methods: The survival and recurrence rates of pelvic sarcomas patients were collected from research reports from CNKI, MEDLINE, EMBASE, the Cochrane Database, and Google Scholar until April 2022. The quality of included articles was evaluated by two independent reviewers. Differences between patients undergoing internal and external hemipelvectomy were analyzed based on postoperative survival and recurrence rates.
Results: Five articles were included according to selection criteria. There were 183 patients in total from these studies. Our results showed that there was no significant difference between limb salvage surgery and amputation according to survival; however, patients with internal hemipelvectomy had a lower recurrence rate.
Conclusions: Internal hemipelvectomy results in a lower recurrence rate and similar survival rate, while not increasing the risk of metastasis and complications. This study provided more pieces of evidence to support internal hemipelvectomy as a favorable treatment of pelvic sarcomas.

KEYWORDS
internal hemipelvectomy, external hemipelvectomy, five-year survival rate, meta-analysis, local recurrence

Introduction

Hemipelvectomy is a major orthopedic surgical procedure indicated in specific situations and regularly performed in advanced tertiary centers (1). Hemipelvectomy is commonly performed for soft tissue and bone sarcomas of the pelvis region (2). The reconstruction after hemipelvectomy is of importance for the later outcome and quality of life (3). Previously treatment of these tumors has been difficult because of the poor prognosis and the necessity for amputation (4). Hemipelvectomy involves

the following two different approaches: external approach (with limb amputation) and internal approach (with limb preservation) and further internal approaches are divided into four subtypes based on anatomical location (3).

In recent years, the use of external hemipelvectomy for the treatment of pelvic tumors has declined, and new surgical techniques and efforts for resection with limb preservation (internal hemipelvectomy) and reconstruction have been introduced (5, 6). This major development in the medical field demands comparisons between these two vastly different procedures, as both procedures have their advantages and disadvantages. Survival and complications after hemipelvectomy might be related to several different factors, such as tumor size and histopathology, disease stage, patient general condition, and resection type (7). In patients with pelvic tumors, the 5-year survival rate and recurrence are expected to be high in number. Large tumors and bone and vascular involvement might be indicators of poor survival (8). A large previous study reported a survival rate of 50% after hemipelvectomy (9). Reoccurrence and metastasis also mainly depend upon tumor stage and resection.

There are not many studies focusing on these procedures and analyzing their short comes and benefits. There is a need for a study elaborating on these because of the poor quality of life that patients suffer after this extensive surgery. We conducted a meta-analyses study on survival, local reoccurrence, and metastasis in patients with pelvic tumors undergoing internal and external hemipelvectomy. In addition, our study focused on whether patients undergoing internal hemipelvectomy had a better 5-year survival rate and less recurrence, metastasis, and complications than external hemipelvectomy.

Through searching more abundant hemipelvectomy literature, we conduct this meta-analysis to get a comprehensive conclusion in hemipelvectomy patients treated with external and internal approaches. These results will help us to establish the most appropriate method to treat a tumor in the pelvic region. In our study, internal hemipelvectomy was set as the experimental group and external hemipelvectomy as a control group.

Methods

This study was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**) (10).

Literature search

PUBMED, MEDLINE, Cochrane, EMBASE, and Google Scholar databases were searched for relevant data until April 30, 2022. The reference studies of relevant studies were also searched on different databases. Searches were expanded to 35 years, because of the lack of the study published on relevant

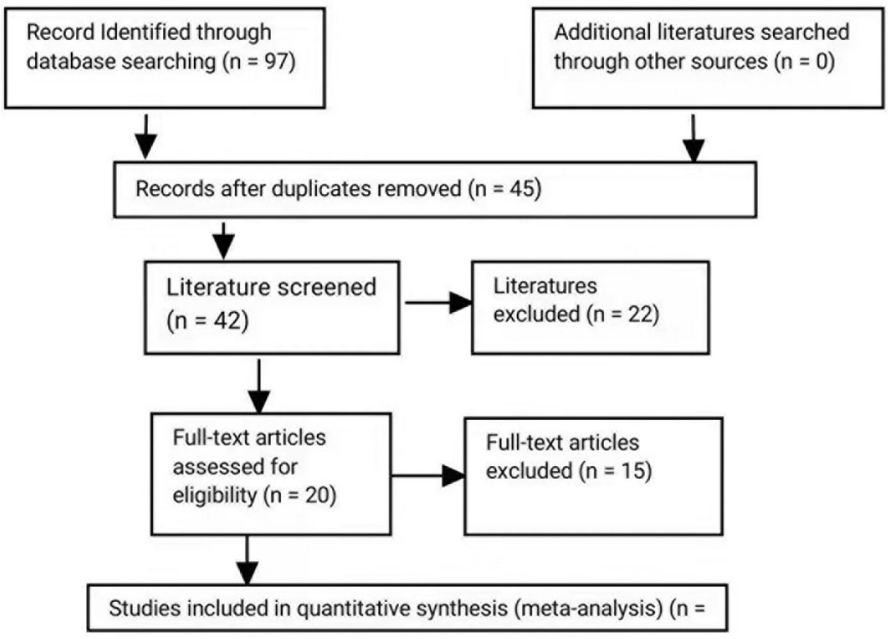

FIGURE 1
Flow chart of studies included and excluded.

topics. Keywords used for searching included internal hemipelvectomy, external hemipelvectomy, pelvic tumor, survival, recurrence, complications, and metastasis.

Included studies

Inclusion criteria:

(1) English language studies including patients diagnosed with pelvic tumors;
(2) Use of internal and external hemipelvectomy for pelvic tumors; and
(3) Studies providing information on the 5-year survival rate, recurrence rate, metastasis, and complication after these two surgeries.

Exclusion criteria:

(1) Non-English studies;
(2) Non-comparative studies between internal and external hemipelvectomy;
(3) Case reports, review, letter to the editors; and
(4) Studies that lack adequate clinical data.

Study selection and data extraction

Outcomes were collected from the articles by three authors of our study. The authors made a descriptive and informative table and then collected all the data into a database. The following data were extracted from articles according to the inclusion criteria: the name of the first author, year of publication, design scheme, number of patients in each group, patients' age and gender, and short and long-term after surgery. Data were extracted for (a) demographic characteristics, (b) 5-year survival rate, (c) recurrence rate (local and distant recurrence), (d) Metastases local and distant metastases), and (e) complications (wound complications, genitourinary complications, and flail hip).

Quality assessment and outcome measurement

Literature focusing on similar research issues was included, and all studies were retrospective. In this study, the authors attempted to include randomized control trial (RCT) and prospective studies for a better outcome of the study, but the authors could not find any studies matching our criteria due to minimal studies published in this section. All studies had a low bias as studies were moreover similar with similar inclusion criteria, similar surgical procedures, and study periods. Inconsistencies were resolved on the assessment by the corresponding author. Quality assessment was done by the Newcastle-Ottawa Scale (NOS) (11) and the table is shown in the **Supplementary File**. In our study, the primary outcome was set as a 5-year survival rate and the secondary outcomes in our study were local recurrence, metastasis, and complications. The 5-year survival rate is defined operated patient having a life expansion of a minimum of 5 years after surgery.

Statistical analysis

The outcome of measurement used in our study was the 5-year survival rate, local recurrence, metastasis, and complications which were all dichotomous data. We used the software of the Cochrane Collaboration (ReviewManager5.2) to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for all outcomes. Statistical heterogeneity among the included studies was defined by the I^2 tests. Statistically, significant heterogeneity was defined as an I^2 value >0.5 (12). I^2 illustrates the percentage of the total variability in effect estimates among trials that is because of heterogeneity rather than coincidence (13). Heterogeneity was defined as low, moderate, and high based on the I square value (<40%: low; 30%–60%: moderate; 50%–90%: substantial >75%: high). Heterogeneity with a high I square value >50% was considered statistically significant. A random-effects model was selected for heterogeneous data; otherwise, a fixed-effect model was selected. Publication bias was identified through funnel plots, which exhibited the intervention effect from the individual study against the respective standard error. An asymmetrical plot suggested there was no publication bias, and any asymmetry of the plot suggests the existence of publication bias.

Results

Study selection

In the primary study search, 97 relevant articles were retrieved and 45 were excluded based on the exclusion criteria (**Figure 1**). The abstracts of the remaining 42 were screened, and 22 were excluded based on the exclusion criteria. After all the reviews of the remaining 20 studies, 10 were excluded due to lacking outcome of ($n = 10$) and duplication in the study population with other articles ($n = 5$). In a word, a total of five articles were included in the meta-analysis. Characteristics of the studies are summarized in **Table 1**, and outcomes are summarized in **Table 2**.

Five-year survival rate and tests for heterogeneity

Among all the eligible studies, three of the five studies reported a 5-year survival rate. Data were recorded as patients not surviving for 5 years and the result was moreover similar in both groups. In the analysis of the fixed model effects, the I^2 score was 76%, thus random-effect model was conducted. There was no significant

TABLE 1 Characteristics of the included studies.

Studies	Study period	Patient number	Male/Female	Median age	Study design	Newcastle-Ottawa Scale (NOS)	Country
Griesser 2011	2002–2007	15	11/4	46.9	Retrospective	8	United States
Guder 2015	1999–2012	34	21/13	70.2	Retrospective	8	Germany
Guo 2011	1996–2005	60	37/23	45.5	Retrospective	8	United States
Ham 1997	1970–1995	21	14/7	43	Retrospective	8	Netherland
Huth 1988	1974–1986	53	31/22	40	Retrospective	8	United States

TABLE 2 Outcomes of the included studies.

Reference	Local recurrence (internal/external)	5-year survival (internal/external)	Metastatic (internal/external)	Complications (internal/external)		
				Wound infection	GU	Flail hip
Griesser 2011	1/15		3/15	1/15	1/15	
Guder 2015	3/34	29/34	5/34			
Guo 2011	25/60		16/60	12/30		5/60
Ham 1997	5/21	14/21	8/21	5/21	3/21	4/21
Huth 1988	4/33	17/33		3/33		

GU, Genitourinary.

heterogeneity in the comparison of 5-year overall survival between the internal and external hemipelvectomy groups (OR = 1.15, 95% CI 0.07–18.18, $P = 0.93$).

Recurrence rate

All five studies reported recurrence. Recurrence occurred in all five studies either in the internal group or the external group. A fixed-effects model of analysis was used (14). There was a significant difference in the local recurrence rate between internal and external hemipelvectomy, fewer recurrences were seen in the internal group (OR = 0.15, 95% CI 0.06–0.36, $P < 0.0001$) as shown in Figure 2. Recurrence in our study included both local and distant recurrence.

Metastasis

Among all the eligible studies, four of the five studies reported metastasis. In our studies, both distant and local metastases were included in metastases titled outcome. The outcome was moreover similar in both groups suggesting no significance relating to this outcome (OR = 0.89, 95% CI 0.40–1.96, $P = 0.77$) as shown in Figure 3.

Complications

Many local and systemic complications are associated with both these procedures; our studies only included three complications wound, genitourinary, and flail hip which were moreover common in all our studies. Wound complications were reported in four of our included studies, more complications were associated with the external group than the internal group (OR = 0.40, 95% CI 0.15–1.05, $P = 0.06$). Genitourinary complications were also reported in four of our studies but were only recorded in two studies. The I^2 value was recorded as 68%, hence analysis was conducted through random effects. The outcome was moreover similar in both groups (OR = 0.85, 95% CI 0.02–47.77, $P = 0.08$). Flail hip was also reported in four of our studies but only recorded in two studies. These complications less occurred in the internal group than external as suggested by the Forrest plot curve in Figure 4 (OR = 0.48, 95% CI 0.11–2.07, $P = 0.32$). As suggested by the P-value, there were not any significant results, but still, there were few complications associated with internal hemipelvectomy thus favoring the experimental group.

Sensitivity analysis

Sensitivity analyses indicated that included studies were performed to determine the reliability of the results, with each study removed in turn (15). The magnitude and dynamics of the combined estimates did not have any difference markedly with the exclusion of individual studies, indicating that the findings of the meta-analysis are reliable and the result obtained by conducting a meta-analysis is stable. The statistical value when the first study was excluded (OR = 0.71, 95% CI 0.01–70.38, $P = 0.88$), when the second study was only excluded (OR = 4.56, 95% CI 0.9–23.14, $P = 0.07$), and when

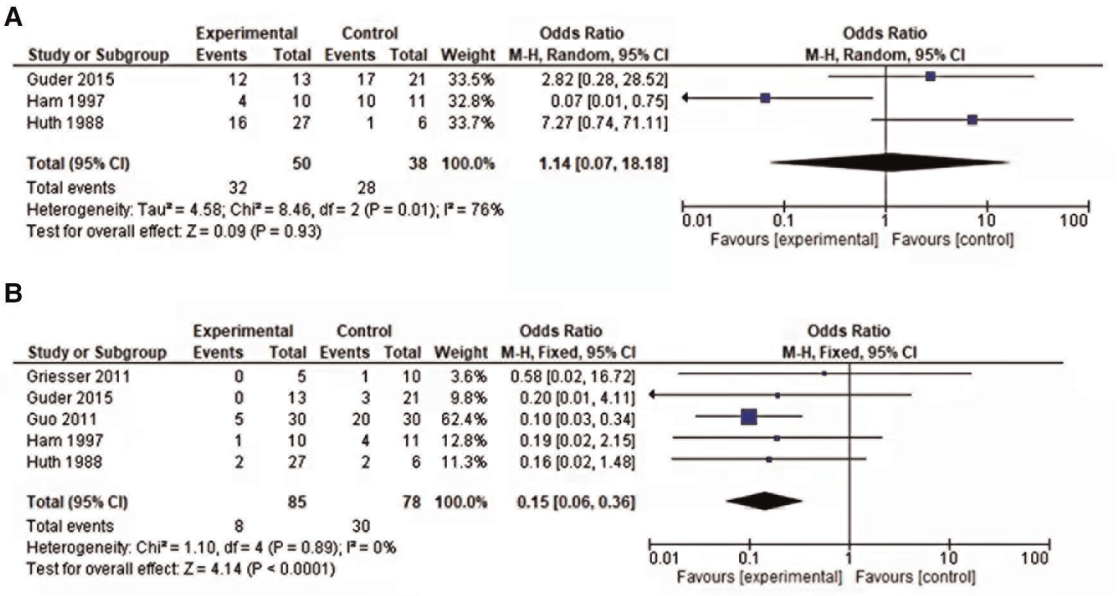

FIGURE 2
(A) Forest plot of comparison 5-year survival rate of internal vs. external hemipelvectomy in pelvic tumors. (B) Forest plot comparing local recurrence of internal vs. external hemipelvectomy in pelvic tumors.

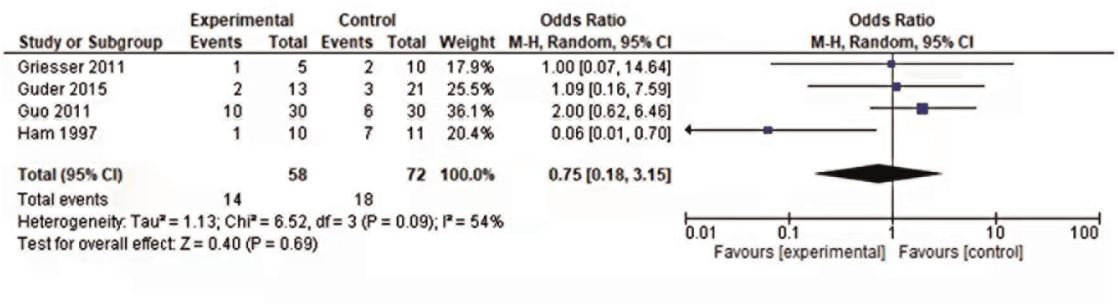

FIGURE 3
Forest plot of comparison metastasis of internal vs. external hemipelvectomy in pelvic tumors.

the third study was only excluded (OR = 0.44, 95% CI 0.01–17.33, $P = 0.66$). All sensitivity analysis figures are shown in the **Supplementary File**.

Publication bias

Funnel plots of the local recurrence rates and 5-year survival rates were shown in **Figure 5**. Funnel plots were used only in two primary outcomes of our studies which were local recurrence and 5-year survival rates. The findings showed that there is no evidence of publication bias for each of the two outcomes.

Discussion

Malignant and giant pelvic tumors are aggressive and difficult to resect with unfavorable outcomes. The anatomical location makes it more complex and close and an adhered to major visceral organ adds to its poor prognosis (16). Most pelvic tumors are diagnosed at a late stage which also adds to their poor prognosis (17). Limb salvage surgery for malignant tumors of the pelvis is a formidable surgical undertaking, both from the viewpoint of surgical resection and reconstruction (18). The surgeon's primary goal is local control of the tumor by complete resection and the secondary goal is to preserve a functional limb (18). Many metastatic

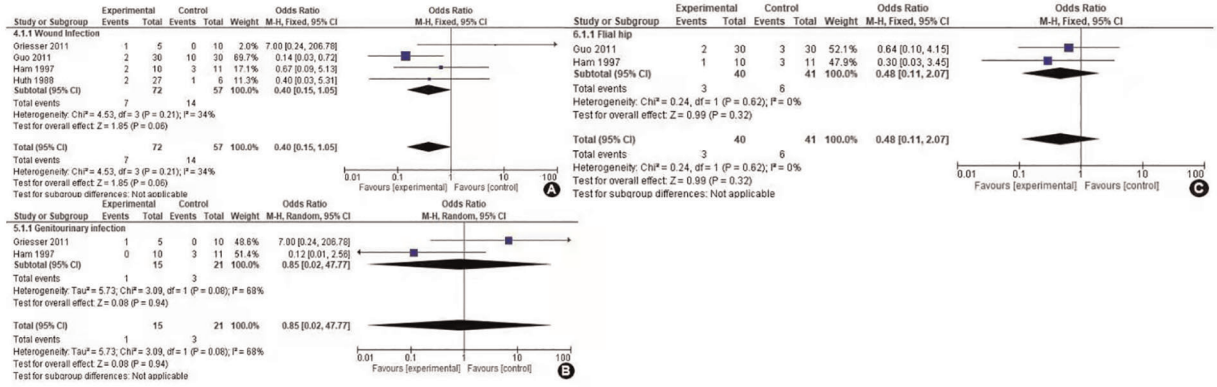

FIGURE 4
Forest plot of comparison complications of internal vs. external hemipelvectomy in pelvic tumors: (A) Wound complication, (B) genitourinary complications, and (C) flail hip.

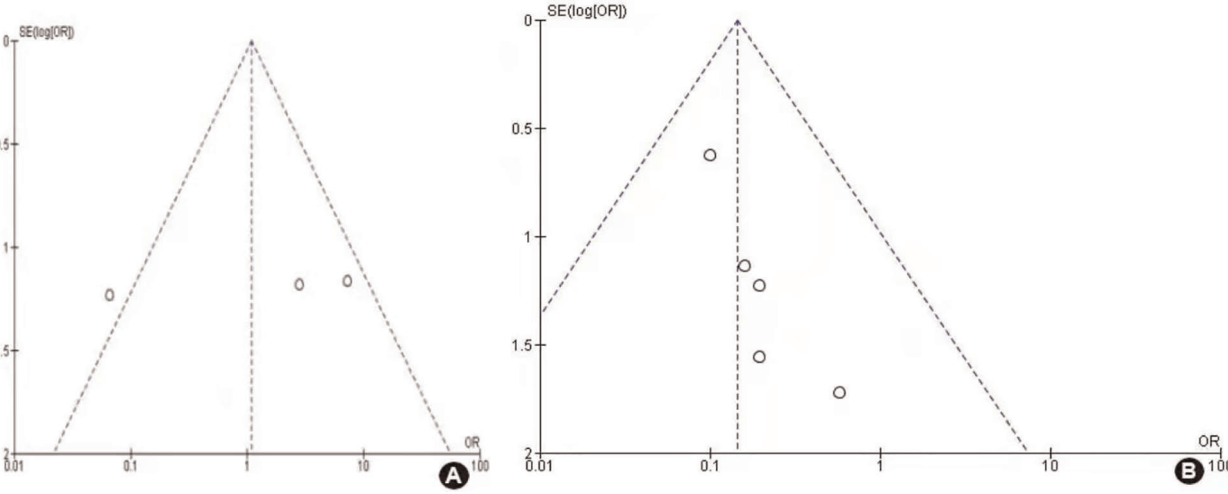

FIGURE 5
Funnel plot for publication bias, 4A. Five year survival rate, 4B. Local recurrence.

and malignant tumors can be observed in the pelvic region, due to their aggressive nature or extension to adjacent structures prognosis has been poor. Whether internal or external, hemipelvectomies are a major operative procedure and may be associated with significant functional impairments and morbidity including injury to the genitourinary tract, neurovascular injury, considerable soft tissue defects, blood loss, wound infections, and delayed wound healing (14, 19). Radiotherapy and chemotherapy have helped in improving the outcome of these major procedures. Adjuvant and neoadjuvant therapy are accepted treatments in the tumors of the pelvis region and the study conducted by Ng et al., justified this therapy by increasing the survival rate in Ewing sarcoma patients (20).

Any surgeon desires and aims to give hemipelvectomies patients a functional and comfortable postoperative life. There are very few studies comparing these procedures, as pelvic tumors are rare and many patients do not choose surgery as their treatment option due to its postoperative and financial burden. Chondrosarcoma is the most frequent primary tumor of the pelvis, followed by Ewing's sarcoma and osteosarcoma (21). Patients with these tumors seldom have desirable outcomes regardless of undergoing surgery or not. The survival rates in any tumor are often related to recurrence and metastasis, in the case of Ewing sarcoma 5-year survival is less than 10% (22). In a retrospective study by Shin et al., there was no significant difference between these two procedures based on survival and complications outcomes on

a long-term basis, and found prognosis was better in lower-grade sarcomas (23). Survival is also influenced by older age (17) and associated comorbidity. A reconstructive procedure helps in maintaining joint stability but is associated with more complications (5, 24). Minimal studies have been conducted comparing the functional outcomes of these two procedures; a retrospective study by Guo et al., found that internal hemipelvectomy patients had better functional outcomes, shorter lengths of stay, and were early ambulators (2). Extensive muscle and soft tissue resection in external hemipelvectomy may have been an influencing factor in eliciting the results of this retrospective study (2). A retrospective study done by Apffelstaedt et al., reviewed 68 external hemipelvectomies and 32 internal hemipelvectomies and their study was focused on surgical complications and mobility after these procedures (25). Their total mortality rates from the surgery were 6% for external hemipelvectomies and 9% for internal hemipelvectomies (25). With respect to mobility, external hemipelvectomy patients as expected were in crutches with prosthesis or without prosthesis, and among that 9% of patients were wheelchair bound and 6% were bedridden (25). In another study conducted by Beck et al., quality of life was compared using the linear analog self-assessment (LASA) subcategory among these two procedures; no differences were noted between groups for any parameter except pain severity. Participants with external hemipelvectomies experienced a higher level of pain (26).

In our study only, three studies (4, 27, 28) reported 5-year survival rates and the outcome were moreover similar in both groups (OR = 1.15 *P*-value = 0.93). Then in the heterogeneity test, one large study (27) was excluded, there was apparent heterogeneity as findings were moreover similar. In contrast to our study, a retrospective study by Couto et al. found that the 5-year survival rate was significantly lower in patients who underwent external hemipelvectomy than in those who underwent internal hemipelvectomy ($P = 0.043$) (7). In the context of the internal approach comparative research are very few and hard to distinguish on an anatomical basis which internal approach has a better prognosis, a study done by Penna et al., suggested type I and III resection has good survival outcomes (29). Local recurrence in our study was found less in the internal group compared to the external group (OR = 0.15 $P = 0.89$). Local recurrence may be associated with larger tumor size and the absence of neoadjuvant chemotherapy (19). Metastasis was also similar to recurrence and among three complications wound complication was the most common in our meta-analysis literature, which also corresponds to other studies (30, 31). Internal hemipelvectomy presents an alternative procedure in the struggle against pelvic tumors and an adequate and tumor-free resection margin is of great value for the long-term oncological outcome (3). External hemipelvectomy is currently performed in specific situations of more advanced diseases such as failed neoadjuvant therapy, severe deep infection, sciatic nerve, and femoral vessel infiltration, local tumor recurrence, improvement of the resection margin, and as a life-saving or palliative procedure could explain the higher chances of survival in the internal hemipelvectomy group (7). Although we did not notice any significant statistical, based on less recurrence and other outcomes moreover similar in both groups, this study may suggest as internal hemipelvectomy is a favorable procedure.

A few limitations of this meta-analysis should be illustrated. First, the lack of detailed and verified data from original studies made it hard to adjust estimates by age, menopausal, lifestyle, smoking, race, and so on, while more accurate analysis needed this kind of adjusting. Second, there was no detailed data on our primary outcomes survival and no additional data to analyze the functional mobility of the patients. Third, there were only limited studies, so it is hard to get a statistically significant result.

Otherwise, our meta-analysis also has some beneficial points. First, a systematic review of the association of survival, recurrence, and metastasis in pelvic sarcomas patients with internal or external hemipelvectomy treatment was statistically more powerful than any single study. Second, all of the retrospective studies had a high quality and conformed to our inclusion criteria. Third, even though included studies were few and without statistically significant results, our study highlighted the importance of limb preservation leading to quality of life and encourages more literature on these rare topics.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

NB, HD, and HY contributed to the conception and design. NB, HY, and XF contributed to the provision of study material. NB, HY, and DY contributed to the collection and/or assembly of data. WZ, NB, HY, and XF contributed to the data analysis and interpretation. NB and HY contributed to manuscript writing. HD and WZ contributed to the final approval of manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Fundamental Research Funds for the Central Universities (2019SCUH).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.988331/full#supplementary-material.

References

1. Anderson MR, Jeng CL, Wittig JC, Rosenblatt MA. Anesthesia for patients undergoing orthopedic oncologic surgeries. *J Clin Anesth*. (2010) 22(7):565–72. doi: 10.1016/j.jclinane.2010.02.011

2. Guo Y, Fu J, Palmer JL, Hanohano J, Cote C, Bruera E. Comparison of postoperative rehabilitation in cancer patients undergoing internal and external hemipelvectomy. *Arch Phys Med Rehabil*. (2011) 92(4):620–5. doi: 10.1016/j.apmr.2010.11.027

3. Wedemeyer C, Kauther MD. Hemipelvectomy—only a salvage therapy? *Orthop Rev (Pavia)*. (2011) 3(1):e4. doi: 10.4081/or.2011.e4

4. Huth JF, Eckardt JJ, Pignatti G, Eilber FR. Resection of malignant bone tumors of the pelvic girdle without extremity amputation. *Arch Surg*. (1988) 123(9):1121–4. doi: 10.1001/archsurg.1988.01400330097015

5. O'Connor MI. Malignant pelvic tumors: limb-sparing resection and reconstruction. *Semin Surg Oncol*. (1997) 13(1):49–54. doi: 10.1002/(SICI)1098-2388(199701/02)13:1<49::AID-SSU8>3.0.CO;2-4

6. Harrington KD. The use of hemipelvic allografts or autoclaved grafts for reconstruction after wide resections of malignant tumors of the pelvis. *J Bone Joint Surg Am*. (1992) 74(3):331–41. doi: 10.2106/00004623-199274030-00003

7. Couto AG, Araújo B, Torres de Vasconcelos RA, Renni MJ, Da Fonseca CO, Cavalcanti IL. Survival rate and perioperative data of patients who have undergone hemipelvectomy: a retrospective case series. *World J Surg Oncol*. (2016) 14(1):255. doi: 10.1186/s12957-016-1001-7

8. Apffelstaedt JP, Zhang PJ, Driscoll DL, Karakousis CP. Various types of hemipelvectomy for soft tissue sarcomas: complications, survival and prognostic factors. *Surg Oncol*. (1995) 4(4):217–22. doi: 10.1016/S0960-7404(10)80038-6

9. Mankin HJ, Hornicek FJ. Internal hemipelvectomy for the management of pelvic sarcomas. *Surg Oncol Clin N Am*. (2005) 14(2):381–96. doi: 10.1016/j.soc.2004.11.010

10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. (2009) 62(10):1006–12. doi: 10.1016/j.jclinepi.2009.06.005

11. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (2013). Avaiable from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

12. Li X, Zhang Y, Wan S, Li H, Li D, Xia J, et al. A comparative study between limb-salvage and amputation for treating osteosarcoma. *J Bone Oncol*. (2016) 5(1):15–21. doi: 10.1016/j.jbo.2016.01.001

13. He X, Gao Z, Xu H, Zhang Z, Fu P. A meta-analysis of randomized control trials of surgical methods with osteosarcoma outcomes. *J Orthop Surg Res*. (2017) 12(1):5. doi: 10.1186/s13018-016-0500-0

14. Mat Saad AZ, Halim AS, Faisham WI, Azman WS, Zulmi W. Soft tissue reconstruction following hemipelvectomy: eight-year experience and literature review. *Sci World J*. (2012) 2012:702904. doi: 10.1100/2012/702904

15. Hudson M, Jaffe MR, Jaffe N, Ayala A, Raymond AK, Carrasco H, et al. Pediatric osteosarcoma: therapeutic strategies, results, and prognostic factors derived from a 10-year experience. *J Clin Oncol*. (1990) 8(12):1988–97. doi: 10.1200/JCO.1990.8.12.1988

16. Sherman CE, O'Connor MI, Sim FH. Survival, local recurrence, and function after pelvic limb salvage at 23 to 38 years of followup. *Clin Orthop Relat Res*. (2012) 470(3):712–27. doi: 10.1007/s11999-011-1968-x

17. Han I, Lee YM, Cho HS, Oh JH, Lee SH, Kim HS. Outcome after surgical treatment of pelvic sarcomas. *Clin Orthop Surg*. (2010) 2(3):160–6. doi: 10.4055/cios.2010.2.3.160

18. Pant R, Moreau P, Ilyas I, Paramasivan ON, Younge D. Pelvic limb-salvage surgery for malignant tumors. *Int Orthop*. (2001) 24(6):311–5. doi: 10.1007/s002640000197

19. Umer M, Ali M, Rashid RH, Mohib Y, Rashid HU. Outcomes of internal hemipelvectomy for pelvic tumors: a developing country's prospective. *Int J Surg Oncol (N Y)*. (2017) 2(4):e07. doi: 10.1097/IJ9.0000000000000007

20. Ng VY, Jones R, Bompadre V, Louie P, Punt S, Conrad EU 3rd. The effect of surgery with radiation on pelvic Ewing sarcoma survival. *J Surg Oncol*. (2015) 112(8):861–5. doi: https://doi.org/10.1002/jso.24081

21. Hillmann A, Hoffmann C, Gosheger G, Rödl R, Winkelmann W, Ozaki T. Tumors of the pelvis: complications after reconstruction. *Arch Orthop Trauma Surg*. (2003) 123(7):340–4. doi: 10.1007/s00402-003-0543-7

22. Porsch M, Kornhuber B, Hovy L. Functional results after partial pelvic resection in Ewing's sarcoma of the ilium. *Arch Orthop Trauma Surg*. (1999) 119(3–4):199–204. doi: 10.1007/s004020050390

23. Shin KH, Rougraff BT, Simon MA. Oncologic outcomes of primary bone sarcomas of the pelvis. *Clin Orthop Relat Res*. (1994) 304:207–17. PMID: 8020218

24. Ozaki T, Hoffmann C, Hillmann A, Gosheger G, Lindner N, Winkelmann W. Implantation of hemipelvic prosthesis after resection of sarcoma. *Clin Orthop Relat Res*. (2002) 396:197–205. doi: 10.1097/00003086-200203000-00030

25. Apffelstaedt JP, Driscoll DL, Spellman JE, Velez AF, Gibbs JP, Karakousis CP. Complications and outcome of external hemipelvectomy in the management of pelvic tumors. *Ann Surg Oncol*. (1996) 3(3):304–9. doi: https://doi.org/10.1007/BF02306287

26. Beck LA, Einertson MJ, Winemiller MH, DePompolo RW, Hoppe KM, Sim FF. Functional outcomes and quality of life after tumor-related hemipelvectomy. *Phys Ther*. (2008) 88(8):916–27. doi: https://doi.org/10.2522/ptj.20070184

27. Guder WK, Gosheger G, Henrichs MP, Nottrott M, Streitbürger A. Analysis of surgical and oncological outcome in internal and external hemipelvectomy in 34 patients above the age of 65 years at a mean follow-up of 56 months. *BMC Musculoskelet Disord*. (2015) 16:33. doi: 10.1186/s12891-015-0494-5

28. Ham SJ, Schraffordt Koops H, Veth RP, van Horn JR, Eisma WH, Hoekstra HJ. External and internal hemipelvectomy for sarcomas of the pelvic girdle: consequences of limb-salvage treatment. *Eur J Surg Oncol*. (1997) 23(6):540–6. doi: 10.1016/S0748-7983(97)93173-5

29. Penna V, Toller EA, Pinheiro CA, Becker RG. Hemipelvectomies: treatment, functional outcome and prognostic of the pelvic tumors. *Acta Ortop Bras*. (2010) 19:328–32. doi: 10.1590/S1413-78522011000600001

30. Freitas RR, Crivellaro AL, Mello GJ, Neto MA, Filho Gde F, Silva LV. Hemipelvectomy: Erasto Gaertner Hospital's experiences with 32 cases in 10 years. *Rev Bras Ortop*. (2010) 45(4):413–9. doi: 10.1590/S0102-36162010000400013

31. Asavamongkolkul A, Pimolsanti R, Waikakul S, Kiatsevee P. Periacetabular limb salvage for malignant bone tumours. *J Orthop Surg (Hong Kong)*. (2005) 13(3):273–9. doi: 10.1177/230949900501300310

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 18 October 2022
DOI 10.3389/fonc.2022.985281

OPEN ACCESS

EDITED BY
Mohamed Rahouma,
Weill Cornell Medical Center,
NewYork-Presbyterian, United States

REVIEWED BY
Vishal G. Shelat,
Tan Tock Seng Hospital, Singapore
Jinze Li,
Sichuan University, China
Massimo Baudo,
Spedali Civili Brescia, Italy

*CORRESPONDENCE
Kuo Liang
liangkuo611@xwh.ccmu.edu.cn

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 03 July 2022
ACCEPTED 29 September 2022
PUBLISHED 18 October 2022

CITATION
Wang Z, Li S, Jia Y, Liu M, Yang K, Sui M, Liu D and Liang K (2022) Clinical prognosis of intraoperative blood salvage autotransfusion in liver transplantation for hepatocellular carcinoma: A systematic review and meta-analysis.
Front. Oncol. 12:985281.
doi: 10.3389/fonc.2022.985281

Clinical prognosis of intraoperative blood salvage autotransfusion in liver transplantation for hepatocellular carcinoma: A systematic review and meta-analysis

Zheng Wang[1], Saixin Li[1], Yitong Jia[2], Miao Liu[2], Kun Yang[3], Minghao Sui[1], Dongbin Liu[1] and Kuo Liang[1]*

[1]Department of General Surgery, Xuanwu Hospital, Capital Medical University, Beijing, China, [2]Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China, [3]Department of Evidence-Based Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China

Background: Intraoperative blood salvage autotransfusion(IBSA) has been widely used in a variety of surgeries, but the use of IBSA in hepatocellular carcinoma (HCC) patients undergoing liver transplantation (LT) is controversial. Numerous studies have reported that IBSA used during LT for HCC is not associated with adverse oncologic outcomes. This systematic review and meta-analysis aims to estimate the clinical prognosis of IBSA for patients with H+CC undergoing LT.

Methods: MEDLINE, Embase, Web of Science, and Cochrane Library were searched for articles describing IBSA in HCC patients undergoing LT from the date of inception until May 1, 2022, and a meta-analysis was performed. Study heterogeneity was assessed by I^2 test. Publication bias was evaluated by funnel plots, Egger's and Begg's test.

Results: 12 studies enrolling a total of 2253 cases (1374 IBSA and 879 non-IBSA cases) are included in this meta-analysis. The recurrence rate(RR) at 5-year (OR=0.75; 95%CI, 0.59-0.95; P=0.02) and 7-year(OR=0.65; 95%CI, 0.55-0.97; P=0.03) in the IBSA group is slightly lower than non-IBSA group. There are no significant differences in the 1-year RR(OR=0.77; 95% CI, 0.56-1.06; P=0.10), 3-years RR (OR=0.79; 95% CI, 0.62-1.01; P=0.06),1-year overall survival outcome (OS) (OR=0.90; 95% CI, 0.63-1.28; P=0.57), 3-year OS(OR=1.16; 95% CI, 0.83-1.62; P=0.38), 5-year OS(OR=1.04; 95% CI, 0.76-1.40; P=0.82),1-year disease-free survival rate(DFS) (OR=0.80; 95%CI, 0.49-1.30; P=0.36), 3-year DFS (OR=0.99; 95%CI, 0.64-1.55; P=0.98), and 5-year DFS(OR=0.88; 95%CI, 0.60-1.28; P=0.50). Subgroup analysis shows a difference in the use of

leukocyte depletion filters group of 5-year RR(OR=0.73; 95%CI, 0.55-0.96; P=0.03). No significant differences are found in other subgroups.

Conclusions: IBSA provides comparable survival outcomes relative to allogeneic blood transfusion and does not increase the tumor recurrence for HCC patients after LT.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42022295479.

KEYWORDS

hepatocellular carcinoma, intraoperative blood salvage autotransfusion, liver transplantation, leukocyte depletion filters, treatment outcome, meta-analysis.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancers, the sixth most common neoplasm, and the third most common cause of cancer death (1). Liver transplantation(LT) is the most curative treatment for HCC on cirrhosis in the absence of metastases and macroscopic vascular invasion, as it effectively treats both the tumor burden and the underlying liver disease. Milan criteria established LT as a valid treatment option for HCC patients with cirrhosis (2, 3). However, elevated portal pressure, increased collateral circulation and the hyperdynamic, dilated, thin-walled splanchnic circulation all contribute to an increased risk of hemorrhage during the LT which are distinct causes of bleeding that are different from those in other surgeries (4). Intraoperative hemorrhage has been recognized as a mortality risk, necessitating massive blood transfusions during LT (5).

Blood transfusion could be divided into autotransfusion and allogenic blood transfusion (ABT) based on the blood source. Three types of autologous transfusion exist: prestored autotransfusion, dilution autotransfusion, and intraoperative blood salvage autotransfusion(IBSA). ABT is the primary technique employed in conventional application, but it may transmit hepatitis virus and human immunodeficiency virus, as well as cause an immunological transfusion reaction (6, 7). Noninfectious risks are also well known, such as transfusion-associated circulatory overload and acute lung injury. In particular, ABT may impair the immune function of tumor patients (8), which could increase the risk of postoperative infections, lengthen hospital stays, and, in severe circumstances, even result in death (9). With the rising demand for clinical blood, the shortage of blood supply and the underlying risk of transfusion of banked blood, autologous blood transfusion is becoming more common in clinics to avoid or reduce the risks associated with ABT (10, 11).

The use of IBSA in HCC patients involving LT is controversial, the critical point is whether IBSA increases the risk of recurrence or metastasis due to reperfusion of tumor cells (12, 13). Even though this hypothesis is unwarranted, it still limits the utilization of IBSA. Foltys et al. have demonstrated IBSA does not modify the risk of HCC recurrence, the use of IBSA appears to be justified in highly selected HCC patients undergoing LT (14), and the European Society of Anesthesiology does not contraindicate its use in cancer patients (15), but there is still no consensus on its usage in patients undergoing LT for HCC (16). Since the published results were largely based on a retrospective analysis of cases from a single center, and randomized controlled trials (RCTs) are difficult to conduct in this setting, we conduct this meta-analysis to fully estimate the clinical prognosis of IBSA for patients with HCC undergoing LT which may be helpful in elucidating the issue.

Methods

This systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary Table 1) and has been registered with the International Prospective Register of Systematic Review (PROSPERO) database (registration number CRD42022295479) (17). This systematic review is conducted using the methodological guidance in the Cochrane Handbook for Systematic Reviews of Interventions (18). Any modifications to this protocol made over the

Abbreviations: ABT, allogenic blood transfusion; CI, confidence interval; DFS, disease-free survival rate; HCC, hepatocellular carcinoma; IBSA, intraoperative blood salvage autotransfusion; LDFs, leukocyte depletion filters; LT, liver transplantation; OR, odds ratio; OS, overall survival outcome; PROSPERO, International Prospective Register of Systematic Review; RCTs, randomized controlled trials; RR, the recurrence rate.

course of the study will be reported in PROSPERO and the final manuscript.

Study identification and selection

The search strategies were created by an investigator (KY) with database search experience. We conducted database searches in the following databases: Medline (via PubMed), Web of Science databases, EMBASE and The Cochrane Library. Databases were used to identify suitable studies that were published up to 1 May 2022. Three search themes were combined with the Boolean operator 'and' in searching databases, and the search terms were as follows: 'Autotransfusion', 'Liver Transplantation' and 'Hepatocellular Carcinoma'. Detailed search strategy was shown in Supplementary Methods. Only English-language publications with human subjects were included in the searches. The following inclusion criteria were used: (a) a study that investigated the clinical prognosis during LT for HCC patients; (b) randomized clinical trial, high-quality case–control study, cohort study; (c) adults (over the age of 18). The exclusion criteria were as follows: (a) comments, case reports, and letters to the editors; (b) duplicate reports; (c) systematic reviews or meta-analyses. Two reviewers(YJ and SL) independently screened the articles according to the inclusion criteria. In case of discrepancies, consistencies will be ensured by a third reviewer(ZW). If several studies present data from the same study population, or multiple publications from the same research series are published in chronological sequence, the study with the most direct interventions or the largest sample size was kept.

Data extraction and quality assessment

The following parameters were extracted from the full-text article: the name of the first author, periodical titles, country, publication year, type of study, characteristics of IBSA group and non-IBSA group (eg, age, sex, follow-up years, sample size, overall survival outcome, disease-free survival outcome, recurrence rate and any adverse events caused by the preventive interventions). Two reviewers(YJ and DL) extracted data from studies in accordance with the screening process, and any inconsistencies were resolved by a third reviewer(SL). In case of any ambiguity or insufficient information, wherever possible, authors of primary studies were contacted by either telephone, email or post to obtain missing data. We made a summary sheet containing all the data fore-mentioned. On the other hand, we assessed the quality of published literature by two independent reviewers (ZW and YJ). The risk of bias of RCTs was assessed with items in the Cochrane Collaboration's tool (19). Non-RCTs (observational cohort and case-control studies) were assessed with the Newcastle-Ottawa Scale (20). Studies were classified as poor quality if their quality scores fell below 7, which was the threshold for high quality studies.

Outcome measures

The primary outcome of this meta-analysis is the tumor-related recurrence rate of use IBSA during LT for HCC. The recurrence time points will be 1-year, 3-year, 5-year and 7-year after LT. Radiological data was used to determine whether HCC had recurred (21). Other survival outcomes, such as the overall survival and the disease-free survival, if available, would also be analyzed and reported.

Statistical analysis

Meta-analyses were conducted when appropriate using Review Manager 5.4 and STATA 16.0 statistical software. For each outcome, odds ratio (OR) and corresponding 95% confidence intervals(CI) were used to measure the association for each study. We will apply mathematical operations to convert data that is presented in the literature as median and quartiles into mean and standard deviation format (22). Forest plots will be used to visualize pooled estimates and the extent of heterogeneity among studies. The I^2 statistic were used to assess statistical heterogeneity among the included studies (I^2 values of <40%, 40%–60%, 50%-90%, and 75%-100% represent mild, moderate, substantial and considerable heterogeneity, respectively) (23). $I^2 > 50\%$ will be considered as having a substantial heterogeneity, the random-effects model (the DerSimonian and Laird method) will be used to analyze the outcomes, otherwise, a fixed-effect model(the Mantei-Haenszle method) would be applied. The sources of heterogeneity will be explored by using sensitivity analyses. A subgroup analysis will be conducted to determine whether the results differed according to the use of leukocyte depletion filters (LDFs). The potential for publication bias will be assessed by the funnel plot, Egger test and Begg's test (24–26).

Results

The database searches returned 123 results, 22 of which were excluded due to duplication. Further, 34 studies were excluded because they were reviews or qualitative study or were not relevant to the topic being studied. The remaining articles were fully read. Finally, 12 studies enrolling a total of 2253 cases (1374 IBSA cases and 879 non-IBSA cases) were included in the meta-analysis (14, 27–37). The process used for article selection is presented in Figure 1.

The selected studies had been published between 2005 and 2022. The sample size of studies ranged from 23 to 397. All of the studies were cohort studies. There were no randomized controlled trials. According to the Newcastle-Ottawa Scale, most (n = 11, 91.67%) of the studies were defined as high-quality studies (score more than 7), the detailed assessments are shown in Supplement Table 2. The baseline characteristics of the included studies are presented in Table 1.

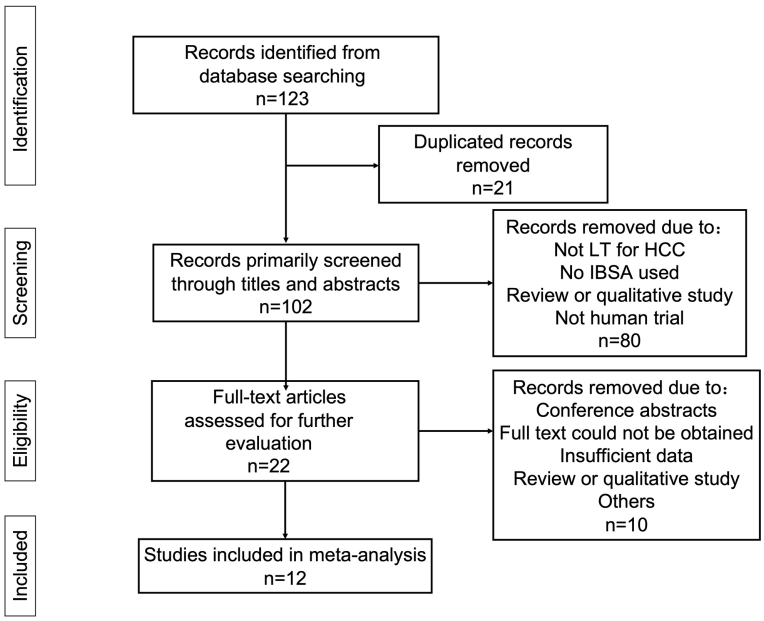

FIGURE 1
Flow diagram of the selection and screening process for eligible studies.

TABLE 1 Characteristics of included studies.

Study	Year	Study type	LDFs used	>Sample size		Age (year, Mean ±SD)		Sex, male		Outcome	NOS score
				IBSA group	Non-IBSA group	IBSA group	Non-IBSA group	IBSA group	Non-IBSA group		
Akbulut (27)	2013	RCS	0	24	59	52.0±1.8	51.0±1.2	22	52	RR,OS,DFS	7
Araujo (28)	2016	RCS	1	122	36	57.9±2.1*	61.8±1.4*	95	27	RR,OS	8
Foltys (14)	2011	RCS	1	40	96	54.9±6.6*	59.8±7.6*	28	74	RR,OS	7
Han (29)	2016	RCS	1	283	114	31.9±11.2	30.7±1.3	197	77	RR	9
Ivanics (30)	2021	RCS	0	76	34	56.0±1.9*	54.7±2.6*	61	30	RR,OS	8
Kim (31)	2012	RCS	1	121	109	52.3±7.1	52.6±7.5	97	86	RR	8
Kwon (32)	2021	RCS	1	220	129	54.0±1.6*	53.0±1.7*	192	121	RR,OS	8
Muscari (33)	2005	RCS	1	31	16	53.0±12.0	58.0±6.0	26	14	RR	7
Nutu (34)	2021	RCS	0	192	186	59.2±7.3	58.4±7.7	NA	NA	RR,OS,DFS	8
Pinto (35)	2021	RCS	0	122	34	59.0±7.0	60.0±6.0	75	20	RR,OS,DFS	7
Sutton (36)	2021	RCS	0	131	55	59.0±1.4*	61.8±1.3*	98	45	RR,OS	7
Weller (37)	2021	RCS	0	12	11	54.8±6.7	58.3±7.4	9	9	RR	6

0, don't use LDFs; 1, use LDFs; DFS, Disease-free survival; IBSA, intraoperative blood salvage autotransfusion; NOS, Newcastle-Ottawa Scale; OS, Overall survival; RR, recurrence rate; RCS, retrospective cohort study; SD, standard deviations.
*Switched to mean ± SD according to the formula of Cochrane handbook.

Primary outcomes: Tumor recurrence

Twelve studies reported the recurrence rate(RR) outcomes of IBSA and non-IBSA patients. Of them, seven studies provided a specified description of criteria for determining the recurrence and follow-up methods (14, 27, 29, 32, 35–37). The meta-analysis data is displayed in Figure 2, the RR at 5-year (OR=0.75; 95%CI, 0.59-0.95; P=0.02) and 7-year(OR=0.65; 95%CI, 0.44-0.95; P=0.03) in the IBSA group was slightly lower than non-IBSA group. There were no significant differences in the 1-, and 3-years RR. The RR at 1-, and 3-year had ORs of 0.77 (95% CI, 0.56-1.06; P=0.10), and 0.79 (95% CI,

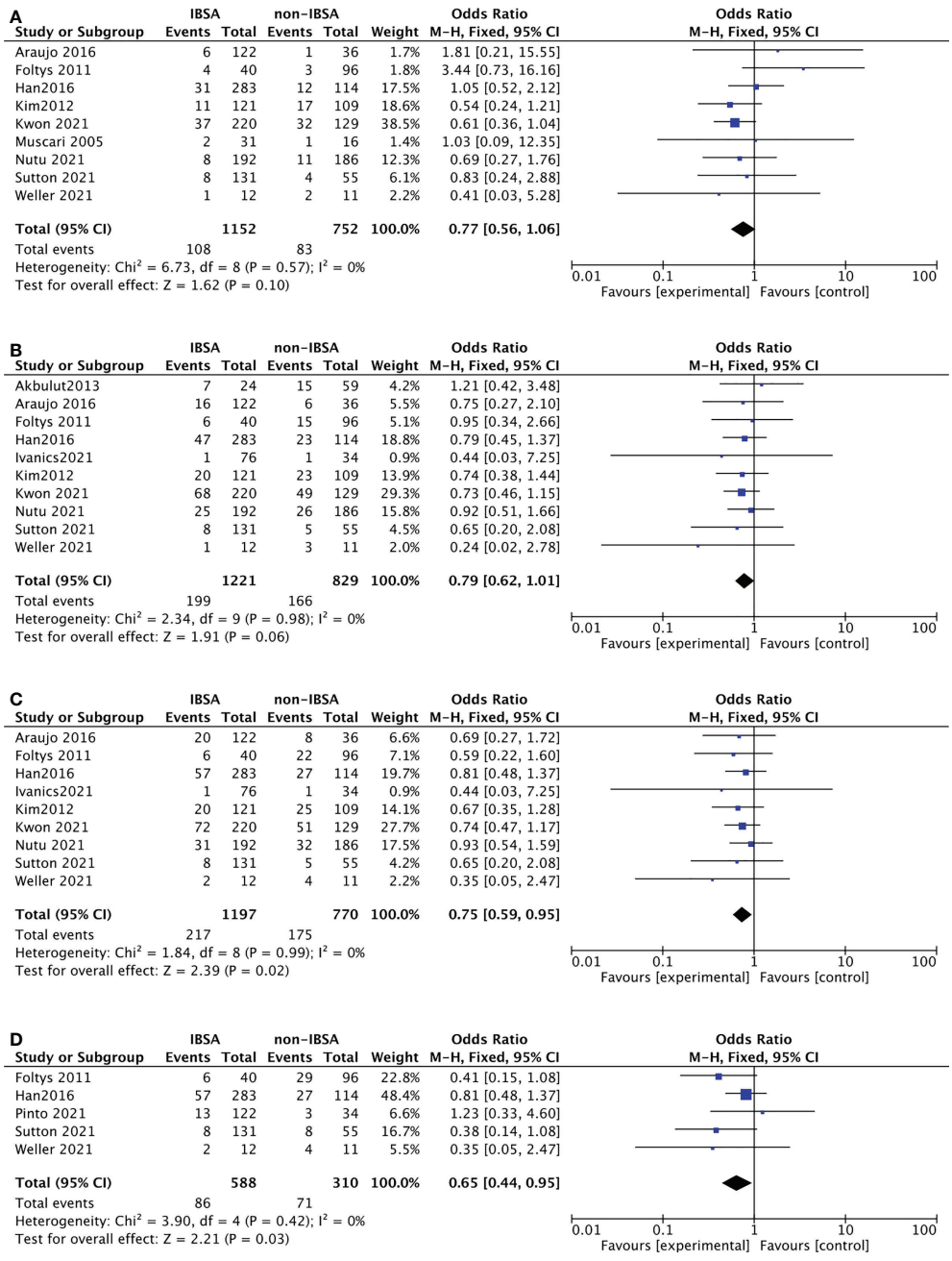

FIGURE 2
Meta-analysis forest plot of the recurrence rate. **(A)**, 1-year RR; **(B)**, 3-year RR; **(C)**, 5-year RR; **(D)**, 7-year RR.

0.62-1.01; P=.06), respectively. No heterogeneity was found in 1-year RR (I^2 = 0%), 3-year RR (I^2 = 0%), 5-year RR (I^2 = 0%), and 7-year RR(I^2 = 0%), the fixed effect model was adopted.

Overall survival and disease-free survival

Eight studies reported the overall survival(OS) outcomes of IBSA and non-IBSA patients (Figure 3). The overall survival outcomes at 1-, 3-, and 5-year were not significantly different. The OS at 1, 3, and 5-year had RRs of 0.90 (95% CI, 0.63-1.28; P=0.57), 1.16 (95% CI, 0.83-1.62; P=0.38), and 1.04 (95% CI, 0.76-1.40; P=0.82). Mild heterogeneity was observed in 1-year OS (I^2 = 0%), 3-year OS (I^2 = 29%), 5-year OS (I^2 = 28%). For all included studies performed in statistics of disease-free survival (DFS), there were no significant differences at 1-year DFS (OR=0.80; 95%CI, 0.49-1.30; P=0.36), 3-year DFS(OR=0.99; 95%CI, 0.64-1.55; P=0.98), 5-year DFS(OR=0.88; 95%CI, 0.60-1.28; P=0.50) (Figure 4). Mild heterogeneity was found in 1-year DFS (I^2 = 0%), 3-year DFS (I^2 = 20%), and 5-year DFS (I^2 = 0%).

Subgroup analysis

A predesigned subgroup analysis was conducted according to the use of LDFs. Six studies attached LDFs to IBSA during LT (14, 28, 29, 31–33). The RR and OS outcomes were evaluated according to the use of LDFs, DFS was not evaluated due to lack of data. We observed a difference in the LDFs-using group of 5-year RR (OR=0.73; 95%CI, 0.55-0.96; P=0.03). No significant differences were found in other subgroups. Pooled ORs are detailed in Figures 5, 6.

Sensitivity analysis

For primary outcomes, pooled effects of ORs remained stable after removing any single study at 1-, 3-, 5-, and 7-year RR. For secondary outcomes, the removal of Kwon's study led to a reduction in heterogeneity at 3-year and 5-year OS (32). Filled pooled effects were adjusted for 3-year OS(OR=0.95; 95%CI,

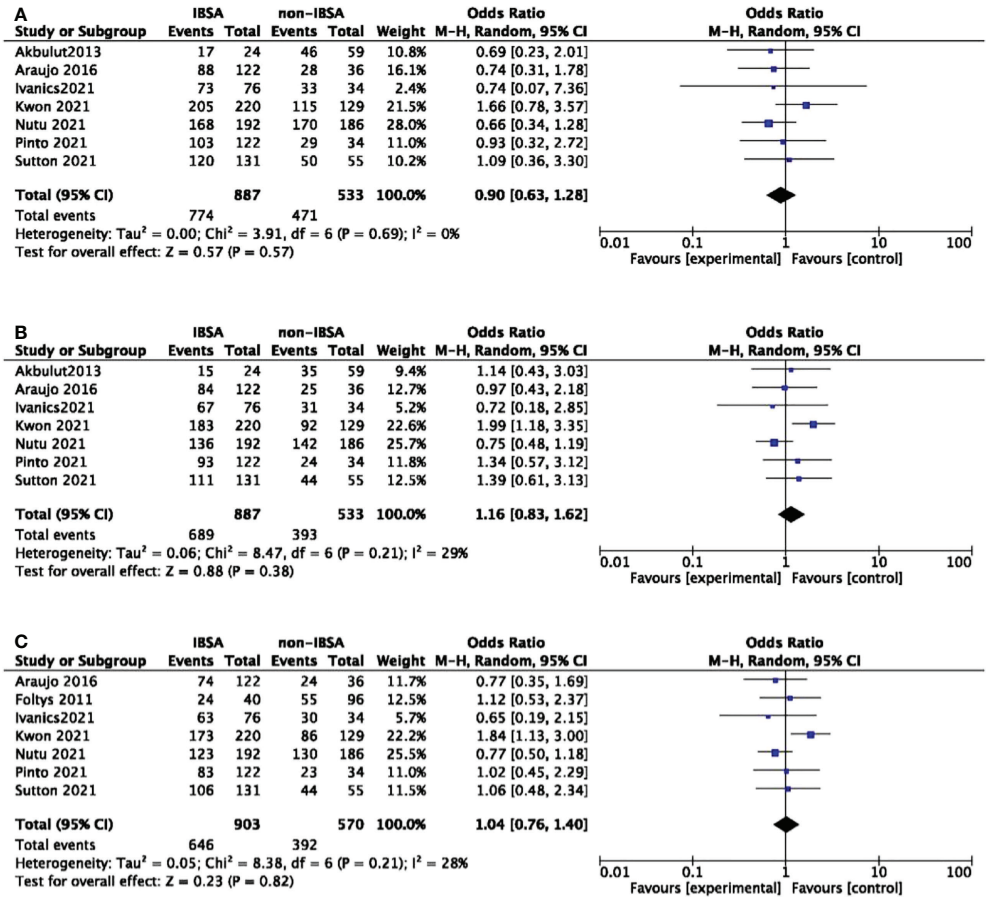

FIGURE 3
Meta-analysis forest plot of the overall survival. **(A)**, 1-year OS; **(B)**, 3-year OS; **(C)**, 5-year OS.

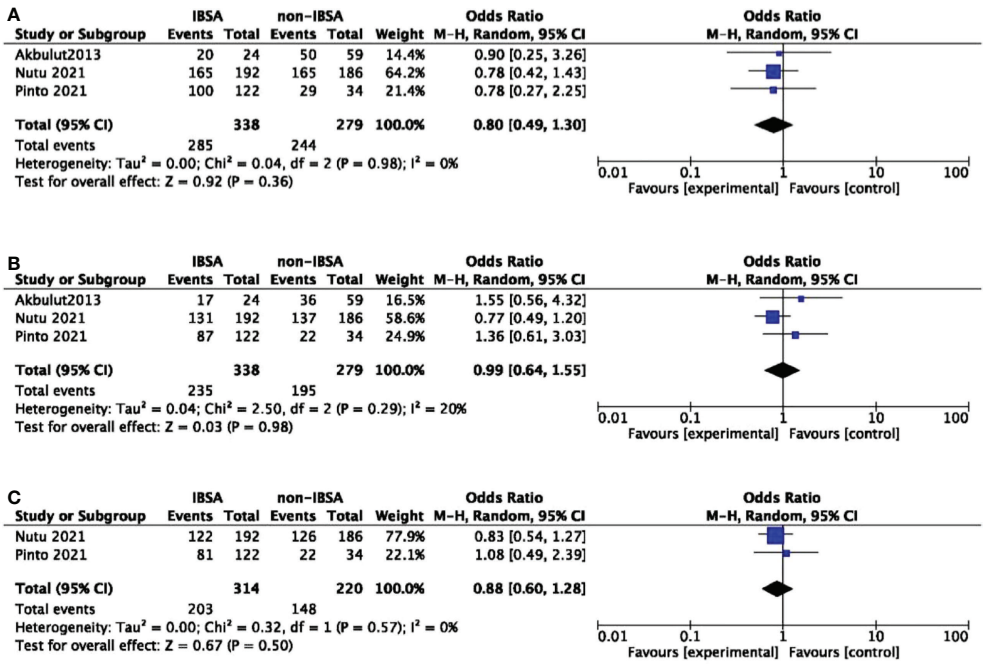

FIGURE 4
Meta-analysis forest plot of the disease-free survival. **(A)**, 1-year DFS; **(B)**, 3-year DFS; **(C)**, 5-year DFS.

0.70-1.29; P=0.73), 5-year OS(OR=0.86; 95%CI, 0.65-1.14; P=0.30), which were consistent with the initial meta-analysis. For 1-year OS, OR did not change much by removing either study (Supplementary Figure 1). Sensitivity analysis was not performed for DFS due to fewer studies.

Publication bias

We used Egger's test and Begg's test to evaluate the publication bias for RR and OS outcomes. No indication of publication bias was observed for 1-year RR (Egger's test, P = 0.158; Begg's test, P = 0.7205), 3-year RR (Egger's test, P = 0.694; Begg's test, P = 0.4743), 5-year RR (Egger's test, P = 0.901; Begg's test, P = 0.0763), and for 1-year OS (Egger's test, P = 0.943; Begg's test, P = 0.8065), 3-year OS (Egger's test, P = 0.943; Begg's test, P = 0.7639), 5-year OS (Egger's test, P = 0.517; Begg's test, P = 0.7639). Funnel plots were visually examined for symmetry for all outcomes reported (Supplementary Figures 2, 3).

Discussion

In this comprehensive systematic review and meta-analysis, we identified 12 cohort studies investigating the clinical prognosis of IBSA during LT for HCC. The recurrence rate was used as the primary outcome, and the overall survival and disease-free survival were used as the secondary outcomes. The analyses showed that the RR at 5- and 7-year in the IBSA group was slightly lower than non-IBSA group. No significant differences were found between the IBSA and non-IBSA groups in the 1-, and 3-year RR outcomes. For secondary outcomes, the OS outcomes at 1-, 3-, and 5-year and the DFS outcomes at 1-, 3-, and 5-year were not significantly different. Sensitivity analysis was carried out to evaluate whether the result is stable and reliable, adjusted effects did not fluctuate much by omitting each study. Given the above, though no randomized studies were included, results of the meta-analysis could be considered relatively solid and trustworthy based on the current studies.

The use of IBSA reduces the requirement for allogeneic blood during surgery, preventing adverse transfusion reactions without having a negative impact on other clinical outcomes. However, oncological surgery is still regarded as a relative contraindication to IBSA over concern of reinfusing tumor cells and thereby causing tumor dissemination (13, 38, 39). The presence of neoplastic cells in blood samples from an autotransfusion system in 1975 established a link between the usage of IBSA and the occurrence of metastasis, although there is no proof that these cells have the capacity to cause recurrence or metastasis (40). In our study, IBSA did not increase the tumor recurrence rate and had comparable survival outcomes with non-IBSA. Based on existing literature, the European Society of Anesthesiology does not contraindicate the use of IBSA in

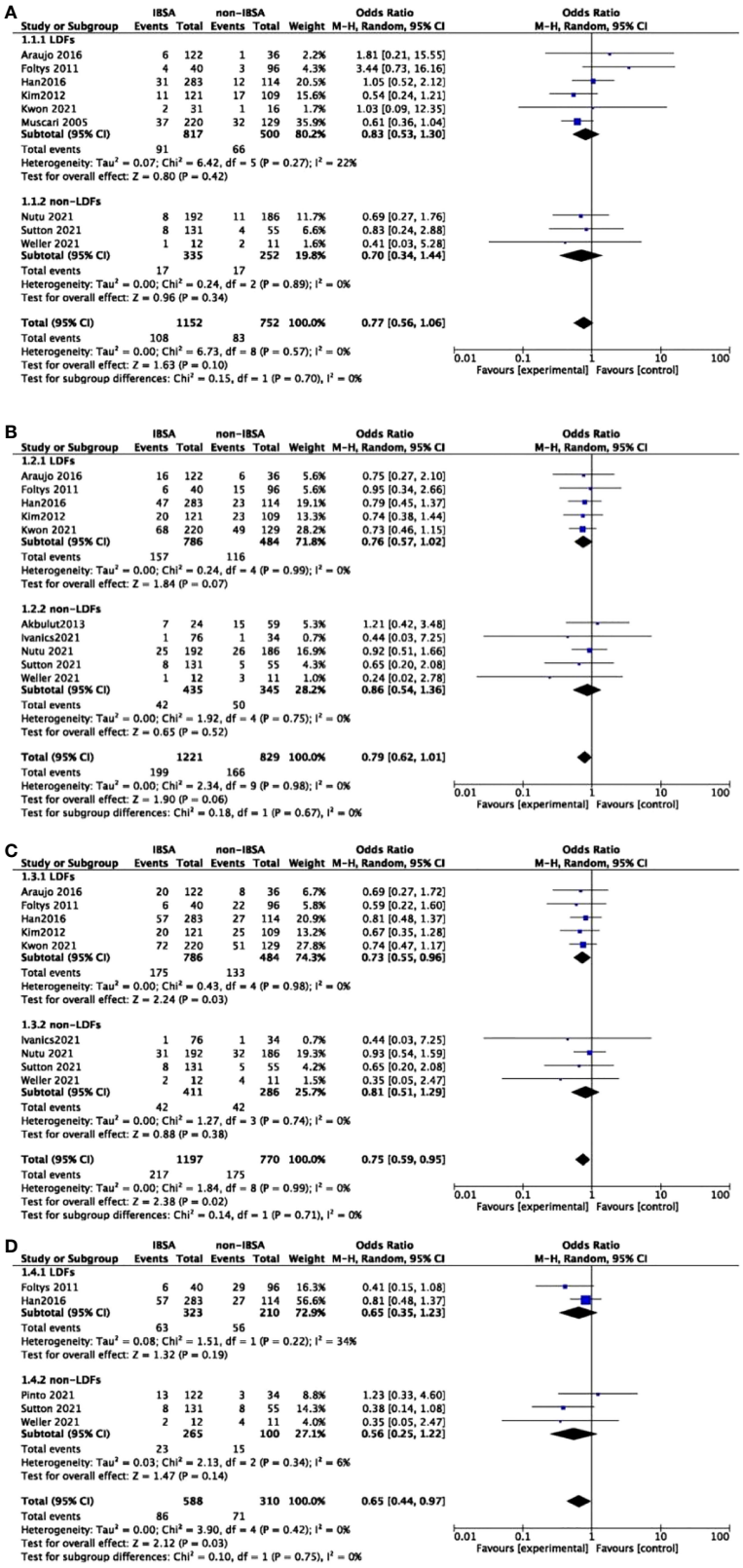

FIGURE 5
Meta-analysis forest plot of subgroup analysis of the recurrence rate. **(A)**, 1-year RR; **(B)**, 3-year RR; **(C)**, 5-year RR; **(D)**, 7-year RR.

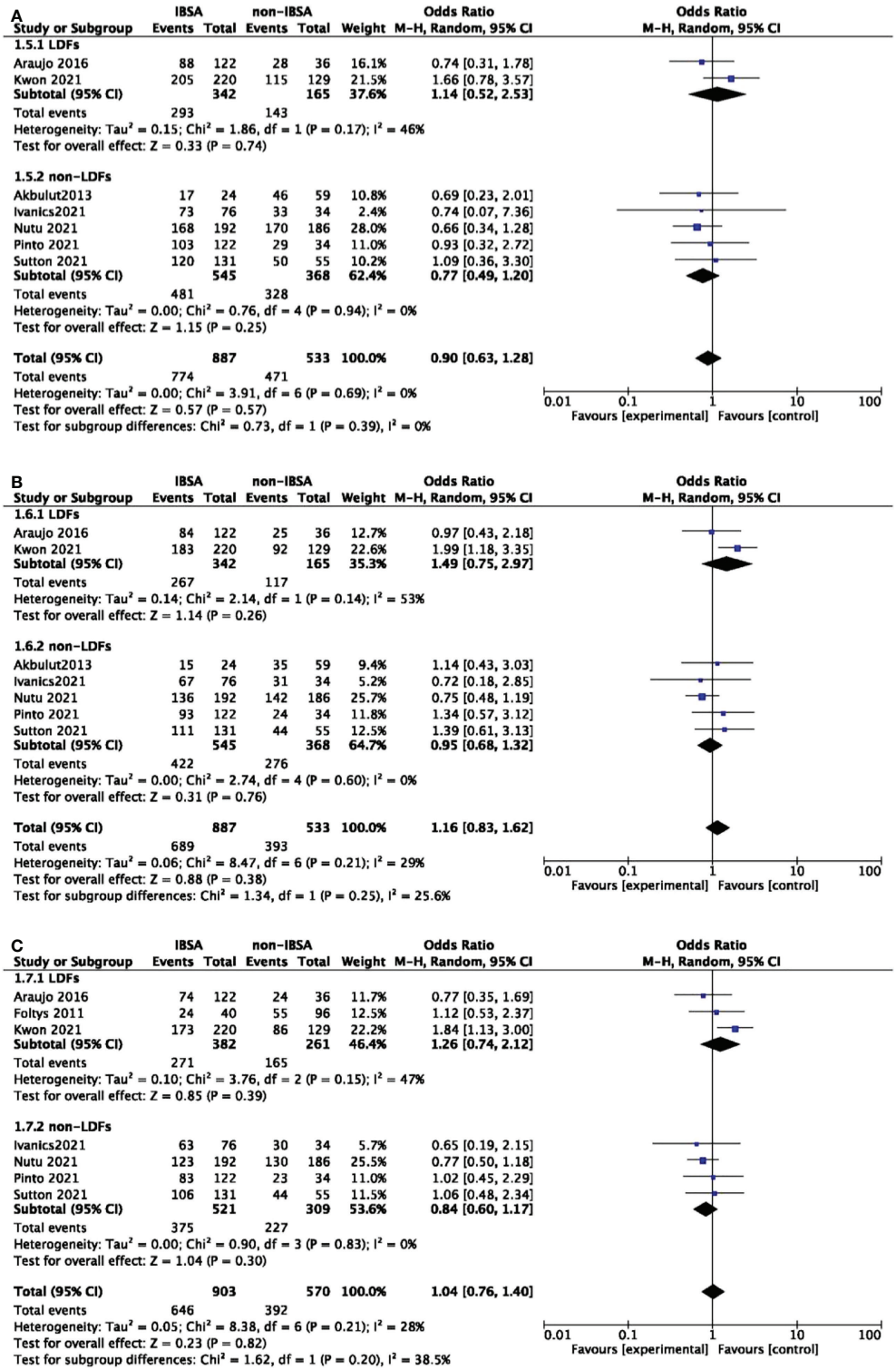

FIGURE 6
Meta-analysis forest plot of subgroup analysis of the overall survival. **(A)**, 1-year OS; **(B)**, 3-year OS; **(C)**, 5-year OS.

patients with cancer (15). Furthermore, a rencent study has demonstrated the effectiveness of IBSA in reducing the need for ABT for LT (41). A sizable prospective analysis that was conducted confirmed the cost effectiveness of IBSA. With the use of autologous transfusion over the study period, a cost saving of $188618 United States dollars was achieved (42). In a multicenter research encompassing more than 33000 individuals, the risk of side effects associated with the usage of IBSA was estimated to range from 0% to 0.006% (11). Even though we need more evidence with large-sample size randomized control studies, those studies suggest that we should reduce the use of ABT.

Subgroup analysis was performed to determine whether results were differed due to the use of LDFs. LDFs were added to IBSA in the 1990s to increase the safety of the procedure (43). But it is still debatable whether LDFs completely decrease the risk of tumor cell metastasis. Several reports have demonstrated that LDFs are effective at eliminating tumor cells *in vitro* and vivo studies (39, 44, 45). However, there have been few reports using HCC cells. Unless there were large cell loads, according to Gwak's experimental results, LDF could filter HCC cells *in vitro* (46). And LDFs incorporated into cell salvage circuits have shown to effectively remove malignant cells when used during LT of patients with nonruptured hepatocellular tumors (16). Those studies support the hypothesis that tumor cells could be efficiently removed during collection, processing, and leukocyte filtration.

Six studies included in this meta-analysis attached LDFs to IBSA, in the subgroup analysis, IBSA-group has a low 5-year RR than non-IBSA group with the use of LDFs. This might be as a result of ABT's effect on immune function of patients with tumors. Besides 5-year RR outcome, non-LDFs-using group had similar results as the LDFs group. The above studies are insufficient to explain the adverse effects of the presence of tumor cells on clinical prognosis and to demonstrate negative effects associated with the use of IBSA. Some organizations, including the National Institute of Clinical Excellence, the Association of Anaesthetists of Great Britain and Ireland and the American College of Obstetricians and Gynecologists have developed guidelines to support the use of IBSA or in combination with LDFs in cancer surgery (14, 47–49). The findings in this study imply that using LDFs in combination may be a preferable way.

To our knowledge, a meta-analysis included eleven studies suggests that cancer recurrence after the use of IBSA is not inferior to traditional intraoperative allogeneic transfusion, with an odds ratio of 0.65 (95% CI, 0.43-0.98; P = 0.0391). But the included studies of this meta-analysis ranged from different cancer types, only three studies involved patients with hepatocellular carcinoma (50). In addition, another meta-analysis included 9 studies demonstrated that IBSA did not increase the tumor recurrence rate and had comparable survival outcomes with ABT. In the subgroup analysis of five studies for liver cancer surgery, IBSA did not increase the mortality risk with long-term follow-up for patients with hepatocellular carcinoma (51). The results presented above are approximately consistent with those of this meta-analysis, indicating that IBSA is not inferior to ABT and may even be better than ABT. In comparison, this review included 12 studies and provided the first comprehensive meta-analysis of effect of IBSA on clinical prognosis after LT for HCC, due to the lack of data, this analysis mainly focused on the clinical prognosis of IBSA. Predesigned subgroup analyses were conducted to evaluate whether the results were different with the use of LDFs. Multiple methods were adopted for sensitivity analyses, funnel plot and Egger regression test were used to estimate publication bias, which demonstrated the validity and robustness of the meta-analysis.

Several limitations of our study should be mentioned. First, the included studies were retrospective research and selection bias should not be ignored, since no RCT research on this question has been found after searching the databases. Well-designed, randomized, controlled, prospective trials are urgently required to clarify the existing concerns. Second, we only included English language studies due to the constraints of translating foreign language studies. Third, the included studies did not explore the use of allogeneic blood products, which may affect survival outcomes and prognosis due to their impact on immunity. Moreover, although significant heterogeneity was not found, patients' characteristics varied across included studies. Only part of included studies use a propensity score to control for the effect of confounding and address selection bias, more detailed subgroup analyses were difficult to conduct, because of multiple outcomes and insufficient studies.

Conclusion

These 12 studies represent the best reliable evidence to date. This meta-analysis may at least indicate that intraoperative blood salvage autotransfusion provided comparable survival outcomes relative to allogeneic blood transfusion and did not increase the tumor recurrence for hepatocellular carcinoma patients after liver transplantation. A reappraisal of the appropriate strategy for blood management during liver transplantation is warranted. High quality researches are required in the future to provide more sufficient evidence.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

ZW developed the initial idea for this study. SL and KY developed and revised the search strategy. MS and ML finished the study design. KY and KL carried out data extraction and assessment of risk of bias. ZW, SL and YJ contributed to the original draft. DL and KL and were responsible for the revision of the draft. All of the authors approved the final work prior to submission ZW, SL and YJ have contributed equally to this work. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank all the authors of the original studies included in this meta-analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.985281/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Meta-analysis forest plot of the overall survival after sensitivity analysis. **(A)**, 1-year OS; **(B)**, 3-year OS; **(C)**, 5-year OS.

SUPPLEMENTARY FIGURE 2
Funnel plot of publication bias test for RR outcomes. Upper left, 1-year RR; Upper right, 3-year RR; Lower left, 5-year RR; Lower right, 7-year RR.

SUPPLEMENTARY FIGURE 3
Funnel plot of publication bias test for OS outcomes. Left, 1-year OS; Middle, 3-year OS; Right, 5-year OS.

References

1. Sugawara Y, Hibi T. Surgical treatment of hepatocellular carcinoma. *Biosci Trends* (2021) 15(3):138–41. doi: 10.5582/bst.2021.01094

2. European Association For The Study Of The Liver and European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* (2012) 56 (4):908–43. doi: 10.1016/j.jhep.2011.12.001

3. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* (2004) 127:S261–7. doi: 10.1053/j.gastro.2004.09.040

4. Cleland S, Corredor C, Ye JJ, Srinivas C, McCluskey SA. Massive haemorrhage in liver transplantation: Consequences, prediction and management. *World J Transplant* (2016) 6(2):291–305. doi: 10.5500/wjt.v6.i2.291

5. Feltracco P, Brezzi M, Barbieri S, Galligioni H, Milevoj M, Carollo C, et al. Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. *World J Hepatol* (2013) 5(1):1–15. doi: 10.4254/wjh.v5.i1.1

6. Liu L, Wang Z, Jiang S, Shao B, Liu J, Zhang S, et al. Perioperative allogenenic blood transfusion is associated with worse clinical outcomes for hepatocellular carcinoma: a meta-analysis. *PloS One* (2013) 8(5):e64261. doi: 10.1371/journal.pone.0064261

7. Feltracco P, Michieletto E, Barbieri S, Serra E, Rizzi S, Salvaterra F, et al. Microbiologic contamination of intraoperative blood salvaged during liver transplantation. *Transplant Proc* (2007) 39(6):1889–91. doi: 10.1016/j.transproceed.2007.05.005

8. Gong Y, Tang Y, Xue Y, Chen L. Impact of intraoperative allogenic and autologous transfusion on immune function and prognosis in patients with hepatocellular carcinoma. *Med (Baltimore)* (2020) 99(41):e22568. doi: 10.1097/MD.0000000000022568

9. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma* (2003) 54(5):908–14. doi: 10.1097/01.TA.0000022460.21283.53

10. Elmalky M, Yasin N, Rodrigues-Pinto R, Stephenson J, Carroll C, Smurthwaite G, et al. The safety, efficacy, and cost-effectiveness of intraoperative cell salvage in metastatic spine tumor surgery. *Spine J* (2017) 17(7):977–82. doi: 10.1016/j.spinee.2017.03.004

11. DeAndrade D, Waters JH, Triulzi DJ, Alarcon L, Wisniewski MK, Dyga R, et al. Very low rate of patient-related adverse events associated with the use of intraoperative cell salvage. *Transfusion* (2016) 56(11):2768–72. doi: 10.1111/trf.13791

12. Fahrner R, Dondorf F, Ardelt M, Dittmar Y, Settmacher U, Rauchfuß F. Liver transplantation for hepatocellular carcinoma - factors influencing outcome and disease-free survival. *World J Gastroenterol* (2015) 21(42):12071–82. doi: 10.3748/wjg.v21.i42.12071

13. Trudeau JD, Waters T, Chipperfield K. Should intraoperative cell-salvaged blood be used in patients with suspected or known malignancy? *Can J Anaesth* (2012) 59(11):1058–70. doi: 10.1007/s12630-012-9781-x

14. Foltys D, Zimmermann T, Heise M, Kaths M, Lautem A, Wisser G, et al. Liver transplantation for hepatocellular carcinoma–is there a risk of recurrence caused by intraoperative blood salvage autotransfusion? *Eur Surg Res* (2011) 47 (3):182–7. doi: 10.1159/000330746

15. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European society of anaesthesiology: First update 2016. *Eur J Anaesthesiol* (2017) 34(6):332–95. doi: 10.1097/EJA.0000000000000630

16. Pinto MA, Chedid MF, Sekine L, Schmidt AP, Capra RP, Prediger C, et al. Intraoperative cell salvage with autologous transfusion in liver transplantation. *World J Gastrointest Surg* (2019) 11(1):11–8. doi: 10.4240/wjgs.v11.i1.11

17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* (2021) 10(1):89. doi: 10.1186/s13643-021-01626-4

18. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* (2019) 10:ED000142. doi: 10.1002/14651858.ED000142

19. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* (2011) 343:d5928. doi: 10.1136/bmj.d5928

20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z

21. Bruix J, Sherman MAmerican Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* (2011) 53 (3):1020–2. doi: 10.1002/hep.24199

22. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* (2014) 14:135. doi: 10.1186/1471-2288-14-135

23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* (2002) 21(11):1539–58. doi: 10.1002/sim.1186

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629

25. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* (2011) 343:d4002. doi: 10.1136/bmj.d4002

26. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. the CONSORT statement. *JAMA* (1996) 276(8):637–9. doi: 10.1001/jama.276.8.637

27. Akbulut S, Kayaalp C, Yilmaz M, Ince V, Ozgor D, Karabulut K, et al. Effect of autotransfusion system on tumor recurrence and survival in hepatocellular carcinoma patients. *World J Gastroenterol* (2013) 19(10):1625–31. doi: 10.3748/wjg.v19.i10.1625

28. Araujo RL, Pantanali CA, Haddad L, Rocha Filho JA, D'Albuquerque LA, Andraus W. Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence? *World J Gastrointest Surg* (2016) 8(2):161–8. doi: 10.4240/wjgs.v8.i2.161

29. Han S, Kim G, Ko JS, Sinn DH, Yang JD, Joh JW, et al. Safety of the use of blood salvage and autotransfusion during liver transplantation for hepatocellular carcinoma. *Ann Surg* (2016) 264(2):339–43. doi: 10.1097/SLA.0000000000001486

30. Ivanics T, Shubert CR, Muaddi H, Claasen MPAW, Yoon P, Hansen BE, et al. Blood cell salvage and autotransfusion does not worsen oncologic outcomes following liver transplantation with incidental hepatocellular carcinoma: A propensity score-matched analysis. *Ann Surg Oncol* (2021) 28(11):6816–25. doi: 10.1245/s10434-021-09863-6

31. Kim JM, Kim GS, Joh JW, Suh KS, Park JB, Ko JS, et al. Long-term results for living donor liver transplant recipients with hepatocellular carcinoma using intraoperative blood salvage with leukocyte depletion filter. *Transpl Int* (2013) 26 (1):84–9. doi: 10.1111/tri.12001

32. Kwon JH, Han S, Kim D, Kuk JH, Cho H, Kim S, et al. Blood salvage and autotransfusion does not increase the risk of tumor recurrence after liver transplantation for advanced hepatocellular carcinoma. *Ann Surg* (2021). doi: 10.1097/SLA.0000000000004866

33. Muscari F, Suc B, Vigouroux D, Duffas JP, Miqueres I, Mathieu A, et al. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int* (2005) 18(11):1236–9. doi: 10.1111/j.1432-2277.2005.00207.x

34. Nutu OA, Sneiders D, Mirza D, Isaac J, Perera MTPR, Hartog H. Safety of intra-operative blood salvage during liver transplantation in patients with hepatocellular carcinoma, a propensity score-matched survival analysis. *Transpl Int* (2021) 34(12):2887–94. doi: 10.1111/tri.14150

35. Pinto MA, Grezzana-Filho TJM, Chedid AD, Leipnitz I, Prediger JE, Alvares-da-Silva MR, et al. Impact of intraoperative blood salvage and autologous transfusion during liver transplantation for hepatocellular carcinoma. *Langenbecks Arch Surg* (2021) 406(1):67–74. doi: 10.1007/s00423-020-01997-7

36. Sutton TL, Pasko J, Kelly G, Maynard E, Connelly C, Orloff S, et al. Intraoperative autologous transfusion and oncologic outcomes in liver transplantation for hepatocellular carcinoma: a propensity matched analysis. *HPB (Oxford)* (2022) 24(3):379–85. doi: 10.1016/j.hpb.2021.06.433

37. Weller A, Seyfried T, Ahrens N, Baier-Kleinhenz L, Schlitt H, Peschel G, et al. Cell salvage during liver transplantation for hepatocellular carcinoma: A retrospective analysis of tumor recurrence following irradiation of the salvaged blood. *Transplant Proc* (2021) 53(5):1639–44. doi: 10.1016/j.transproceed.2021.03.025

38. Zhai B, Sun XY. Controversy over the use of intraoperative blood salvage autotransfusion during liver transplantation for hepatocellular carcinoma patients. *World J Gastroenterol* (2013) 19(22):3371–4. doi: 10.3748/wjg.v19.i22.3371

39. Hansen E, Bechmann V, Altmeppen J. Intraoperative blood salvage in cancer surgery: safe and effective? *Transfus Apher Sci* (2002) 27(2):153–7. doi: 10.1016/s1473-0502(02)00037-x

40. Yaw PB, Sentany M, Link WJ, Wahle WM, GGlover JL. Tumor cells carried through autotransfusion. contraindication to intraoperative blood recovery? *JAMA* (1975) 231(5):490–1.

41. Massicotte L, Thibeault L, Beaulieu D, Roy JD, Roy A. Evaluation of cell salvage autotransfusion utility during liver transplantation. *HPB (Oxford)* (2007) 9 (1):52–7. doi: 10.1080/13651820601090596

42. Phillips SD, Maguire D, Deshpande R, Muiesan P, Bowles MJ, Rela M, et al. A prospective study investigating the cost effectiveness of intraoperative blood salvage during liver transplantation. *Transplantation* (2006) 81(4):536–40. doi: 10.1097/01.tp.0000199318.17013.c5

43. Edelman MJ, Potter P, Mahaffey KG, Frink R, Leidich RB. The potential for reintroduction of tumor cells during intraoperative blood salvage: reduction of risk with use of the RC-400 leukocyte depletion filter. *Urology* (1996) 47(2):179–81. doi: 10.1016/S0090-4295(99)80411-7

44. Futamura N, Nakanishi H, Hirose H, Nakamura S, Tatematsu M. The effect of storage on the survival of cancer cells in blood and efficient elimination of contaminating cancer cells by a leukocyte depletion filter. *Am Surg* (2005) 71 (7):585–90.

45. Frühauf NR, Dumpich O, Kaudel CP, Kasimir-Bauer S, Oldhafer KJ. Filtration of malignant cells: tumour cell depletion in an ex vivo model using a leukocyte adhesion filter. *Perfusion* (2001) 16 Suppl:51–5. doi: 10.1177/026765910101600i107

46. Gwak MS, Lee KW, Kim SY, Lee J, Joh JW, Kim SJ, et al. Can a leukocyte depletion filter (LDF) reduce the risk of reintroduction of hepatocellular carcinoma cells? *Liver Transpl* (2005) 11(3):331–5. doi: 10.1002/lt.20346

47. Catling S, Williams S, Freites O, Rees M, Davies C, Hopkins L. Use of a leucocyte filter to remove tumour cells from intra-operative cell salvage blood. *Anaesthesia* (2008) 63(12):1332–8. doi: 10.1111/j.1365-2044.2008.05637.x

48. Esper SA, Waters JH. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfus* (2011) 9(2):139–47. doi: 10.2450/2011.0081-10

49. Bouras I, Mingo O. Should cell salvage be used in oncological surgery? *Br J Hosp Med (Lond)* (2010) 71(1):57. doi: 10.12968/hmed.2010.71.1.45980

50. Waters JH, Yazer M, Chen YF, Kloke J. Blood salvage and cancer surgery: a meta-analysis of available studies. *Transfusion* (2012) 52(10):2167–73. doi: 10.1111/j.1537-2995.2011.03555.x

51. Wu WW, Zhang WY, Zhang WH, Yang L, Deng XQ, Ou MC, et al. Survival analysis of intraoperative blood salvage for patients with malignancy disease: A PRISMA-compliant systematic review and meta-analysis. *Med (Baltimore)* (2019) 98(27):e16040. doi: 10.1097/MD.0000000000016040

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 26 October 2022
DOI 10.3389/fsurg.2022.971030

OPEN ACCESS

EDITED BY
Congxin Dai,
Capital Medical University, China

REVIEWED BY
Takahiro Kogawa,
Cancer Institute Hospital of Japanese Foundation for Cancer Research, Japan
Ali-Farid Safi,
Craniologicum - Center for Craniomaxillofacial Surgery, Switzerland

*CORRESPONDENCE
Guozhong Cui
916291826@qq.com
Yunjiang Liu
lyj818326@outlook.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 16 June 2022
ACCEPTED 26 September 2022
PUBLISHED 26 October 2022

CITATION
Liu J, Li Y, Zhang W, Yang C, Yang C, Chen L, Ding M, Zhang L, Liu X, Cui G and Liu Y (2022) The prognostic role of lymph node ratio in breast cancer patients received neoadjuvant chemotherapy: A dose-response meta-analysis.
Front. Surg. 9:971030.
doi: 10.3389/fsurg.2022.971030

The prognostic role of lymph node ratio in breast cancer patients received neoadjuvant chemotherapy: A dose-response meta-analysis

Jinzhao Liu[1], Yifei Li[2], Weifang Zhang[3], Chenhui Yang[3], Chao Yang[3], Liang Chen[1], Mingjian Ding[1], Liang Zhang[1], Xiaojun Liu[1], Guozhong Cui[1]* and Yunjiang Liu[3,4]*

[1]The Second Department of Thyroid and Breast Surgery, Cangzhou Central Hospital, Cangzhou, China, [2]Department of Pathology, Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [3]Department of Breast Cancer Center, Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [4]Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Hebei Medical University, Shijiazhuang, China

Background: As neoadjuvant chemotherapy is widely used in breast cancer patients, the lymph node ratio has not been fully validated as a prognostic indicator of breast cancer received neoadjuvant chemotherapy. This study was conducted to investigate the prognostic value of lymph node ratio in breast cancer patients received neoadjuvant chemotherapy.
Methods: Systematic searches were performed in the PubMed, Embase, and Cochrane Library databases until 15 December 2021 for studies on the association between lymph node ratio and the prognosis of breast cancer after neoadjuvant chemotherapy. Overall survival and disease-free survival were used as outcome events, and hazard ratio was chosen as the parameter to evaluate the correlation. The dose-response relationship was assessed by restricted cubic splines. In the subgroup analyses, which were used to explore potential heterogeneity among the included studies according to study region and sample size. Sensitivity analysis was performed to assess the stability of individual studies, and publication bias was determined with funnel plots, Begg's test, and Egger's test. All statistical analyses were performed using Stata 15.1.
Results: A total of 12 studies with 4,864 patients were included in this meta-analysis. In this study, high lymph node ratio was significantly associated with decreased overall survival (HR: 4.74; 95%CI: 3.36–6.67; $P < 0.001$) and disease-free survival (HR: 4.77; 95%CI: 3.69–6.17; $P < 0.001$). Moreover, the dose-response meta-analysis showed a linear association between higher lymph node ratio and shorter overall survival and disease-free survival in breast cancer patients after neoadjuvant chemotherapy.
Conclusions: The meta-analysis suggested that high lymph node ratio was significantly associated with short overall survival and disease-free survival in breast cancer patients after neoadjuvant chemotherapy. Therefore, lymph node ratio is an independent predictive factor for the prognosis of breast cancer patients after neoadjuvant chemotherapy, which may better refine the cancer staging system.

KEYWORDS
lymph node ratio, breast cancer, neoadjuvant chemotherapy, prognosis, meta-analysis

Introduction

Today, neoadjuvant chemotherapy is a standard treatment option for patients with locally advanced operable breast cancer and is increasingly used in early breast cancer (1). Neoadjuvant chemotherapy can not only convert inoperable disease to operable disease and reduce the scope of operable surgeries, but also provide confirmation of drug-sensitive disease, thereby guiding subsequent treatment with a view to improving patient outcomes (2). Although neoadjuvant chemotherapy improves overall survival (OS) and disease-free survival (DFS) in breast cancer patients, the prognosis of patients with lymph node positive breast cancer after neoadjuvant chemotherapy remain poor (3). The number of metastatic axillary lymph nodes is an important predictor of prognosis in patients with breast cancer, and accurate lymph node staging can provide an important reference value for guiding adjuvant therapy in patients. In clinical practice, due to the varying effects of neoadjuvant chemotherapy on axillary lymph node status and the technique of axillary lymph node dissection among clinicians, the number of axillary lymph nodes detected in postoperative patients after neoadjuvant chemotherapy is significantly lower than that in patients who did not receive neoadjuvant chemotherapy (4). According to the American Joint Committee on cancer (AJCC) staging of breast cancer, the recommendation regarding dissection of at least 10 lymph nodes after axillary lymph node dissection is clearly influenced by neoadjuvant chemotherapy. AJCC staging tends to underestimate the true status of axillary lymph nodes in breast cancer patients received neoadjuvant chemotherapy, thus affecting the accuracy of guiding treatment and assessing prognosis. Therefore, optimization of methods for assessing axillary lymph node status in breast cancer patients received neoadjuvant chemotherapy is essential.

Lymph nodes ratio (LNR) is defined as the ratio between positive lymph nodes and the total number of retrieved lymph nodes. It not only contains information about lymph node metastasis, but also has the degree of lymph node dissection. Previous studies have reported the independent prognostic value of the LNR in lung cancer, gastric cancer and colorectal cancer patients after neoadjuvant chemotherapy (5–7). Liu D et al. (8) proved that LNR is a prognostic factor for breast cancer in a meta-analysis, but the study did not conduct a subgroup analysis of patients received neoadjuvant chemotherapy, and the accuracy of LNR in evaluating the prognosis of patients received neoadjuvant chemotherapy is not clear. Some studies showed that LNR has important value in predicting the prognosis of breast cancer patients receiving neoadjuvant chemotherapy and its prognostic value was greater than that of current N staging (9, 10). However, Saxena et al. (11) found that LNR was an independent prognostic factor of breast cancer after neoadjuvant chemotherapy, and its prognostic value was poorer than that of ypN stage. Kim et al. (12) even denied the prognostic value of LNR in patients received neoadjuvant chemotherapy. The prognostic value of LNR in patients with breast cancer after neoadjuvant chemotherapy has been still controversial. Therefore, this study conducted a meta-analysis on the prognostic role of LNR in breast cancer patients received neoadjuvant chemotherapy for the first time, providing more comprehensive evidence for the prognostic value of LNR. We also performed a dose-response meta-analysis to examine the potential online relationship between LNR levels and prognosis after neoadjuvant chemotherapy.

Materials and methods

Search strategy

A comprehensive literature search of the PubMed, Embase and Cochrane Library databases was conducted to find relevant published articles about LNR prognostic prediction of breast cancer after neoadjuvant chemotherapy (updated to December 15, 2021). The retrieval strategy combines terms related to “breast cancer”, “neoadjuvant therapy”, “lymph node ratio” and “prognosis”. Additional studies were identified by hand searching the references of original articles and review articles.

Selection criteria

All retrieved articles were first screened by title and abstract and irrelevant studies were excluded. Then, all the retrieved studies were screened by two reviewers according to the inclusion criteria and exclusion criteria. A third author would be consulted and the decision would be reached through discussions when a disagreement was encountered.

Inclusion criteria: (1) study design: retrospective or prospective cohort study; (2) participants: breast cancer patients received neoadjuvant chemotherapy and lymph node dissection; (3) primary outcomes: OS or DFS; (4) survival outcome was further explored regarding hazard ratio (HR) with confidence interval (CI), HR with *P* value, Kaplan-Meier curves or the needed data for calculating HR and CI;

Exclusion criteria: (1) study design: case-control or cross-sectional study; (2) participants: breast cancer patients complicated with other tumors or distant metastasis; (3) study types: case reports, conference summaries, review articles and reviews; (4) the same patient population were overlapped among publications (the studies with the largest sample size were included).

Data extraction and quality assessmenth

The following information were extracted from the included studies: first author, publication year, country, study design, sample size, follow-up time, tumor stage, cut-off value, HRs and 95% CIs for OS and/or DFS. The quality of the included studies in this meta-analysis was assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS). This scale evaluated each study in three domains including the selection of the participants, the comparability between the groups and the outcome of interest for cohort study. The NOS scores range from 0 to 9, and studies with NOS scores > 6 were considered high quality (13).

Statistical analysis

In this meta-analysis, HR and its 95% CIs were used to evaluate the relationship between LNR level and prognosis in breast cancer patients after neoadjuvant chemotherapy. For each study, the HRs comparing the highest with the lowest category were then displayed in a forest plot. In addition, we performed a dose-response meta-analysis to assess whether LNR was associated with worse OS and DFS in breast cancer patients receiving neoadjuvant chemotherapy. When the included studies reported only the total number of cases and the number of cases in each category, the number of person years in each category was calculated using the method proposed by bekkering Ge et al. (14) and Aune D et al. (15). According to the LNR interval given in the included study, we designated the middle value of the upper and lower boundaries of each category as the average LNR level.

The Cochran's Q test and I^2 statistics were used to analyze heterogeneity between studies; $P < 0.05$ or $I^2 > 50\%$ suggested significant heterogeneity among the included studies. If significant heterogeneity existed, a random effect model was selected; otherwise, the fixed-effects model was used. The subgroup analysis was also conducted to explore the source of heterogeneity based on the study area (Chinese or non-Chinese) and sample size of studies (≤300 vs. >300). The possibility of publication bias was evaluated by visual screening of the Begg's

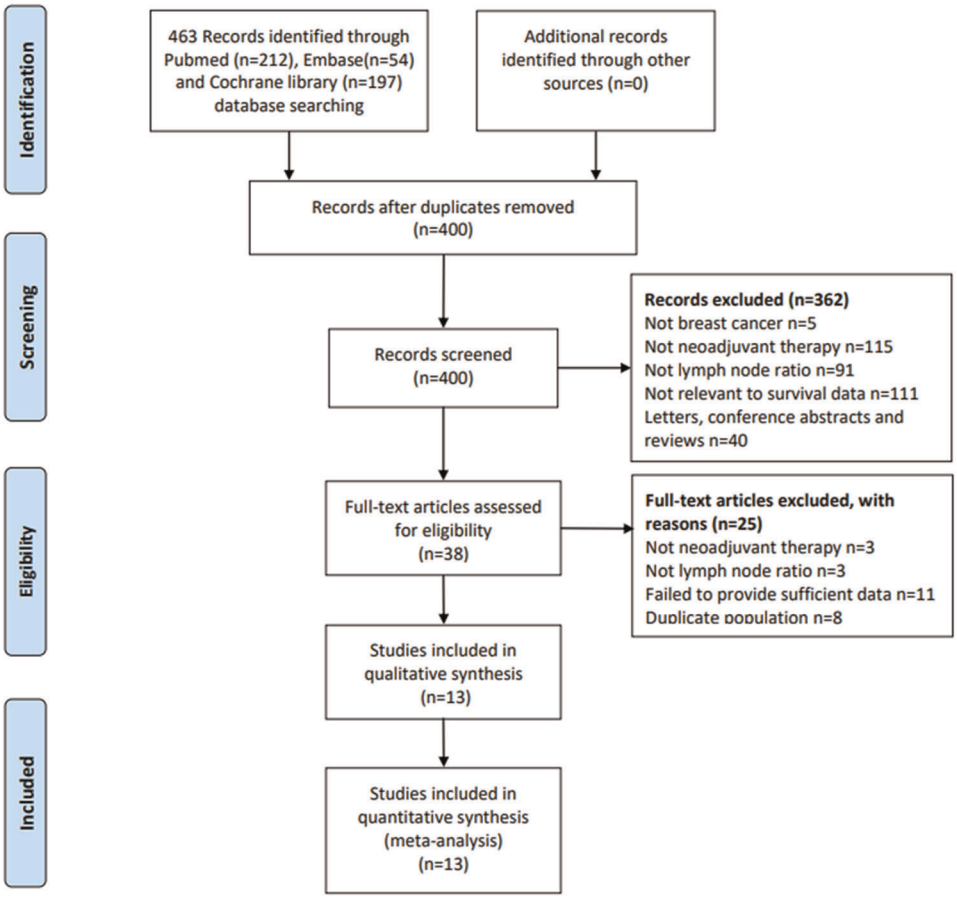

FIGURE 1
Flowchart of the study search and selection.

funnel plot, and both Begg's test and Egger's test were used to evaluate the publication bias. A significance of $P < 0.05$ indicated the possibility of publication bias (16, 17). To further evaluate the robustness of our results, we conducted sensitivity analysis. Sensitivity analysis was performed to explore the potential influence of each individual study on the overall results by deleting one single study each time from the pooled analysis.

Stata se 15.1 (Stata company, Texas College Station, USA) was used for statistical analysis. The study was reported according to the PRISMA Checklist (Stewart et al., 2015).

Results

Selection and characteristics of included studies

A total of 463 articles were retrieved on the initial literature search, of which 212 were retrieved from PubMed, 54 from Embase and 197 from the Cochrane Library. After the exclusion of duplicate studies and non-relevant studies based on a screening of article titles and abstracts, 38 potentially relevant studies were retrieved for full review. According to the pre-established inclusion and exclusion criteria, 13 studies, involving 4,864 breast cancer patients, were included in this study (9–11, 18–27). The flow diagram of the literature search was shown in **Figure 1**. These studies were published between 2009 and 2021. Only one study was a prospective study, and the rest were retrospective studies. Of the 12 studies, 10 studies reported OS and 11 reported DFS. With regard to the study area, four studies were conducted in Chinese (10, 19, 22, 27), while the remaining nine studies were conducted in non-Chinese countries. The median follow-up ranged from 24 to 87 months. The LNR thresholds used in the included studies ranged from 0.1 to 0.8, with most (10/12) using LNR thresholds of 0.2 and 0.65. Overall quality of the included studies was good, and NOS scales ranged from 6 to 8. **Table 1** provides the basic characteristics of included studies.

Relationship between LNR and prognosis of breast cancer patients received neoadjuvant chemotherapy

Among the 13 eligible studies, 10 studies (9–11, 18, 21, 23–27) explored the association between LNR and OS outcomes. Meta-analysis has demonstrated that a significant correlation between higher LNR and shorter OS of breast cancer patients

TABLE 1 Characteristic of the included studies.

Study	Year	Country	Study design	Study period	Sample size	Tumour stage	Follow-up time	Cut-off value	Endpoint	Quality scale
Keam	2009	Korea	Prospective	2002–2007	205	Stage II/III	Median 28.9 months	0.25	OS, DFS	6
Saxena	2011	Geneva Kuala, Singapore, Malaysia	Retrospective	1990–2007	314	Stage I/II/III	NA	0.2, 0.65	OS	7
Chen	2014	China	Retrospective	1999–2009	569	Stage II/III	Median 48 months	0.2, 0.4, 0.8	DFS	7
Tsai	2016	America	Retrospective	2003–2014	428	NA	Mean 36.9 months	0.2, 0.65	DFS	7
Cho	2018	Korea	Retrospective	2006–2015	236	Stage I/II/III	Mean 54 months	0.2, 0.65	OS, DFS	7
Agarwal	2019	India	Retrospective	2004–2014	224	Stage II/III	Median 61 months	0.2, 0.65	OS, DFS	8
Lai	2019	China	Retrospective	2009–2012	339	Stage II/III	Median 62.3 months	0.4, 0.8	DFS	7
Soran	2019	America	Retrospective	2009–2014	179	Stage I/II/III	Median 24 months	0.2	OS	7
Tonellotto	2019	Brazil	Retrospective	2008–2009	628	Stage II/III	Median 58 months	0.2, 0.65	OS, DFS	7
Ai	2020	China	Retrospective	2007–2014	306	Stage II/III	Median 78 months	0.2, 0.65	OS, DFS	7
Gabriel A	2020	Peru	Retrospective	2000–2014	171	Stage II/III	Median 87 months	0.2, 0.65	OS, DFS	6
Silva	2021	Brazil	Retrospective	2010–2014	171	Stage II/III	Median 62.5 months	0.2, 0.65	OS, DFS	7
Li	2021	China	Retrospective	2008–2018	282	Stage I/II/III	Mean 63 months	0.2, 0.65	OS, DFS	7

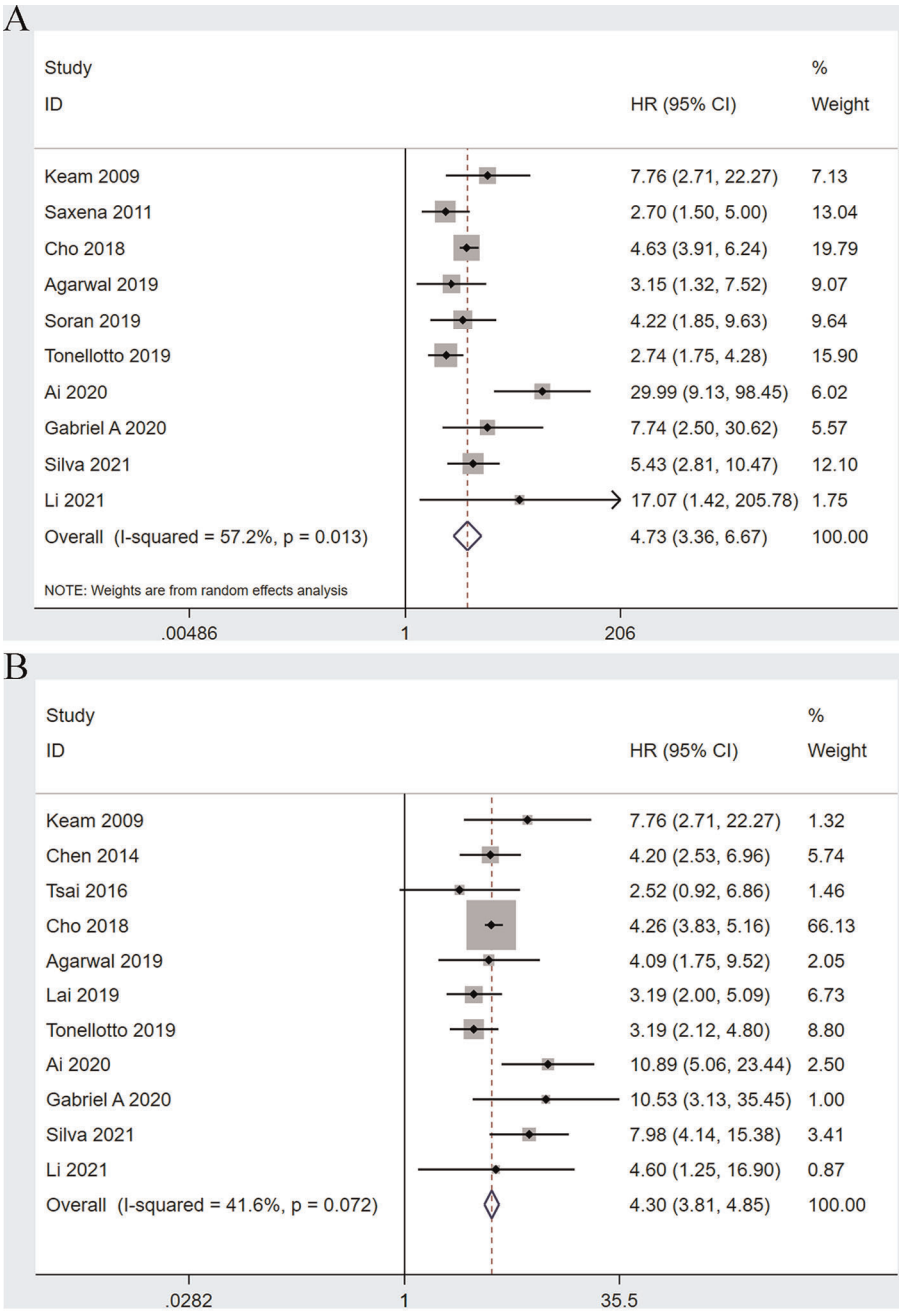

FIGURE 2
Forest plots show the association between lymph node ratio and overall survival (A), disease-free survival (B).

received neoadjuvant chemotherapy (HR: 4.74; 95%CI: 3.36–6.67; $P < 0.001$) with significant heterogeneity ($I^2 = 57.2\%$; $P = 0.013$) (Figure 2A).

Moreover, 11 studies (9, 10, 18–22, 24–27) examined the association between higher LNR and shorter OS of breast cancer patients after neoadjuvant chemotherapy. The results showed a significant association (HR: 4.77; 95%CI: 3.69–6.17; $P < 0.001$) with no heterogeneity ($I^2 = 41.6\%$; $P = 0.072$) (Figure 2B).

Subgroup analysis

In order to explore the potential sources of heterogeneity of the combined HR for OS, we conducted subgroup analyses through stratifying eligible studies by study area (Chinese vs. non- Chinese) and sample size (≤300 vs. >300). When divided into two subgroups by study area, the heterogeneity between studies disappeared. With regard to nation, higher

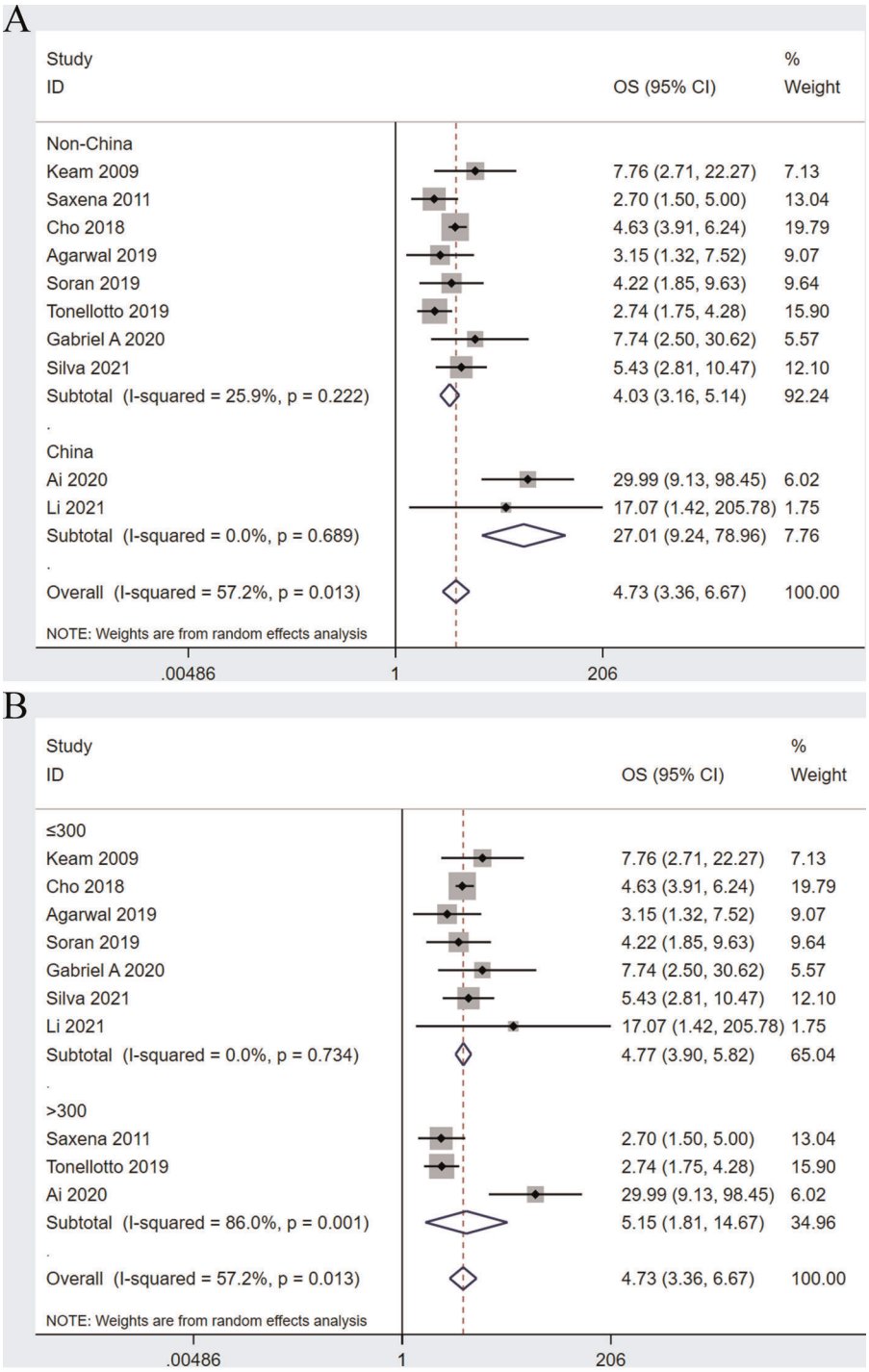

FIGURE 3
Forest plots show the association between lymph node ratio and overall survival stratified by the studied area (A) and sample size (B).

LNR was significantly correlated with shorter OS (HR: 27.01; 95%CI: 3.36–6.67; $I^2 = 0.0\%$; $P < 0.001$) in Chinese patients compared with non-Chinese patients (HR: 4.03; 95% CI: 3.16–5.14; $I^2 = 25.9\%$; $P < 0.001$) (Figure 3A). Based on the subgroup analysis by sample size, this subgroup analysis did not alter the prognostic role of LNR in OS substantially, but significant heterogeneity remained across studies, as shown in Figure 3B.

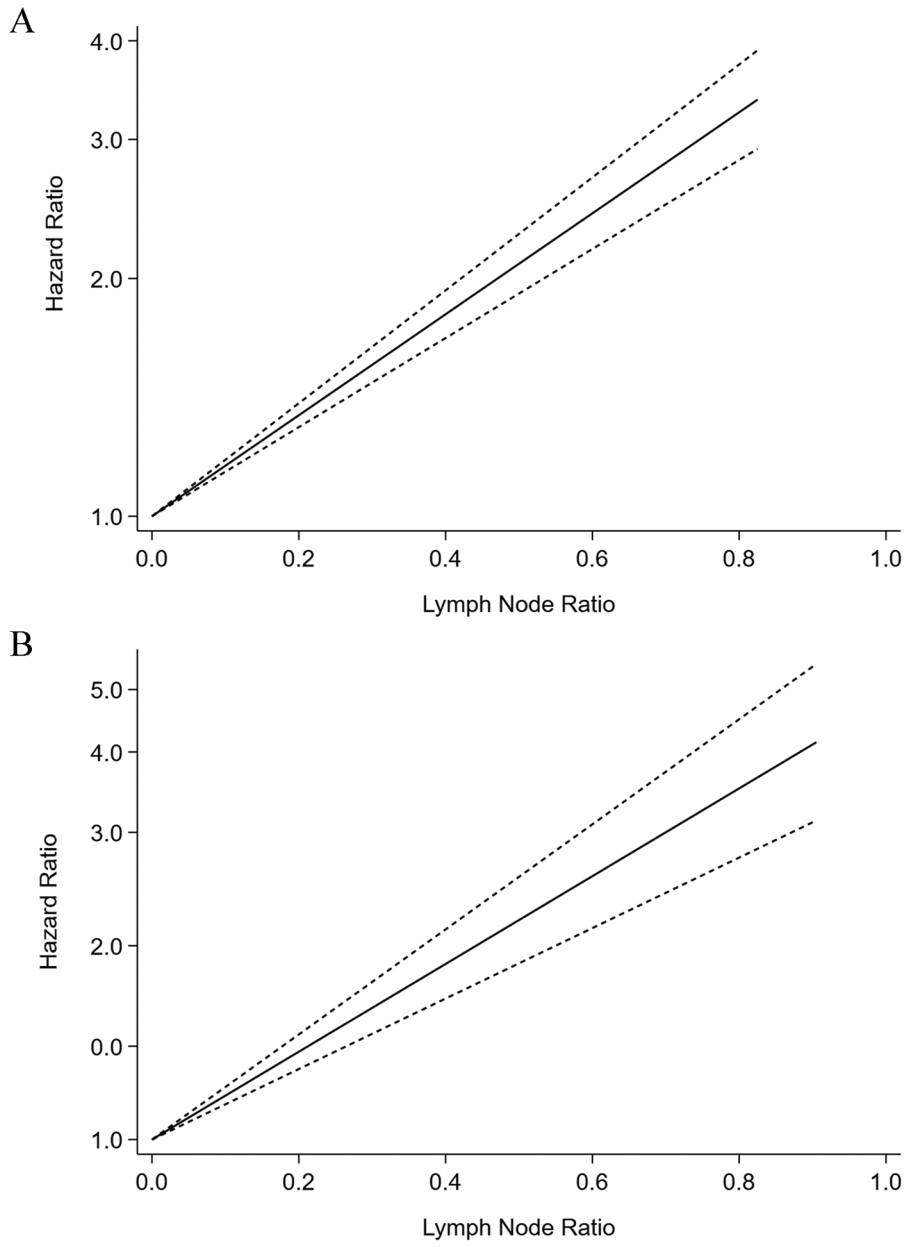

FIGURE 4
Dose-response meta-analysis of the prognostic role of lymph node ratio in overall survival (A) and disease-free survival (B) of the breast cancer patients after neoadjuvant chemotherapy.

Dose-response analysis

Six studies were considered ineligible for inclusion in the dose-response analysis due to a lack of information regarding prognosis of participants or provided LNR levels for less than three categories. Therefore, six cohort studies were eligible to had required data for dose-response analysis. We found a significant linear relationship between higher LNR levels and shorter OS after neoadjuvant chemotherapy (HR = 1.47, 95% CI:1.298–1.646, $P < 0.001$), and there was no evidence of heterogeneity in the study ($Q = 2.17$, $P = 0.83$) (Figure 4A). A total of nine studies participated in the dose-response analysis of the relationship between LNR level and DFS after neoadjuvant chemotherapy. The results showed that there was a linear relationship between higher LNR level and shorter DFS (HR = 1.50, 95% CI: 1.394–1.616, $P < 0.001$), and the heterogeneity across the studies was significant ($Q = 20.72$, $P = 0.008$) (Figure 4B).

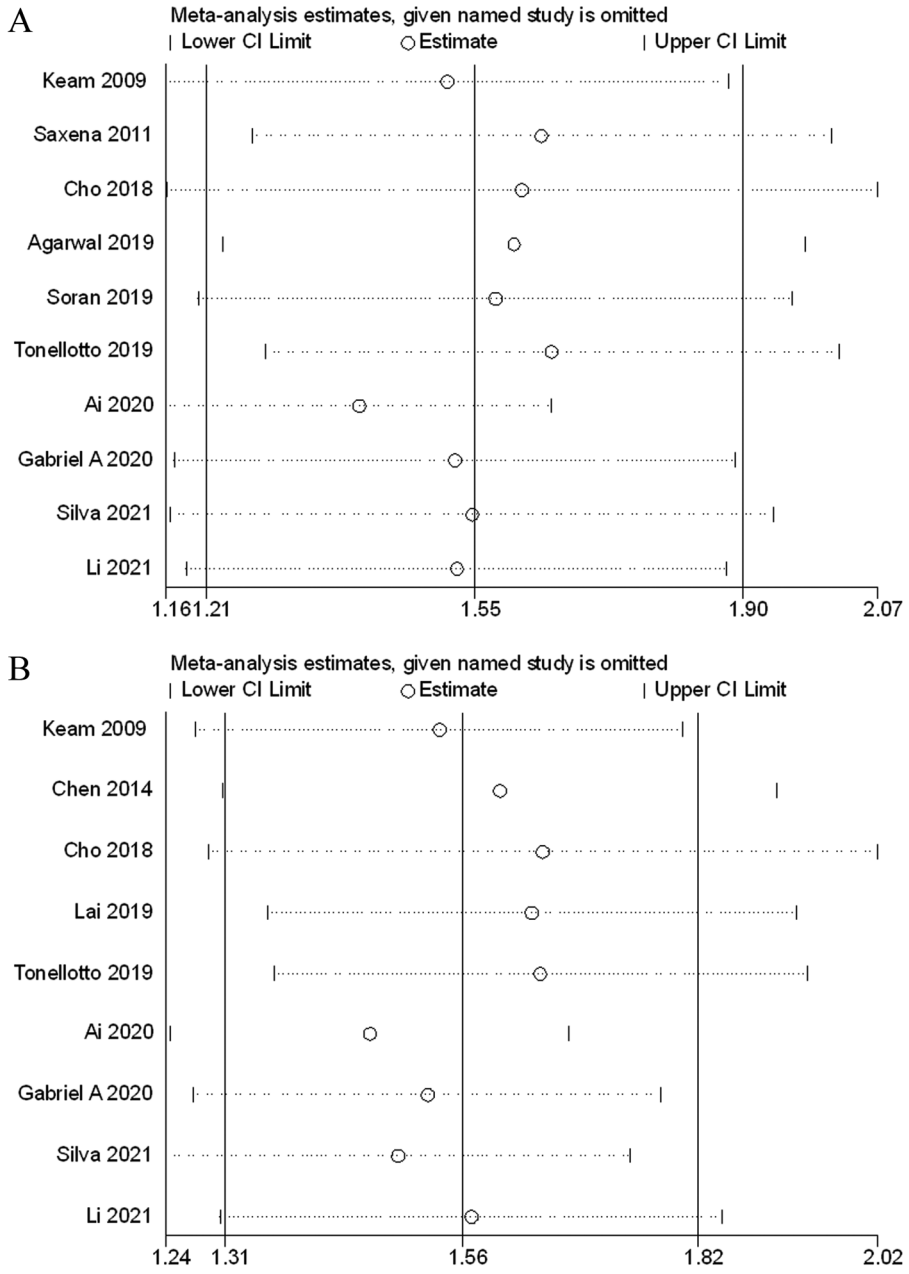

FIGURE 5
Sensitivity analysis of the association between lymph node ratio with overall survival (A), disease-free survival (B).

Sensitivity analysis and publication bias

Sensitivity analyses were performed next. A single study involved in the meta-analysis was deleted each time to unveil the influence of the individual data set to the pooled HRs. In the current study, removing any of the included studies had no significant impact on the meta-analytic results, indicating the robustness of the results (Figure 5). The Begg's funnel showed no significant asymmetry for all included studies (Figure 6). Similarly, the quantitative evaluation results of Begg's test and egger's test showed that there was no statistically significant publication bias in the studies reporting OS (egger's test: $P = 0.479$; Begg's test: $P = 0.858$) and DFS (egger's test: $P = 0.194$; Begg's test: $P = 0.118$).

Discussion

Today, neoadjuvant chemotherapy treatment is widely accepted as a standard treatment for locally advanced breast

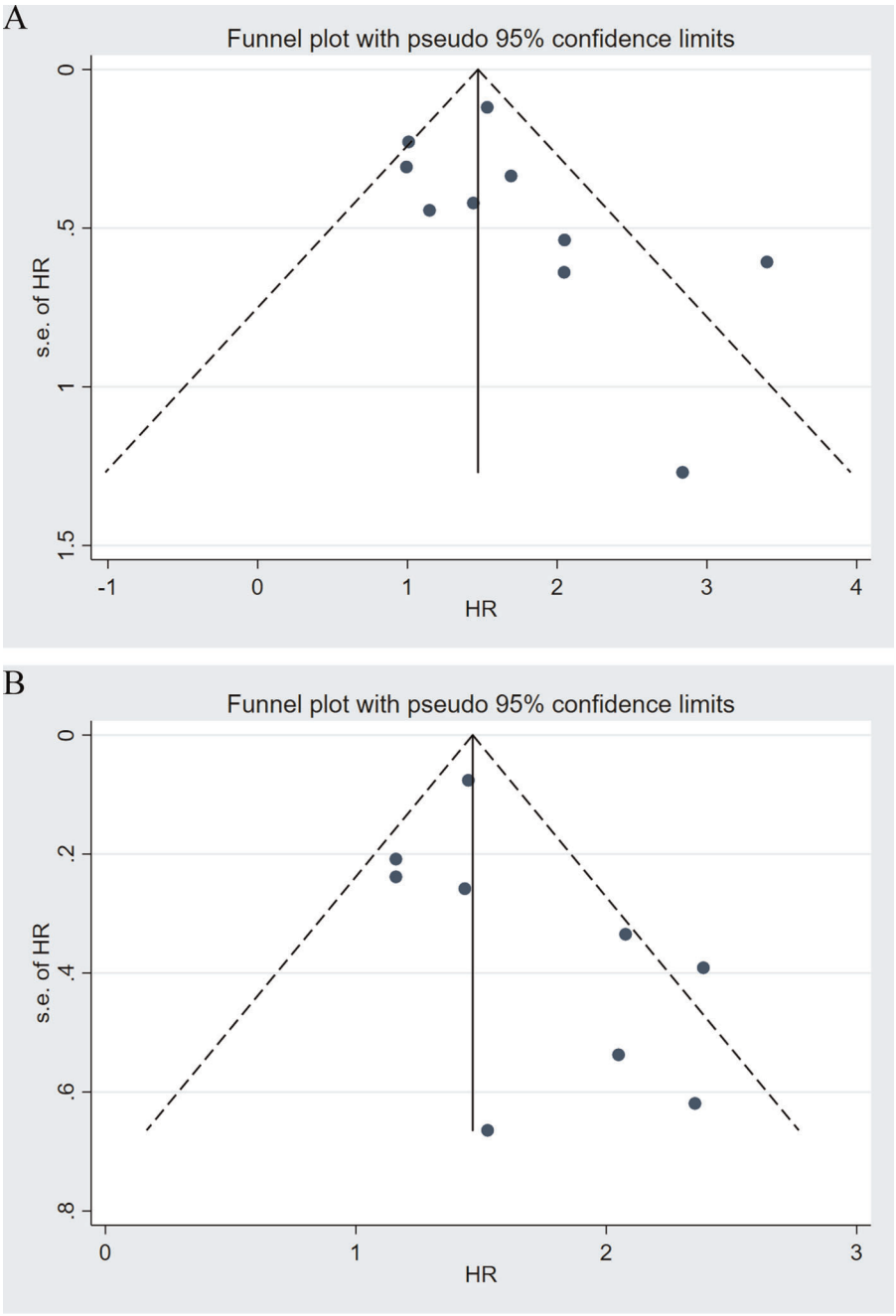

FIGURE 6
Funnel plot of the association between lymph node ratio with overall survival (A), disease-free survival (B).

cancer and plays an important role in the comprehensive treatment of breast cancer (28). The management of the axilla after neoadjuvant chemotherapy is still dominated by axillary lymph node dissection, which aimed to establish nodal status and guide adjuvant treatment indication to maximize survival and regional control of cancer in breast cancer patients (29). The National Comprehensive Cancer Network (NCCN) defines an adequate axillary lymph node dissection as retrieval of least 10 lymph nodes to accurately stage the axilla (30). Rosenberger LH et al. (31) found that fewer dissected lymph nodes were associated with poorer OS in breast cancer patients with positive axillary lymph nodes, possibly due to insufficient axillary staging and missed opportunities for adjuvant therapy. Previous studies reported the lower lymph node yield after axillary lymph node dissection in breast cancer patients received neoadjuvant chemotherapy, and found that

neoadjuvant chemotherapy was an important factor associated with dissection of fewer than 10 lymph nodes (32, 33). Neoadjuvant chemotherapy can induce histomorphological changes within lymph nodes regarding the features lymphoid depletion, diffuse fibrosis, disruption or blockage of lymphatic vessels, calcifications and signs of bleeding (34, 35). These histomorphological changes may lead to decreased lymph node harvest rates. Erbes t et al. found that lymphoid cell depletion was an important factor with the low lymph node yield after neoadjuvant chemotherapy (33). This might be explained by the fact that lymphoid cell depletion will lead to shrinkage of lymph nodes as well as to regression of lymphoid tissue. In a retrospective study using data from the National Cancer Database, it was found that the yield of axillary lymph node dissection was significantly lower in patients received neoadjuvant chemotherapy than those who underwent surgery alone, and that patients received neoadjuvant chemotherapy were more likely to not meet the criteria of axillary lymph node dissection. In addition, the study also found that low lymph node yield was independently associated with pCR of the primary tumor (36). With the development of chemotherapy regimens and targeted anti-HER2 treatment, the primary tumor and axillary pCR rates have increased substantially. A previous study found that fewer than 10 lymph nodes were found in 41.7% of 139 breast cancer patients who underwent axillary dissection and received neoadjuvant pertuzumab, however in patients who received neoadjuvant chemotherapy but did not receive pertuzumab, only 18.6% of patients had less than 10 axillary lymph nodes dissected (37). Therefore, the low lymph node yield will underestimate the number of metastatic lymph nodes and may lead to improper prediction of prognosis and improper treatment. In the era of neoadjuvant treatment, the 10-lymph node guideline for axillary lymph node dissection in breast cancer may need to be revised.

Currently, lymph node status remains an important factor in the AJCC prognostic staging and remains an essential determinant of adjuvant treatment decision-making (38). Lymph node staging is still based on positive lymph node count in breast cancer patients received neoadjuvant chemotherapy, but the varying effects of neoadjuvant chemotherapy on axillary lymph nodes is not considered. Therefore, LNR can overcome the limitation of only taking positive lymph node count, improve and complement the assessment of ypN stage in post-neoadjuvant chemotherapy breast cancer patients, especially for those with fewer than 10 lymph nodes dissected. To the best of our knowledge, this is the first meta-analysis to demonstrate the prognostic role of LNR in neoadjuvant chemotherapy for breast cancer patients. The results of the present study prove that increased LNR levels can predict the shortening of OS and DFS in breast cancer patients after neoadjuvant chemotherapy. However, we found that there was heterogeneity between studies explored the relationship of LNR and OS for patients received neoadjuvant chemotherapy. Subgroup analysis of study area and sample size also demonstrated that high LNR level was associated with worse OS, and the heterogeneity disappeared when divided by area. Among them, the correlation between high LNR level and worse OS was greater in Chinese population than in non-Chinese population after neoadjuvant chemotherapy. The sensitivity analysis confirmed the reliability and stability of the meta-analysis. In addition, LNR level showed a linear correlation with shorter OS and DFS after neoadjuvant chemotherapy. Our findings demonstrated the importance of LNR in the prognosis of breast cancer after neoadjuvant chemotherapy. Therefore, we suggest that LNR should be included as a prognostic parameter in future staging systems for breast cancer after neoadjuvant chemotherapy.

Although many studies mainly explore the relationship between LNR and the prognosis of breast cancer after neoadjuvant chemotherapy, the existing evidence of reliable and reproducible LNR cut-off values is inconsistent. The prognostic value of LNRs was calculated for values ranging from 0.05 to 0.95 by Cox regression analysis and validated by bootstrapping. Vinh hung V et al. calculated the prognostic value of LNRs for values ranging from 0.05 to 0.95 by Cox regression analysis and recorded the difference in likelihood between the critical value model and AIC model, and identified a pair of critical values associated with the least negative difference in likelihood (0.20 and 0.65) (39). Kim JY et al. found that 0.25 and 0.55 as the most significant cut-off values of LNR associated with prognosis, by minimum *P*-value approach (40). According to X-tile software results, Xiao XS et al. found that the optimal cut-off values for LNR were 0.3 and 0.8 (41). Until now, the different cut- off for LNR among studies due to different statistical methods for optimal cut-off for LNR. Previous investigations of the prognostic value of LNR in breast cancer have focused on patients who did not receive neoadjuvant chemotherapy, while few studies of patients who received neoadjuvant chemotherapy have been conducted. The cut-off values for LNR of the included studies in this meta-analysis mostly were 0.20 and 0.65, but no study evaluated whether they could well predict the prognosis of breast cancer patients after neoadjuvant chemotherapy. Regarding the selection of the optimal cut-off value for predicting the prognosis of breast cancer patients, more large samples and high-quality studies in the future are needed to stratify and evaluate the effect of different LNRs on the prognosis of breast cancer patients after neoadjuvant therapy, and to determine the optimal LNR cut-off value for clinical practice.

The present meta-analysis has certain limitations. First, most of the studies included in our meta-analysis were retrospective. The different results of these studies may be caused by population heterogeneity, different neoadjuvant chemotherapy regimens and cycles, different number of axillary lymph node resections and varying surgical and pathological quality across medical centers. Second, the cut-off value for defining LNR in each included study is quite different, which may have

contributed to heterogeneity. Third, the value of LNR after neoadjuvant chemotherapy is vague due to treatment impact and the change of lymph node metastases. Therefore, more prospective studies with better designed trials would be warranted for future LNR studies. Finally, due to insufficient information in the included studies, this study could not analyze the relationship between LNR levels and breast cancer prognosis based on a comprehensive analysis including histological grade, molecular typing, TNM stage, or adjuvant therapy.

In conclusion, the results of the present meta-analysis suggest that the level of LNR is a predictive factor for response in breast cancer patients received neoadjuvant chemotherapy. LNR can be used as a supplement to TNM staging in breast cancer patients after neoadjuvant chemotherapy and improve the accuracy of tumor staging.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author contributions

(I) Conception and design: JZ-L, YJ-L; (II) Administrative support: YJ-L, GZ-C; (III) Collection and assembly of data: JZ-L, WF-Z, C-Y; (IV) Data analysis and interpretation: JZ-L, YF-L, CH-Y; (V) Manuscript revising: L-C, MJ-D, L-Z, XJ-L; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors; All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Prakash I, Neely NB, Thomas SM, Sammons S, Blitzblau RC, DiLalla GA, et al. Utilization of neoadjuvant chemotherapy in high-risk, node-negative early breast cancer. *Cancer Med.* (2022) 11(4):1099–108. doi: 10.1002/cam4.4517

2. Shien T, Iwata H. Adjuvant and neoadjuvant therapy for breast cancer. *Jpn J Clin Oncol.* (2020) 50(3):225–9. doi: 10.1093/jjco/hyz213

3. Yu Y, Wu S, Xing H, Han M, Li J, Liu Y. Development and validation of a novel model for predicting prognosis of non-PCR patients after neoadjuvant therapy for breast cancer. *Front Oncol.* (2021) 11:675533. doi: 10.3389/fonc.2021.675533

4. Bélanger J, Soucy G, Sidéris L, Leblanc G, Drolet P, Mitchell A, et al. Neoadjuvant chemotherapy in invasive breast cancer results in a lower axillary lymph node count. *J Am Coll Surg.* (2008) 206(4):704-8. doi: 10.1016/j.jamcollsurg.2007.10.016

5. Wei YL, Cui YH, Dong YH, Shi WJ. Clinical study on the effects of neoadjuvant chemotherapy on lymph node ratio, prognosis, and survival analysis of stage IIIA-N2 non-small cell lung cancer. *Zhonghua Yi Xue Za Zhi.* (2021) 101(4):259–64. doi: 10.3760/cma.j.cn112137-20200523-01630

6. Chen JX, Sun JW, Wang Y, Pan T, Zhuang LP, Lin LZ, et al. Lymph node ratio-based the ypTNrM staging system for gastric cancer after neoadjuvant therapy: a large population-based study. *Surg Today.* (2022) 52(5):783–94. doi: 10.1007/s00595-021-02386-3

7. Jin C, Deng X, Li Y, He W, Yang X, Liu J. Lymph node ratio is an independent prognostic factor for rectal cancer after neoadjuvant therapy: a meta-analysis. *J Evid Based Med.* (2018) 11(3):169–75. doi: 10.1111/jebm.12289

8. Liu D, Chen Y, Deng M, Xie G, Wang J, Zhang L, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer.* (2014) 21(1):1–9. doi: 10.1007/s12282-013-0497-8

9. Cho DH, Bae SY, You JY, Kim HK, Chang YW, Choi YJ, et al. Lymph node ratio as an alternative to pN staging for predicting prognosis after neoadjuvant chemotherapy in breast cancer. *Kaohsiung J Med Sci.* (2018) 34(6):341–7. doi: 10.1016/j.kjms.2017.12.015

10. Ai X, Liao X, Wang M, Hu Y, Li J, Zhang Y, et al. Prognostic value of lymph node ratio in breast cancer patients with adequate pathologic evidence after neoadjuvant chemotherapy. *Med Sci Monit.* (2020) 26:e922420. doi: 10.12659/MSM.922420

11. Saxena N, Hartman M, Aziz R, Rapiti E, Bhoo Pathy N, Lim SE, et al. Prognostic value of axillary lymph node status after neoadjuvant chemotherapy. Results from a multicentre study. *Eur J Cancer.* (2011) 47(8):1186–92. doi: 10.1016/j.ejca.2010.12.009

12. Kim SH, Jung KH, Kim TY, Im SA, Choi IS, Chae YS, et al. Prognostic value of axillary nodal ratio after neoadjuvant chemotherapy of doxorubicin/cyclophosphamide followed by docetaxel in breast cancer: a multicenter retrospective cohort study. *Cancer Res Treat.* (2016) 48(4):1373–81. doi: 10.4143/crt.2015.475

13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z

14. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review

and dose-response meta-analysis of prospective studies. *Am J Clin Nutr*. (2018) 108(5):1069–91. doi: 10.1093/ajcn/nqy097

15. Bekkering GE, Harris RJ, Thomas S, Mayer AM, Beynon R, Ness AR, et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? *Am J Epidemiol*. (2008) 167(9):1017–26. doi: 10.1093/aje/kwn005

16. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J*. (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. (1994) 50:1088–101. doi: 10.2307/2533446

18. Keam B, Im SA, Kim HJ, Oh DY, Kim JH, Lee SH, et al. Clinical significance of axillary nodal ratio in stage II/III breast cancer treated with neoadjuvant chemotherapy. *Breast Cancer Res Treat*. (2009) 116(1):153–60. doi: 10.1007/s10549-008-0160-9

19. Chen S, Liu Y, Huang L, Chen CM, Wu J, Shao ZM. Lymph node counts and ratio in axillary dissections following neoadjuvant chemotherapy for breast cancer: a better alternative to traditional pN staging. *Ann Surg Oncol*. (2014) 21(1):42–50. doi: 10.1245/s10434-013-3245-6

20. Tsai J, Bertoni D, Hernandez-Boussard T, Telli ML, Wapnir IL. Lymph node ratio analysis after neoadjuvant chemotherapy is prognostic in hormone receptor-positive and triple-negative breast cancer. *Ann Surg Oncol*. (2016) 23(10):3310–6. doi: 10.1245/s10434-016-5319-8

21. Agarwal R, Philip A, Pavithran K, Rajanbabu A, Goel G, Vijaykumar DK. Prognostic significance of residual nodal burden using lymph node ratio in locally advanced breast cancer after neoadjuvant chemotherapy. *Indian J Cancer*. (2019) 56(3):228–35. doi: 10.4103/ijc.IJC_652_18

22. Lai J, Pan Z, Chen P, Ye G, Chen K, Su F. Development and validation of a nomogram incorporating axillary lymph node ratio to predict survival in node-positive breast cancer patients after neoadjuvant chemotherapy. *Jpn J Clin Oncol*. (2019) 49(1):22–8. doi: 10.1093/jjco/hyy181

23. Soran A, Ozmen T, Salamat A, Soybir G, Johnson R. Lymph Node Ratio (LNR): predicting prognosis after Neoadjuvant Chemotherapy (NAC) in breast cancer patients. *Eur J Breast Health*. (2019) 15(4):249–55. doi: 10.5152/ejbh.2019.4848

24. Tonellotto F, Bergmann A, de Souza Abrahão K, de Aguiar SS, Bello MA, Thuler LCS. Impact of number of positive lymph nodes and lymph node ratio on survival of women with node-positive breast cancer. *Eur J Breast Health*. (2019) 15(2):76–84. doi: 10.5152/ejbh.2019.4414

25. De la Cruz-Ku GA, Chambergo-Michilot D, Valcarcel B, Rebaza P, Möller M, Araujo JM, et al. Lymph node ratio as best prognostic factor in triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy. *Breast J*. (2020) 26(9):1659–66. doi: 10.1111/tbj.13988

26. da Silva JL, Rodrigues FR, de Mesquita GG, Fernandes PV, Thuler LCS, de Melo AC. Triple-negative breast cancer: assessing the role of immunohistochemical biomarkers on neoadjuvant treatment. *Breast Cancer (Dove Med Press)*. (2021) 13:31–44.

27. Li X, Tan Q, Li H, Yang X. Predictive value of pretreatment peripheral neutrophil-to-lymphocyte ratio for response to neoadjuvant chemotherapy and breast cancer prognosis. *Cancer Manag Res*. (2021) 13:5889–98. doi: 10.2147/CMAR.S313123

28. Wang Y, Li L, Liu X, Wang Y, Tang Z, Wu Y, et al. Treatment response correlation between primary tumor and axillary lymph nodes after neoadjuvant therapy in breast cancer: a retrospective study based on real-world data. *Gland Surg*. (2021) 10(2):656–69. doi: 10.21037/gs-20-686

29. Srour MK, Tseng J, Luu M, Alban RF, Giuliano AE, Chung A. Patterns in the use of axillary operations for patients with node-positive breast cancer after neoadjuvant chemotherapy: a National Cancer Database (NCDB) analysis. *Ann Surg Oncol*. (2019) 26(10): 3305–11. doi: 10.1245/s10434-019-07540-3

30. National Comprehensive Cancer Network. NCCN, Invasive Cancer, Surgical Axillary Staging (2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed January 4, 2019).

31. Rosenberger LH, Ren Y, Thomas SM, Greenup RA, Fayanju OM, Hwang ES, et al. Axillary lymph node dissection in node-positive breast cancer: are ten nodes adequate and when is enough, enough? *Breast Cancer Res Treat*. (2020) 179(3):661–70. doi: 10.1007/s10549-019-05500-9

32. Lee MC, Plews R, Rawal B, Kiluk JV, Loftus L, Laronga C. Factors affecting lymph node yield in patients undergoing axillary node dissection for primary breast cancer: a single-institution review. *Ann Surg Oncol*. (2012) 19(6):1818–24. doi: 10.1245/s10434-011-2199-9

33. Erbes T, Orlowska-Volk M, Zur Hausen A, Rücker G, Mayer S, Voigt M, et al. Neoadjuvant chemotherapy in breast cancer significantly reduces number of yielded lymph nodes by axillary dissection. *BMC Cancer*. (2014) 14:4. doi: 10.1186/1471-2407-14-4

34. Park CK, Jung WH, Koo JS, et al. Pathologic evaluation of breast cancer after neoadjuvant therapy. *J. Pathol. Transl. Med*. (2016) 50:173–80. doi: 10.4132/jptm.2016.02.02

35. Li JJ, Tsang JY, Tse GM. Tumor microenvironment in breast cancer-updates on therapeutic implications and pathologic assessment. *Cancers*. (2021) 13(16):4233. doi: 10.3390/cancers13164233

36. Ozao-Choy J, Moazzez A, Dauphine C. Lower lymph node yield in axillary lymph node dissection specimens in breast cancer patients receiving neoadjuvant chemotherapy: quality concern or treatment effect? *Breast J*. (2021) 27(12):851–6. doi: 10.1111/tbj.14303

37. O'Leary MP, Beckord BJ, Mock KE, Venegas RJ, Yeh JJ, Dauphine CE, et al. A new era of neoadjuvant treatment with pertuzumab: should the 10-lymph node guideline for axillary lymph node dissection in breast cancer be revised? *Cancer Rep*. (2018) 1(4):e1132. doi: 10.1002/cnr2.1132

38. Fei F, Zhang K, Siegal GP, Wei S. A simplified breast cancer prognostic score: comparison with the AJCC clinical prognostic staging system. *Mod Pathol*. (2021) 34(12):2141–7. doi: 10.1038/s41379-021-00890-y

39. Vinh-Hung V, Verkooijen HM, Fioretta G, Neyroud-Caspar I, Rapiti E, Vlastos G, et al. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. *J Clin Oncol*. (2009) 27(7):1062–8. doi: 10.1200/JCO.2008.18.6965

40. Kim JY, Ryu MR, Choi BO, Park WC, Oh SJ, Won JM, et al. The prognostic significance of the lymph node ratio in axillary lymph node positive breast cancer. *J Breast Cancer*. (2011) 14(3):204–12. doi: 10.4048/jbc.2011.14.3.204

41. Xiao XS, Tang HL, Xie XH, Li LS, Kong YN, Wu MQ, et al. Metastatic axillary lymph node ratio (LNR) is prognostically superior to pN staging in patients with breast cancer–results for 804 Chinese patients from a single institution. *Asian Pac J Cancer Prev*. (2013) 14(9):5219–23. doi: 10.7314/APJCP.2013.14.9.5219

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 01 November 2022
DOI 10.3389/fsurg.2022.1006717

OPEN ACCESS

EDITED BY
Andrea Laurenzi,
IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

REVIEWED BY
Olivier Glehen,
Hospices Civils de Lyon, France
Gianni Lazzarin,
Abano Terme Hospital, Italy

*CORRESPONDENCE
Lie Yang
lie_222@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 29 July 2022
ACCEPTED 10 October 2022
PUBLISHED 01 November 2022

CITATION
Chen P, Zhou H, Chen C, Qian X, Yang L and Zhou Z (2022) Laparoscopic vs. open colectomy for T4 colon cancer: A meta-analysis and trial sequential analysis of prospective observational studies.
Front. Surg. 9:1006717.
doi: 10.3389/fsurg.2022.1006717

Laparoscopic vs. open colectomy for T4 colon cancer: A meta-analysis and trial sequential analysis of prospective observational studies

Peng Chen[1,2†], Hang Zhou[1,2†], Chuwen Chen[3†], Xin Qian[4], Lie Yang[1,2*] and Zongguang Zhou[1,2]

[1]Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China, [2]Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Vascular Surgery, West China Hospital, Sichuan University, Chengdu, China, [4]Department of Vascular Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China

Background: To evaluate short- and long-term outcomes of laparoscopic colectomy (LC) vs. open colectomy (OC) in patients with T4 colon cancer.
Methods: Three authors independently searched PubMed, Web of Science, Embase, Cochrane Library, and Clinicaltrials.gov for articles before June 3, 2022 to compare the clinical outcomes of T4 colon cancer patients undergoing LC or OC.
Results: This meta-analysis included 7 articles with 1,635 cases. Compared with OC, LC had lesser blood loss, lesser perioperative transfusion, lesser complications, lesser wound infection, and shorter length of hospital stay. Moreover, there was no significant difference between the two groups in terms of 5-year overall survival (5y OS), and 5-year disease-free survival (5y DFS), R0 resection rate, positive resection margin, lymph nodes harvested ≥12, and recurrence. Trial Sequential Analysis (TSA) results suggested that the potential advantages of LC on perioperative transfusion and the comparable oncological outcomes in terms of 5y OS, 5y DFS, lymph nodes harvested ≥12, and R0 resection rate was reliable and no need of further study.
Conclusions: Laparoscopic surgery is safe and feasible in T4 colon cancer in terms of short- and long-term outcomes. TSA results suggested that future studies were not required to evaluate the 5y OS, 5y DFS, R0 resection rate, positive resection margin status, lymph nodes harvested ≥12 and perioperative transfusion differences between LC and OC.
Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42022297792.

KEYWORDS
laparoscopic colectomy, open colectomy, T4 colon cancer, survival, meta-analysis

Introduction

Colorectal cancer is both the third most commonly diagnosed cancer and the third cause of cancer-related death globally (1). In addition, colon cancers account for nearly 60%, while approximately 106,180 new cases will be confirmed in 2022 (1, 2). Among them, about 15% of colon cancer patients diagnosed with

locally advanced disease (T4 stage) (3). Compared with open colectomy, the widely used minimally invasive surgical technology for colon cancer has better short-term results and comparable tumor prognosis (4–8). Moreover, based on the several large randomized controlled trials such as COLOR, CLASICC, COST, EnROL trial and several recent meta-analyses, the NCCN guidelines for colon cancer (2006) recommended that minimally invasive colectomy was considered for colon cancer and performed only by surgeons experienced in this techniques (9–20). However, since the tumor volume of T4 colorectal cancer is large and invades surrounding tissues or adjacent organs, laparoscopic (Lap) En-bloc resection is difficult and risky. Several large randomized controlled trials have compared laparoscopic and open colectomy. But in the Barcelona, ALCCaS, COST, COLOR, MRC CLASSICC, ACOSOG Z6051 trials, locally advanced colon tumors were portion of the exclusion criteria (20–25). Later, most clinical studies enrolled fewer cases of T4 colorectal cancer (20, 25–27). Therefore, there is limited evidence-based data to prove the safety and effectiveness of laparoscopic resection for T4 colon cancer. Laparoscopic T4 colorectal cancer resection is considered to be a technique demanding accuracy and its efficacy is still controversial. The American Joint Committee on Cancer (AJCC) TNM staging system and guidelines from the European Association of Endoscopic Surgery (EAES) guidelines did not recommend laparoscopic surgery for T4 colon cancer (28). However, due to the innovation and progress of laparoscopic platform and the popularization and improvement of laparoscopic technology, surgeons in some large and well-experienced centers tried to apply laparoscopic technology in T4 colorectal cancer and achieved better short-term benefits and oncological outcomes similar to open surgery (4, 6, 8, 29, 30).

Recently, three updated meta-analyses showed that LC was associated with better perioperative outcomes like a lower complication compared with OC and R0 resection rates, 5y OS, and 5y DFS for OC and LC were similar (4, 6, 8). Nevertheless, most of the cases included in the above three meta-analyses were retrospective studies, and the huge heterogeneity caused by different definitions of T4 (T4a vs. T4b, clinical T4 vs. pathological T4). In addition, with more and more statistical analysis of the accumulated literature, the possibility of observing false negative or false positive results increased (31). Trial Sequential Analysis (TSA) can overcome the above shortcomings (32, 33). Therefore, we used TSA method in meta-analysis to control the risk of type I errors.

In this study, we systematically reviewed the existing relevant literature and performed a meta-analysis comprised of TSA of the data on short- and long-term outcomes of LC vs. OC for pT4 colon cancer.

Methods

This meta-analysis was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines (34). Ethical consent was not applicable. The present study was registered in PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/) and the Registration Number is: CRD42022297792.

Literature search

A systematic literature search was carried out in the PubMed, Web of Science, Embase, Cochrane Library, and Clinicaltrials.gov from inception to June 3, 2022 with no limit. The main terms were: (Colonic Neoplasms OR Colonic Neoplasm OR Colon Neoplasm OR Colon Cancer OR Colonic Cancer OR Colonic malignancy OR Colon tumor OR Colon tumour OR colon carcinoma) AND (Locally advanced OR T4 OR multivisceral OR advanced OR pT4 OR cT4) AND (Laparoscopy OR laparoscopic OR open OR minimally invasive OR minimal invasive). In addition, a manual search of references of relevant literatures and reviews was also conducted obtain more potential research.

Inclusion and exclusion criteria

The inclusion criteria for the meta-analysis were: (1) studies with patients with primary colon cancer; (2) clinical studies that compared LC vs. OC; and (3) raw data that included followings: conversion rate, postoperative complications, perioperative transfusion, mortality, survival, R0 resection rate, resection margin status, number of harvested lymph nodes, and recurrence. The exclusion criteria were: (1) studies did not present data of T4 tumors, (2) mix with rectal cancer or other T stage, (3) studies with no comparison cohort, (4) reviews or meta-analyses, (5) conference abstract, (6) letter, (7) study could not be retrieved.

Study selection and quality assessment

Three authors (PC, HZ and CC) independently used the Methodological Index for Non-Randomized Studies (MINORS) instrument to assess the quality of the included prospective observational studies (35). The items were scored 0 (not reported), 1(reported but not enough) or 2 (reported and enough). The full score of non- comparative research is 16 points, and the total score of comparative research is 24 points. Moreover, the Grading of Recommendations Assessment,

Development, and Evaluation system (GRADE system) was used to rate the level of evidence as very low, low, moderate, or high and created a summary table with the GRADE profiler software (version 3.6.1) (36). Any differences were resolved through consensus discussion between the review group.

Data extraction

Three researchers (PC, HZ and CC) used structured tables to extract data from each study and input the data into the database. The extracted items contained: author, publication year, study period, country, Single or multicenter study, sample size, gender, age, body mass index(BMI), American Society of Anesthesiologists (ASA), Tumor, Node, Metastasis (TNM) staging classification, neoadjuvant therapy, adjuvant chemotherapy, inclusion and exclusion criteria, median follow-up, conversion rate, operation time (min), blood loss (ml), length of hospital stay (days), soft diet start (days), complications, wound infection, intra-abdominal abscess, ileus, anastomotic leakage, perioperative transfusion, diverting stoma, mortality rate, 5y OS, 5y DFS, R0 resection rate, positive resection margin, lymph nodes harvested ≥12, recurrence.

Follow-up plans

The follow-up plans were similar in the 3 studies that evaluated long-term results. Patients were followed up at 3 monthly intervals for the first 2 years and every 6 months thereafter. Physical examination and carcinoembryonic antigen (CEA) were routinely performed, whereas abdominal and chest CT scans were performed with an average interval of 6 months. Colonoscopy was carried out once a year or when abnormalities were detected during any follow-up visit. An 18-FDG PET scan was performed if recurrence was suspected. Biopsies were selectively performed.

Statistical analysis

Analysis was performed using Review Manager (version 5.4.1). Meta-analysis was conducted in which two or more studies assessed the same risk factor in a comparable manner (37). The inverse-variance method and the Mantel-Haenszel estimator were used to calculate pooled mean difference (MD) values and odds ratios (ORs), respectively. MD and pooled ORs were used for continuous variables and dichotomous variables respectively. For continuous variables, if the study only provides median and range values or means and range values, the method described in the previous study was used to calculate the means and standard deviations (38). For the survival endpoints, relative risk (RR) with the corresponding 95% CIs were applied. Statistical heterogeneity was assessed using the Higgins I^2value (39).

The thresholds of low, medium and high heterogeneity(I^2) are 25%, 50% and 75%, respectively. A random-effects model was used for all outcomes (40). Publication bias was evaluated through the funnel plots in Review Manager. $P < 0.05$ was considered statistically significant.

Trial sequential analysis

TSA was used to evaluate the statistical reliability of data in the cumulative meta-analysis. It controlled the α and β Value for repetitive testing on the accumulating data. TSA was a tool to assess whether the currently available evidence is sufficiently conclusive (41). Meta-analysis of small samples may increase the risk of false-positive results, resulting in wrong conclusions. To avoid false-negative/positive results, we performed a TSA using the TSA software (version 0.9.5.10, Copenhagen Trial Unit, Denmark). TSA was performed for both dichotomous and continuous outcomes, in which a 20% relative risk reduction, a low-risk-based MD, a type I error ($\alpha = 0.05$, two-sided), and a type II error ($\beta = 0.20$, power of 80%) were applied to calculate optimal information size.

Results

Selected studies and baseline characteristics

According to the literature search and selection strategy, a total of 7 prospective observational studies that included 1,635 cases with pT4 colon cancer resection (863 LC and 772 OC) were enrolled in this meta-analysis (**Figure 1**) (42–48). Demographic and clinical characteristics of 7 prospective observational studies were shown in **Table 1**. Quality assessment of studies was shown in **Table 2**; 7 studies had a score of >18 points based on MINORS. Meta-analysis for LC vs. OC was shown in **Table 3**.

Short-term outcomes

Table 3 showed the results of meta-analysis for all outcomes. All 7 clinical studies reported data on conversion rate with a pooled rate of 11% (95 cases) (42–48). The conversion rate ranged from 7.1 to 28.2% in the LC group. The pooled results showed no significant difference in the operation time between the two groups (MD = 11.48, 95% CI, −8.85 to 31.81, $P = 0.27$). The pooled results showed a significant reduction (MD = −121.12 ml, 95% CI, −236.08 to −6.15, $P = 0.04$) in blood loss among the LC group. LC group showed a significantly lower

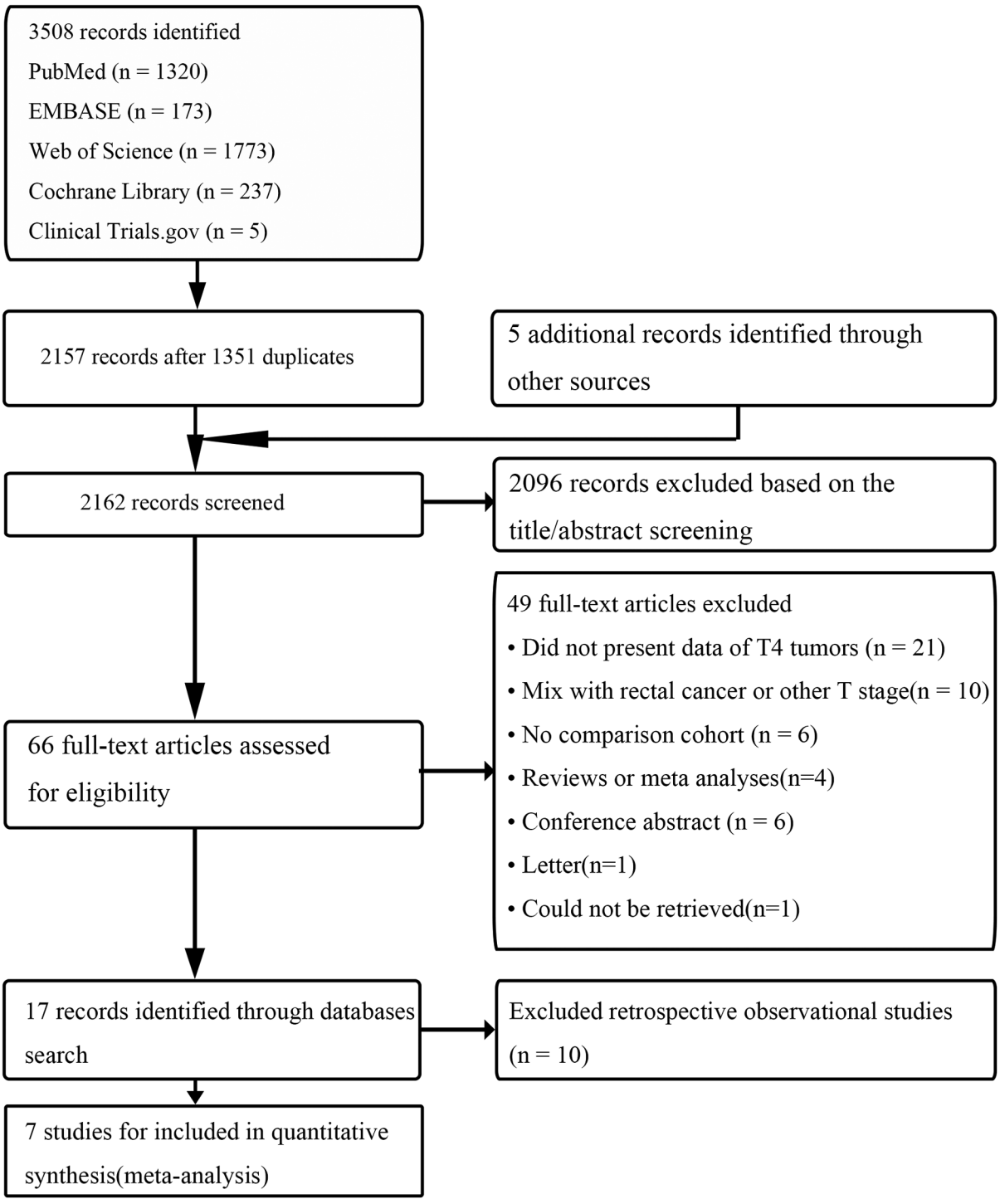

FIGURE 1
The literature search and selection.

hospital stay than OC group (MD = −5.34 days, 95% CI, −9.04 to −1.64, P =0.005). LC group showed a shorter trend duration than OC group in terms of the number of days to the soft diet start (MD = − 3.58, 95% CI, −10.14 to 2.99, P = 0.29).

The morbidity rates of LC group ranged from 13.5% to 28.3%, while the morbidity rates of OC group ranged from 27.1% to 52.6%. The overall complications significantly decreased in LC group compared to OC group (OR =

10.3389/fsurg.2022.1006717

TABLE 1 Basic characteristics of included studies.

Reference		Study period	Location	Single or multicenter	n (laparoscopic/ open)	Male/ female	Mean age (yr)	BMI (mean)	ASA ≥ 3	Tumor stage	T4a/T4b	N + -stage	M1-stage	Neoadjuvant therapy	Adjuvant chemotherapy	Inclusion and exclusion criteria	Median follow-up	MINORS
Bellio 2017	Laparoscopic	2004–2015	Italy	Single	39/38	25/14	73	NR	14/39	II 13/39 III26/39 IV0	38/1	25 (64.1%)	0	NR	11 (28.2%)	Included pT4b	>3 yr	18
	Open					18/20	77	NR	18/38	II 17/38 III21/38 IV0	29/9	21 (55.3%)	0	NR	17 (44.7)			
Chan 2016	Laparoscopic	2008–2014	Singapore	Single	93/59	NR	NR	NR	NR	NR	NR	54 (58%)	NS	NR	NR	Excluded emergency cases; direct invasion to adjacent organs or were already metastatic at presentation were also excluded	6.1 yrb	18
	Open					NR	NR	NR	NR	NR		46 (78%)						
de'Angelis 2016	Laparoscopic	2005–2014	France, Switzerland	Multi	106/106	51/55	70.5[b]	24	22/106	II 45/106 III 61/106 IV 0	pT4a: 91 (86%) pT4b: 15 (14%)	61 (58%)	0	NR	63 (59%)	Excluded emergency setting and those with distant metastasis or synchronous colon cancer	5 yrc	21
	Open					47/59	75.5[b]	25.2	30/106	II 40/106 III 66/106 IV 0	pT4a: 86 (81%) pT4b: 20 (19%)	66 (62%)	0		53 (50%)			
Elnahas 2015	Laparoscopic	2011–2012	International	Multi	455/406	215/240	67[b]	28	27/428	NR	T4a only	296 (69%)	122 (28%)	20 (4.6%)	NR	Excluded pT4b cancer and rectal cancer	30 d	18
	Open					196/210	67[b]	28	28/378	NR		268 (69%)	111 (28%)	19 (4.7%)				
Kang 2016	Laparoscopic	2003–2013	South Korea	Single	52/57	31/21	61.9[b]	23.4	8/52	II 17/52 III 35/52 IV 0	pT4a: 45 (87%) pT4b: 7 (14%)	35 (67%)	0	NR	42 (81%)	M1; Robotic surgery	3.4/ 3.7 yr	20
	Open					39/19	65.4[b]	23.1	3/57	II 24/57 III 33/57 IV 0	pT4a: 39 (69%) pT4b: 18 (32%)	33 (58%)	0		43 (75%)			

(*continued*)

TABLE 1 Continued

Reference		Study period	Location	Single or multicenter	n (laparoscopic/ open)	Male/ female	Mean age (yr)	BMI (mean)	ASA ≥ 3	Tumor stage	T4a/T4b	N + -stage	M1- stage	Neoadjuvant therapy	Adjuvant chemotherapy	Inclusion and exclusion criteria	Median follow-up	MINORS
Takahashi 2017	Laparoscopic	2005–2014	Japan	Single	48/36	29/19	68.5	20.6	NR	II 21/48 III14/48 IV13/48	pT4b: 22 (46%)	14 (29%)	13 (27%)	6.30%	10 (71% of stage III)	Rectal cancer and recurrent cancer were excluded	4.3 yrb	18
	Open					20/16	71.5	19.6	NR	II 21/36 III7/36 IV8/36	pT4b: 20 (56%)	7 (19%)	8 (22%)	25%	4 (57% of stage III)			
Vignali 2013	Laparoscopic	2002–2012	Italy	Single	70/70	37/33	65.2	26.3	1.94 (mean)	II 33/70 III 32/70 IV 5/70	pT4a: 52 (74%) pT4b: 18 (26%)	32 (46%)	5 (7.1%)	0 (0%)	52 (74%)	Included pT4 cancer, Excluded rectal and emergency resections	5 yr	19
	Open					40/30	63.5	25.8	1.94 (mean)	II 33/70 III 32/70 IV 5/70	pT4a: 46 (66%) pT4b: 24 (34%)	32 (46%)	5 (7.1%)	0 (0%)	56 (80%)			

n = number of patients; NR = not reported.

[a]Included 17 hand-assisted laparoscopic procedures.

[b]Median.

10.3389/fsurg.2022.1006717

TABLE 2 Methodological quality assessment based on MINORS.

Refs	Aim[a]	Inclusion[b]	Prospective[c]	End points[d]	Unbiased[e]	Follow-up[f]	Lost to follow-up[g]	Size[h]	Control[i]	Contemporary[j]	Baseline[k]	Statistical analyses[l]	Total
Bellio (20)	2	2	2	2	1	NA	0	1	2	2	2	2	18
Chan (19)	2	2	2	2	1	2	0	1	2	2	0	2	18
de'Angelis (17)	2	2	2	2	1	2	0	2	2	2	2	2	21
Elnahas (25)	2	2	1	2	1	NA	0	2	2	2	2	2	18
Kang (18)	2	2	2	2	1	2	0	1	2	2	2	2	20
Takahashi (21)	2	2	1	2	1	1	0	1	2	2	2	2	18
Vignali (14)	2	2	1	2	1	2	0	1	2	2	2	2	19

MINORS = methodological index for nonrandomized studies; NA = not applicable.
The following items are scored 0–2 (0: not reported, 1: reported but inadequate, 2: reported and adequate).
[a]A clearly stated aim.
[b]Inclusion of consecutive patients.
[c]Prospective collection of data.
[d]End points appropriate to the aim of the study.
[e]Unbiased assessment of the study end point.
[f]Follow-up period appropriate to the aim of the study
[g]Lost to follow-up <5%.
[h]Prospective calculation of the study size.
[i]An adequate control group.
[j]Contemporary groups.
[k]Baseline equivalence of groups.
[l]Adequate statistical analyses.

TABLE 3 Meta-analysis for LC vs. OC.

Outcome and trials (number of studies)	No. of studies	Sample size	Events	Pooled OR or MD (95% CI)	I^2 (%)	*P* value
Conversion	7	863	95	–	–	–
Continuous variables						
Operation time (min)	5	315/307	–	11.48 [−8.85, 31.81]	58	0.27
Blood loss (ml)	4	276/269	–	−121.12 [−236.08, −6.15]	79	0.04
Length of hospital stay (days)	5	315/307	–	−5.34 [−9.04, −1.64]	76	0.005
Soft diet start (days)	2	158/163	–	−3.58 [−10.14, 2.99]	97	0.29
Dichotomous variables						
Complications	5	315/307	70/109	0.49 [0.31, 0.77]	33	0.002
Wound infection	3	197/201	8/21	0.36 [0.15, 0.86]	0	0.02
Intra-abdominal abscess	2	145/144	10/9	1.08 [0.41, 2.81]	0	0.88
Ileus	3	197/201	15/25	0.41 [0.09, 1.80]	66	0.24
Anastomotic leakage	3	215/214	15/11	1.38 [0.61, 3.12]	0	0.44
Perioperative transfusion	3	631/582	87/137	0.39 [0.28, 0.55]	0	<0.01
Diverting stoma	3	215/214	7/13	0.54 [0.21, 1.41]	0	0.21
Mortality rate	4	276/269	3/2	1.39 [0.26, 7.47]	0	0.7
Oncological outcomes						
5-year overall survival	3	228/233	131/140	0.96 [0.82, 1.12][a]	0	0.6
5-year disease-free survival	3	228/233	121/125	0.98 [0.81, 1.20][a]	23	0.85
R0 resection rate	7	863/772	736/665	0.92 [0.69, 1.23]	0	0.57
Positive resection margin	2	561/512	120/100	1.10 [0.81, 1.49]	0	0.53
Lymph nodes harvested ≥12	2	154/142	141/131	0.92 [0.26, 3.25]	48	0.9
Recurrence	2	91/95	28/33	0.84 [0.45, 1.55]	0	0.57

[a]Pooled RR

0.49, 95% CI, 0.31–0.77, $P = 0.002$, Figure 2). Among overall complication, the pooled results showed a significant reduction in wound infection among the LC group (OR = 0.36, 95% CI, 0.15–0.86, $P = 0.02$). In addition, the incidence of perioperative transfusion in the LC group was lower than that in the OC group (OR = 0.39, 95% CI, 0.28–0.55, $P < 0.01$). The pooled results showed no significant differences in terms of intra-abdominal abscess (OR = 1.08, 95% CI, 0.41–2.81, $P = 0.88$), ileus (OR = 0.41, 95% CI, 0.09–1.80, $P = 0.24$), anastomotic leakage (OR = 1.38, 95% CI, 0.61–3.12, $P = 0.44$), diverting stoma (OR = 0.54, 95% CI, 0.21–1.41, $P = 0.21$), mortality (OR = 1.39, 95% CI, 0.26 = 7.47, $P = 0.7$), R0 resection rate (OR = 0.92, 95% CI, 0.69–1.23, $P = 0.57$), positive resection margin (OR = 1.10, 95% CI, 0.81–1.49, $P = 0.53$), and lymph nodes harvested ≥12 (OR = 0.92, 95% CI, 0.26–3.25, $P = 0.9$).

Oncological outcomes

The pooled results showed no significant difference in 5y OS between the LC group and OC group (RR = 0.96, 95% CI, 0.82–1.12, $P = 0.6$, Figure 2). Also, no significant difference was found in the rate of 5y DFS between the groups (RR = 0.98, 95% CI, 0.81–1.20, $P = 0.85$, Figure 2). There was no significant between-group difference in terms of recurrence (OR = 0.84, 95% CI, 0.45–1.55, $P = 0.57$) between the two groups.

Trial sequential analyses

The potential false-positive errors of the meta-analysis were found in the length of hospital stay (days) (Figure 3A), blood loss (Figure 3B), operation time (Figure 3C) and complications (Figure 3E), the TSA results showed that the cumulative Z-curve crossed the conventional boundary but did not cross the futility boundaries or the trial sequential

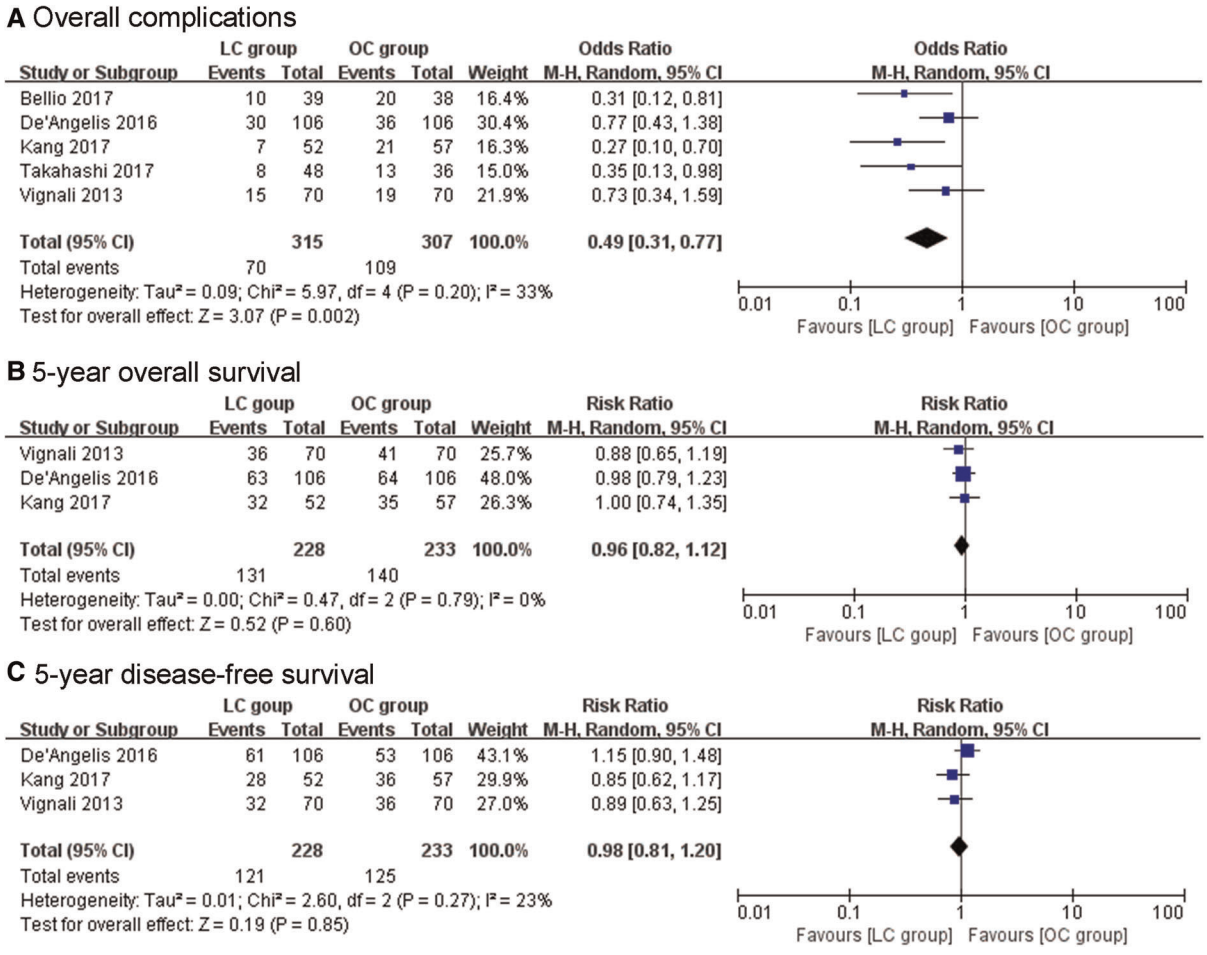

FIGURE 2
(A) The pooled results showed significant decrease in overall complications with LC compared with OC. (B, C) The pooled results showed no significant difference in 5-year overall survival and 5-year disease-free survival between the treatment groups.

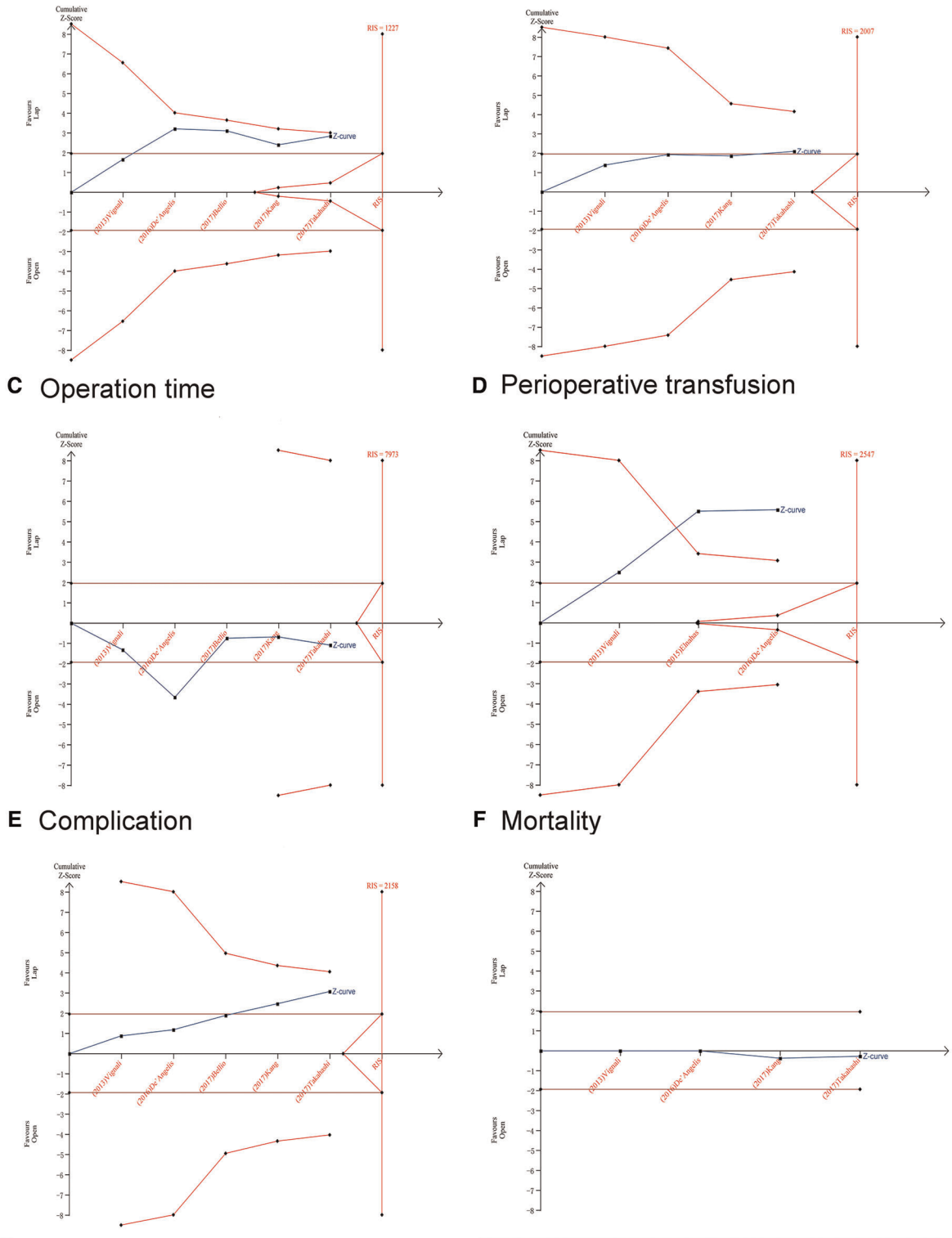

FIGURE 3
Trial sequential analysis (TSA). The adjusted required information size was calculated using α = 0.05 (two-sided), β = 0.20 (power 80%), and an empirical mean difference. (A) Hospital stay (days); (B) Blood loss; (C) Operation time; (D) Perioperative transfusion; (E) Complication; (F) Mortality.

monitoring boundary (TSMB). Therefore, more trials are needed before drawing a definite conclusion. For mortality (Figure 3F), recurrence (Figure 4E), and positive resection margin status (Figure 4F), neither the TSMB nor the traditional boundary was crossed, indicating the lack of specific evidence and the need for more research. For perioperative transfusion (Figure 3D), the cumulative Z-curve crossed the TSMB and the traditional boundary, indicating conclusive evidence in the LC group compared with the OC group. The meta-analyses of 5y OS (Figure 4A) and 5y DFS (Figure 4B) did not differ statistically significant; the cumulative Z-curve crossed neither the traditional boundary nor the TSMB, but it crossed the futility boundaries, suggesting no statistical significance between-group difference and no need of further study. The cumulative Z-curve of lymph nodes harvested ≥12 (Figure 4C) and R0 resection rate (Figure 4D) crossed the RIS, suggesting firm evidence of no statistical significance in the LC group compared with OC group.

GRADE of the outcomes

The GRADE system was applied to synthesize and evaluate the evidence level for the outcomes (Table 4). The power of evidence was moderate in length of hospital stay, complications, ileus, diverting stoma, and wound infection, while it was low in operation time, blood loss, R0 resection rate, mortality, 5y OS, 5y DFS, lymph nodes harvested ≥12, anastomotic leakage, intra-abdominal abscess, infectious complication, recurrence, and adjuvant chemotherapy. The level of evidence was high in perioperative transfusion and very low in soft diet start.

Evaluation of publication bias

A funnel plot of R0 resection rate was applied to visually assess publication bias in this meta-analysis. The funnel plot of R0 resection rate suggested a lack of publication bias (Figure 5).

Discussion

The safety and oncological outcomes of LC for pT4 colon cancer remain controversial. In the meta-analysis, we included 7 prospective observational studies comparing the efficacy of LC with OC for colon cancer, all of which are scored as high-quality studies based on the MINORS scores (42–48). The results showed that LC could be performed with lesser perioperative transfusion, lesser blood loss, lesser complications, lesser wound infection, and shorter length of hospital stay. Furthermore, there was no significant difference between the two groups in terms of 5y OS, 5y DFS, R0 resection rate, positive resection margin, lymph nodes harvested ≥12, and recurrence. Based on the TSA results, the current evidence for the potential advantages of LC on perioperative transfusion appeared reliable and conclusive. Meanwhile, TSA results suggested that the comparable outcomes in terms of 5y OS, 5y DFS, lymph nodes harvested ≥12, and R0 resection rate drawn from this meta-analysis were reliable and no need of further study.

The perioperative short-term outcomes were significantly more superior in the LC group for colon cancer in terms of lesser blood loss, lesser perioperative transfusion, lesser complications, lesser wound infection, and shorter length of hospital stay. Moreover, the evidence of the advantage of LC on perioperative blood transfusion seemed to be reliable and decisive. Based on the existing literature, LC for T4a colon tumor might be safe, but it should be performed cautiously for T4b colon cancer requiring multivisceral resection (MVR) (6, 49, 50). However, several study groups have reported the safety and effectiveness of Lap MVR (47, 51, 52). Both studies considered that patients with urinary tract invasion were not suitable for lap MVR because the technical complexity and possibility of complications outweighed the gains (47, 48). Nevertheless, with the maturity of laparoscopic surgery technology, especially with the appearance of robotic surgery, ureterectomy and anastomosis had accumulated rich experience. Therefore, this technology depends, at least to some extent, on the technology of urologists in each hospital.

However, several studies reported that MVR was related to high postoperative morbidity and increased risk of conversion (49, 50, 53). Some studies have pointed out that preoperative conversion was associated with poor postoperative outcomes, such as increased postoperative complication rate and mortality, and even a poor prognosis (54, 55). However, studies have reported that conversion has been divided into two types: (I) strategic conversion, which is a prescient decision to avoid complications; (II) reactive conversion, i.e., laparotomy due to unexpected surgical difficulties or complications (56, 57). It is well known that strategic conversion can bring better results than reactive conversion (56). Takahashi et al. reported that except for one case of reactive conversion due to intraoperative bleeding, the other five cases were strategic conversion. The results showed that the reported postoperative complication rate was relatively low, the patient's hospital stay was not prolonged, and the oncological results were favorable. This suggested that strategic conversion might not have a significant unfavorable effect on short- and long-term outcomes.

Another worry is the risk of R1 resection-insufficient clearance of cancer tissue. Our meta-analysis results showed that there were no differences in the R0 resection rate treated

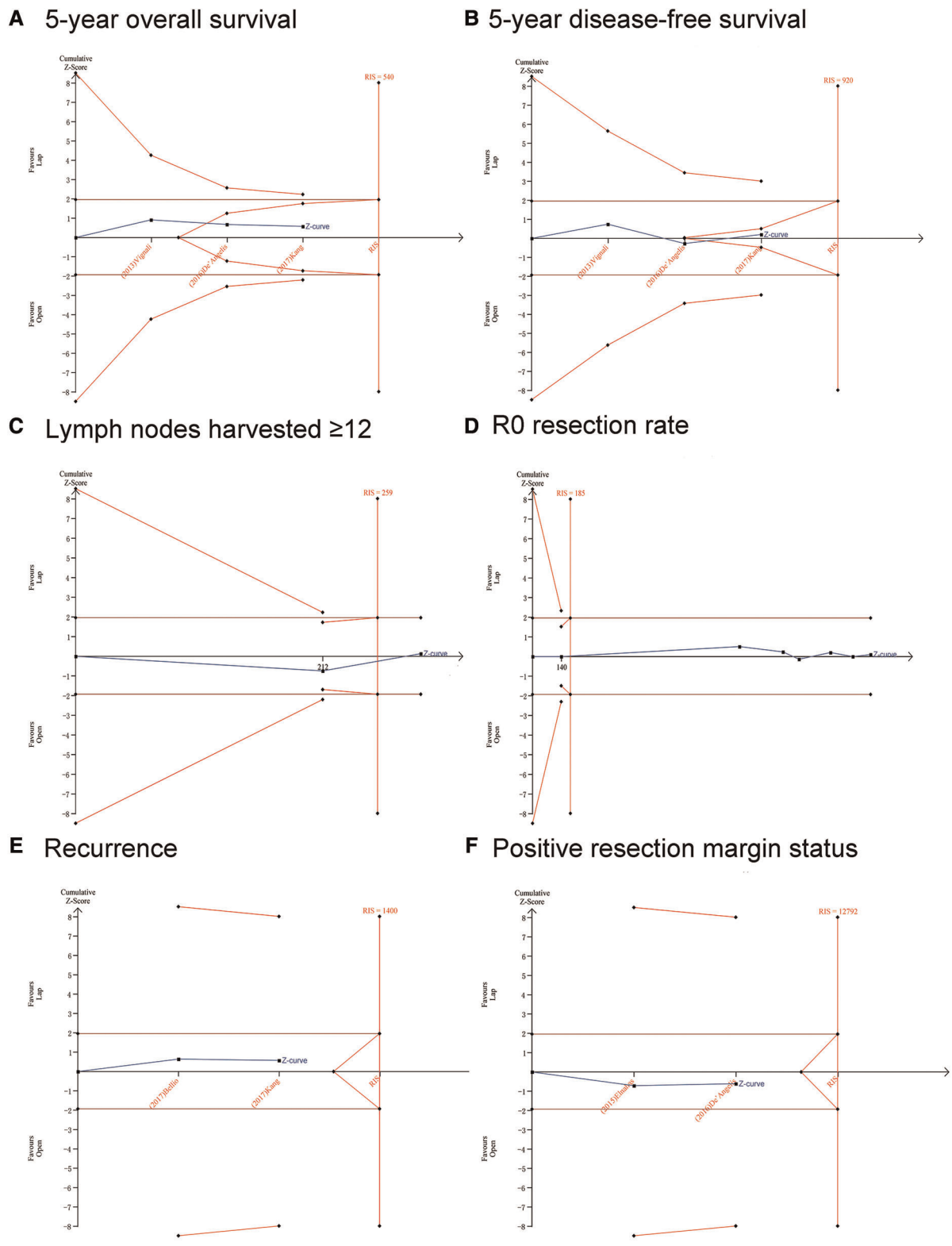

FIGURE 4
Trial sequential analysis (TSA). The adjusted required information size was calculated using α = 0.05 (two-sided), β = 0.20 (power 80%), and an empirical mean difference. (**A**) 5-year overall survival; (**B**) 5-year disease-free survival; (**C**) Lymph nodes harvested ≥12; (**D**) R0 resection rate; (**E**) Recurrence; (**F**) Positive resection margin status.

TABLE 4 Strength of evidence for LC in patients with T4 colon cancer compared with OC.

Outcomes	Anticipated absolute effects: Corresponding risk with Lap	95% CI	No of participants (studies)	Quality of evidence (GRADE)
Operation time	The mean in the intervention groups was 11.48 higher	8.85 lower to 31.81 higher	622 (5 studies)	LOW
Blood loss	The mean in the intervention groups was 121.12 lower	236.08 to 6.15 lower	545 (4 studies)	LOW
Length of hospital stay (days)	The mean in the intervention groups was 5.34 lower	9.04 to 1.64 lower	622 (5 studies)	MODERATE
Soft diet start (days)	The mean in the intervention groups was 3.58 lower	10.14 lower to 2.99 higher	321 (2 studies)	VERY LOW
	Study population Corresponding risk with Lap	**Assumed risk with Open**	**Relative effect (95% CI)**	
Conversion	120 per 1,000 (101–143)			
R0 resection rate	851 per 1,000 (811–884)	861 per 1,000	OR 0.92 (0.69–1.23)	1,635 (7 studies)	LOW
Complications	212 per 1,000 (146–298)	355 per 1,000	OR 0.49 (0.31–0.77)	622 (5 studies)	MODERATE
Mortality	10 per 1,000 (2–53)	7 per 1,000	OR 1.39 (0.26–7.47)	545 (4 studies)	LOW
5-year OS	575 per 1,000 (483–662)	601 per 1,000	OR 0.9 (0.62–1.3)	461 (3 studies)	LOW
5-year DFS	526 per 1,000 (422–630)	536 per 1,000	OR 0.96 (0.63–1.47)	461 (3 studies)	LOW
Resection margin status	211 per 1,000 (164–266)	195 per 1,000	OR 1.1 (0.81–1.49)	1,073 (4 studies)	LOW
Perioperative transfusion	100 per 1,000 (74–135)	222 per 1,000	OR 0.39 (0.28–0.55)	1,213 (3 studies)	HIGH
Ileus	55 per 1,000 (13–204)	124 per 1,000	OR 0.41 (0.09–1.8)	398 (3 studies)	MODERATE
Lymph nodes harvested ≥12	916 per 1,000 (756–975)	923 per 1,000	OR 0.92 (0.26–3.25)	296 (2 studies)	LOW
Diverting stoma	34 per 1,000 (13–84)	61 per 1,000	OR 0.54 (0.21–1.41)	429 (3 studies)	MODERATE
Anastomotic leakage	70 per 1,000 (32–145)	51 per 1,000	OR 1.38 (0.61–3.12)	429 (3 studies)	LOW
Wound infection	40 per 1,000 (17–91)	104 per 1,000	OR 0.36 (0.15–0.86)	398 (3 studies)	MODERATE
Intra-abdominal abscess	67 per 1,000 (27–158)	62 per 1,000	OR 1.08 (0.41–2.81)	289 (2 studies)	LOW
Infectious complication	130 per 1,000 (85–196)	185 per 1,000	OR 0.66 (0.41–1.08)	538 (4 studies)	LOW
Recurrence	309 per 1,000 (193–452)	347 per 1,000	OR 0.84 (0.45–1.55)	186 (2 studies)	LOW
Adjuvant chemotherapy	619 per 1,000 (498–730)	624 per 1,000	OR 0.98 (0.59–1.63)	538 (4 studies)	LOW

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

with laparoscopic surgery and the evidence of comparable R0 resection rates was reliable. R0 resection was very important for the cancer treatment of T4 patients, and it was also the principal factor affecting the survival after MVR (47, 49, 58). Some people worried that choosing the lap method might threaten the implementation of R0 (48). The COLOR trial, about 20% of T4 patients detected a microscope positive edge (R1), compared to 1% of T3 patients; However, the open group had little superiority (T4, 17.6%; T3, 1.0%) (59). Takahashi et.al reported that the R1 rate in lap group did not increase and two patients in lap group underwent R1 palliative resection for stage IV patients (47). Therefore, the risk of R1 resection in the treatment of T4 tumors with Lap method had not been fully confirmed.

Although the oncological safety of LC in the treatment of colon cancer has been confirmed, there were scarce data on LC in the treatment of T4 colon cancer. In this meta-analysis and TSA of 7 prospective observational studies, there was no significant difference in 5y OS, 5y DFS between two group patients, which was in line with previous studies (4, 60). The above results showed that the oncological results of LC for pT4 colon cancer are acceptable.

Our results also revealed that laparoscopic surgery did not increase the recurrence rate of T4 colon cancer patients when compared with open surgery. Consistent with our research, several large meta-analysis and original research had confirmed this conclusion (4, 8, 61, 62). However, after literature search, there were still several reports that

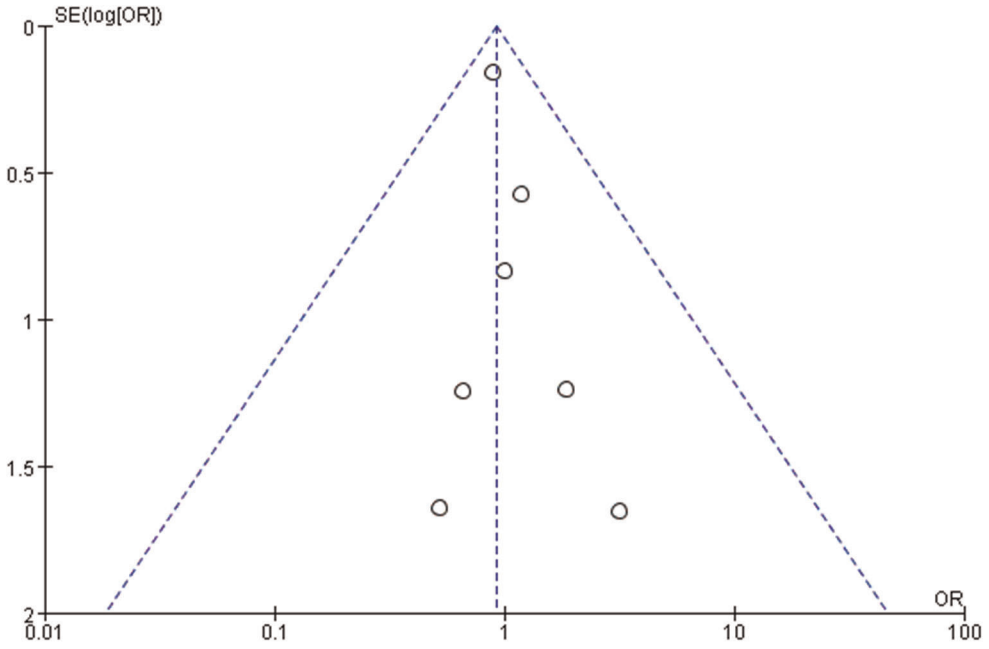

FIGURE 5
The bilateral symmetry shaped funnel plot of R0 resection rate indicated a lack of publication bias.

laparoscopic surgery could increase the peritoneal and trocar recurrence rate of T4 colon cancer patients (63–67). Wang et al. reported that laparoscopic colectomy for T4 colon cancer had a higher peritoneal recurrence rate than open surgery (18.1 vs. 10.6 percent; RR 1.56, 1.23–1.99; $P = 0.0003$) (66). In addition, a review published in 1998 showed that trocar recurrence seemed to be secondary to a variety of factors, including pneumoperitoneum, laparoscopic instruments, biologic properties of the tumor, local trauma, and individual surgical skills (63). Therein, careful patient selection in operative approach for T4 colon cancer is needed especially for patients at high risk of intraperitoneal tumor spread.

Recently, there had also been studies on the safety and effectiveness of robot approaches for T4 colon cancer (68–70). An NCDB propensity score-matched analysis of open, laparoscopic, and robotic approaches demonstrated that compared with T4 colon cancer open resection, laparoscopic and robot-assisted surgery had achieved better tumor prognosis and survival rate and robot-assisted surgery was significantly associated with a lower conversion rate compared with laparoscopic surgery (69). This case-matching study demonstrated the safety of using minimally invasive techniques in T4 colon cancers (69). Further multicenter, large-sample randomized controlled trials are needed to verify these results.

Our present meta-analysis has several advantages. The search methodology and inclusion criteria were rigorous, with a systematic literature search to determine the relevant prospective observational studies without restrictions. Further, TSA integrated information indicators and effect indicators, which was more conservative and might be more accurate. In the evaluation setting of non-significant results, TSA could help determine whether "more studies needed" to reduce uncertainty when cumulative Z-curve did not cross the futility boundary. However, this study has some shortcomings. First, there were no randomized controlled trials and no information on quality of life in the literature included in this meta-analysis. Second, because different literatures had different definitions of T4 (T4a vs. T4b, clinical T4 vs. pathological T4), there was heterogeneity between the studies.

Conclusion

In conclusion, laparoscopic surgery is as acceptable as open surgery for T4 colon cancer in terms of the conversion rate, R0 resection rate, short-term and oncological outcomes. laparoscopic surgery is an innovative and promising approach for the treatment of T4 colon cancer. TSA results demonstrated that further research is not needed to evaluate the 5y OS, 5y DFS, R0 resection rate, positive resection margin status, lymph nodes harvested ≥12 and perioperative transfusion differences between two techniques. Additional multicenter, large-sample randomized controlled trials to

evaluate the safety and effectiveness of robot and laparoscope technology for T4 colon cancer are needed in the future.

Author contributions

LY and PC: participated in the conception and design of this meta-analysis. PC and HZ: conducted the literature searching and performed a quality evaluation of included studies by MINORS. PC, HZ and CC: acquired the data. PC, HZ and XQ: performed the statistical analysis and interpretation of data. PC: wrote the manuscript. LY and ZZ: reviewed the manuscript. LY: revised and supervised the study. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by National Key Research and Development Program of China [grant no. 2016YFC0906000 (2016YFC0906003)]; National Natural Science Foundation of China [grant no. 81472304]; Sichuan Science and Technology Program [grant no. 2017JY0020]; and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (grant no. 2016105, ZYGD20006)

Acknowledgments

The authors thank the reviewers for their helpful comments on this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA: Cancer J Clin*. (2022) 72:7–33. doi: 10.3322/caac.21708

2. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol*. (2019) 16:713–32. doi: 10.1038/s41575-019-0189-8

3. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet*. (2014) 383:1490–502. doi: 10.1016/s0140-6736(13)61649-9

4. Feinberg AE, Chesney TR, Acuna SA, Sammour T, Quereshy FA. Oncologic outcomes following laparoscopic vs. open resection of pT4 colon cancer: a systematic review and meta-analysis. *Dis Colon Rectum*. (2017) 60:116–25. doi: 10.1097/dcr.0000000000000641

5. Kumamoto T, Toda S, Matoba S, Moriyama J, Hanaoka Y, Tomizawa K, et al. Short- and long-term outcomes of laparoscopic multivisceral resection for clinically suspected T4 colon cancer. *World J Surg*. (2017) 41:2153–9. doi: 10.1007/s00268-017-3976-9

6. Klaver CEL, Kappen TM, Borstlap WAA, Bemelman WA, Tanis PJ. Laparoscopic surgery for T4 colon cancer: a systematic review and meta-analysis. *Surg Endosc*. (2017) 31:4902–12. doi: 10.1007/s00464-017-5544-7

7. Yamanashi T, Nakamura T, Sato T, Naito M, Miura H, Tsutsui A, et al. Laparoscopic surgery for locally advanced T4 colon cancer: the long-term outcomes and prognostic factors. *Surg Today*. (2018) 48:534–44. doi: 10.1007/s00595-017-1621-8

8. Liu ZH, Wang N, Wang FQ, Dong Q, Ding J. Oncological outcomes of laparoscopic vs. open surgery in pT4 colon cancers: a systematic review and meta-analysis. *Int J Surg*. (2018) 56:221–33. doi: 10.1016/j.ijsu.2018.06.032

9. Rondelli F, Trastulli S, Avenia N, Schillaci G, Cirocchi R, Gullà N, et al. Is laparoscopic right colectomy more effective than open resection? A meta-analysis of randomized and nonrandomized studies. *Colorectal Disease*. (2012) 14:e447–469. doi: 10.1111/j.1463-1318.2012.03054.x

10. Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. *J Cancer*. (2012) 3:49–57. doi: 10.7150/jca.3621

11. Montie JE, Clark PE, Eisenberger MAJJotNCCNJ. National comprehensive cancer network. *Colon Cancer Guidel*. (2006).

12. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. *Cancer Treat Rev*. (2008) 34:498–504. doi: 10.1016/j.ctrv.2008.03.011

13. Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, et al. Multicenter randomized controlled trial of conventional vs. laparoscopic surgery for colorectal cancer within an enhanced recovery programme: enrol. *J Clin Oncol*. (2014) 32:1804–11. doi: 10.1200/jco.2013.54.3694

14. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK mrc clasicc trial group. *J Clin Oncol*. (2007) 25:3061–8. doi: 10.1200/jco.2006.09.7758

15. Jackson TD, Kaplan GG, Arena G, Page JH, Rogers Jr SO. Laparoscopic vs. open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg*. (2007) 204:439–46. doi: 10.1016/j.jamcollsurg.2006.12.008

16. Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, et al. Long-term follow-up of the medical research council clasicc trial of conventional vs. laparoscopically assisted resection in colorectal cancer. *Br J Surg*. (2013) 100:75–82. doi: 10.1002/bjs.8945

17. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart Jr RW, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the cost study group trial. *Ann Surg*. (2007) 246:655–62; discussion 662-654. doi: 10.1097/SLA.0b013e318155a762

18. Di B, Li Y, Wei K, Xiao X, Shi J, Zhang Y, et al. Laparoscopic vs. open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes. *Surg Oncol*. (2013) 22:e39–43. doi: 10.1016/j.suronc.2013.03.002

19. Deijen CL, Vasmel JE, de Lange-de Klerk ESM, Cuesta MA, Coene PLO, Lange JF, et al. Ten-year outcomes of a randomised trial of laparoscopic vs. open surgery for colon cancer. *Surg Endosc*. (2017) 31:2607–15. doi: 10.1007/s00464-016-5270-6

20. Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, et al. Survival after laparoscopic surgery vs. open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol*. (2009) 10:44–52. doi: 10.1016/s1470-2045(08)70310-3

21. Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. (2004) 350:2050–9. doi: 10.1056/NEJMoa032651

22. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of conventional vs. laparoscopic-assisted surgery in patients with colorectal cancer (mrc clasicc trial): multicentre, randomised controlled trial. *Lancet (London, England)*. (2005) 365:1718–26. doi: 10.1016/s0140-6736(05)66545-2

23. Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, et al. The long-term results of a randomized clinical trial of laparoscopy-assisted vs. open surgery for colon cancer. *Ann Surg*. (2008) 248:1–7. doi: 10.1097/SLA.0b013e31816a9d65

24. Bagshaw PF, Allardyce RA, Frampton CM, Frizelle FA, Hewett PJ, McMurrick PJ, et al. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the australasian laparoscopic colon cancer study trial. *Ann Surg*. (2012) 256:915–9. doi: 10.1097/SLA.0b013e3182765ff8

25. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of laparoscopic-assisted resection vs open resection of stage ii or iii rectal cancer on pathologic outcomes: the acosog z6051 randomized clinical trial. *Jama*. (2015) 314:1346–55. doi: 10.1001/jama.2015.10529

26. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, et al. Open vs. laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (corean trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol*. (2010) 11:637–45. doi: 10.1016/s1470-2045(10)70131-5

27. Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. Open vs. laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (corean trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol*. (2014) 15:767–74. doi: 10.1016/s1470-2045(14)70205-0

28. Mathis KL, Nelson H. Controversies in laparoscopy for colon and rectal cancer. *Surg Oncol Clin N Am*. (2014) 23:35–47. doi: 10.1016/j.soc.2013.09.006

29. Shukla PJ, Trencheva K, Merchant C, Maggiori L, Michelassi F, Sonoda T, et al. Laparoscopic resection of T4 colon cancers: is it feasible? *Dis Colon Rectum*. (2015) 58:25–31. doi: 10.1097/dcr.0000000000000220

30. de'Angelis N, Landi F, Vitali GC, Memeo R, Martínez-Pérez A, Solis A, et al. Multicentre propensity score-matched analysis of laparoscopic vs. open surgery for T4 rectal cancer. *Surg Endosc*. (2017) 31:3106–21. doi: 10.1007/s00464-016-5332-9

31. Borm GF, Donders AR. Updating meta-analyses leads to larger type i errors than publication bias. *J Clin Epidemiol*. (2009) 62:825–830.e810. doi: 10.1016/j.jclinepi.2008.08.010

32. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*. (2008) 61:64–75. doi: 10.1016/j.jclinepi.2007.03.013

33. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol*. (2009) 38:276–86. doi: 10.1093/ije/dyn179

34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *Br Med J*. (2009) 339:b2535. doi: 10.1136/bmj.b2535

35. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. (2003) 73:712–6. doi: 10.1046/j.1445-2197.2003.02748.x

36. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J*. (2008) 336:924–6. doi: 10.1136/bmj.39489.470347.AD

37. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg*. (2016) 103:e21–28. doi: 10.1002/bjs.10062

38. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. (2005) 5:13. doi: 10.1186/1471-2288-5-13

39. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

40. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. (1986) 7:177–88. doi: 10.1016/0197-2456(86)90046-2

41. Bobo Z, Xin W, Jiang L, Quan W, Liang B, Xiangbing D, et al. Robotic gastrectomy vs. laparoscopic gastrectomy for gastric cancer: meta-analysis and trial sequential analysis of prospective observational studies. *Surg Endosc*. (2019) 33:1033–48. doi: 10.1007/s00464-018-06648-z

42. Bellio G, Lo Cicero A, Barbieri V, Tarchi P, Casagranda B NDEM. Is T4 colon cancer still an absolute contraindication to laparoscopic surgery? *Minerva Chir*. (2017) 72:483–90. doi: 10.23736/s0026-4733.17.07378-3

43. Chan DK, Tan KK. Laparoscopic surgery should be considered in T4 colon cancer. *Int J Colorectal Dis*. (2017) 32:517–20. doi: 10.1007/s00384-016-2702-7

44. de'Angelis N, Vitali GC, Brunetti F, Wassmer CH, Gagniere C, Puppa G, et al. Laparoscopic vs. Open surgery for T4 colon cancer: a propensity score analysis. *Int J Colorectal Dis*. (2016) 31:1785–97. doi: 10.1007/s00384-016-2646-y

45. Elnahas A, Sunil S, Jackson TD, Okrainec A, Quereshy FA. Laparoscopic vs. open surgery for T4 colon cancer: evaluation of margin status. *Surg Endosc*. (2016) 30:1491–6. doi: 10.1007/s00464-015-4360-1

46. Kang J, Baik SH, Lee KY, Sohn SK. Outcomes of laparoscopic surgery in pathologic T4 colon cancers compared to those of open surgery. *Int J Colorectal Dis*. (2017) 32:531–8. doi: 10.1007/s00384-016-2720-5

47. Takahashi R, Hasegawa S, Hirai K, Hisamori S, Hida K, Kawada K, et al. Safety and feasibility of laparoscopic multivisceral resection for surgical T4b colon cancers: retrospective analyses. *Asian J Endosc Surg*. (2017) 10:154–61. doi: 10.1111/ases.12355

48. Vignali A, Ghirardelli L, Di Palo S, Orsenigo E, Staudacher C. Laparoscopic treatment of advanced colonic cancer: a case-matched control with open surgery. *Colorectal Dis*. (2013) 15:944–8. doi: 10.1111/codi.12170

49. Hoffmann M, Phillips C, Oevermann E, Killaitis C, Roblick UJ, Hildebrand P, et al. Multivisceral and standard resections in colorectal cancer. *Langenbeck's Arch Surg*. (2012) 397:75–84. doi: 10.1007/s00423-011-0854-z

50. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: a systematic review. *Ann Surg Oncol*. (2013) 20:2929–36. doi: 10.1245/s10434-013-2967-9

51. 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. doi: 10.1007/s00464-011-1907-7

52. Nagasue Y, Akiyoshi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, et al. Laparoscopic vs. open multivisceral resection for primary colorectal cancer: comparison of perioperative outcomes. *J. Gastrointest. Surg*. (2013) 17:1299–305. doi: 10.1007/s11605-013-2222-5

53. Nakafusa Y, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K. Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. *Dis Colon Rectum*. (2004) 47:2055–63. doi: 10.1007/s10350-004-0716-7

54. Marusch F, Gastinger I, Schneider C, Scheidbach H, Konradt J, Bruch HP, et al. Importance of conversion for results obtained with laparoscopic colorectal surgery. *Dis Colon Rectum*. (2001) 44:207–14; discussion 214-206. doi: 10.1007/bf02234294

55. Clancy C, O'Leary DP, Burke JP, Redmond HP, Coffey JC, Kerin MJ, et al. A meta-analysis to determine the oncological implications of conversion in laparoscopic colorectal cancer surgery. *Colorectal Disease*. (2015) 17:482–90. doi: 10.1111/codi.12875

56. Yang C, Wexner SD, Safar B, Jobanputra S, Jin H, Li VK, et al. Conversion in laparoscopic surgery: does intraoperative complication influence outcome? *Surg Endosc*. (2009) 23:2454–8. doi: 10.1007/s00464-009-0414-6

57. Blikkendaal MD, Twijnstra AR, Stiggelbout AM, Beerlage HP, Bemelman WA, Jansen FW. Achieving consensus on the definition of conversion to laparotomy: a delphi study among general surgeons, gynecologists, and urologists. *Surg Endosc*. (2013) 27:4631–9. doi: 10.1007/s00464-013-3086-1

58. Valentini V, Coco C, Rizzo G, Manno A, Crucitti A, Mattana C, et al. Outcomes of clinical T4m0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. *Surgery*. (2009) 145:486–94. doi: 10.1016/j.surg.2009.01.007

59. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic surgery vs. open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol*. (2005) 6:477–84. doi: 10.1016/s1470-2045(05)70221-7

60. Völkel V, Draeger T, Gerken M, Klinkhammer-Schalke M, Fürst A. Long-term oncologic outcomes after laparoscopic vs. Open colon cancer resection: a high-quality population-based analysis in a southern German district. *Surg Endosc*. (2018) 32:4138–47. doi: 10.1007/s00464-018-6158-4

61. Sueda T, Tei M, Nishida K, Yoshikawa Y, Matsumura T, Koga C, et al. Oncological outcomes following laparoscopic surgery for pathological T4 colon cancer: a propensity score-matched analysis. *Surg Today*. (2021) 51:404–14. doi: 10.1007/s00595-020-02106-3

62. Podda M, Pisanu A, Morello A, Segalini E, Jayant K, Gallo G, et al. Laparoscopic vs. open colectomy for locally advanced T4 colonic cancer: meta-analysis of clinical and oncological outcomes. *Br J Surg*. (2022) 109:319–31. doi: 10.1093/bjs/znab464

63. Schaeff B, Paolucci V, Thomopoulos J. Port site recurrences after laparoscopic surgery. A review. *Dig Surg*. (1998) 15:124–34. doi: 10.1159/000018605

64. Nagata H, Kawai K, Hata K, Tanaka T, Nozawa H, Ishihara S. Laparoscopic surgery for T4 colon cancer: a risk factor for peritoneal recurrences? *Surgery*. (2020) 168:119–24. doi: 10.1016/j.surg.2020.02.026

65. Huynh C, Minkova S, Kim D, Stuart H, Hamilton TD. Laparoscopic vs. open resection in patients with locally advanced colon cancer. *Surgery*. (2021) 170:1610–5. doi: 10.1016/j.surg.2021.07.027

66. Wang X, Zheng Z, Xie Z, Chi P. Laparoscopic colectomy for T4 colon cancer conferred an increased risk of peritoneal recurrence: a meta-analysis. *Asian J Surg*. (2022) 45:2285–6. doi: 10.1016/j.asjsur.2022.05.010

67. Kwong MLM, Sampah MES, Bello BL, Sugarbaker PH. Port site metastases after minimally invasive resection for colorectal cancer: a retrospective study of 13 patients. *Surg Oncol*. (2019) 29:20–4. doi: 10.1016/j.suronc.2019.02.008

68. Crolla R, Tersteeg JJC, van der Schelling GP, Wijsman JH, Schreinemakers JMJ. Robot-assisted laparoscopic resection of clinical T4b tumours of distal sigmoid and rectum: initial results. *Surg Endosc*. (2018) 32:4571–8. doi: 10.1007/s00464-018-6210-4

69. Parascandola SA, Horsey ML, Hota S, Sparks AD, Tampo MMT, Kim G, et al. Surgical resection of T4 colon cancers: an ncdb propensity score-matched analysis of open, laparoscopic, and robotic approaches. *J Robot Surg*. (2021) 15:701–10. doi: 10.1007/s11701-020-01166-4

70. Huscher CGS, Lazzarin G, Marchegiani F, Marks J. Robotic right colectomy with robotic-sewn anastomosis: a pilot case series. *J Robot Surg*. (2022). doi: 10.1007/s11701-022-01435-4

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 08 November 2022
DOI 10.3389/fsurg.2022.960698

OPEN ACCESS

EDITED BY
Wei Li,
Xiangya Hospital, Central South University, China

REVIEWED BY
Guiliang Wang,
Central South University, China
Sawsan A. Zaitone,
Suez Canal University, Egypt

*CORRESPONDENCE
Xiao-hong Deng,
dengxiaohong_1107@163.com
Yufen Jiang,
51860781@qq.com
Yuancai Xie,
xyc0505@163.com

†These authors contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 03 June 2022
ACCEPTED 17 October 2022
PUBLISHED 08 November 2022

CITATION
Zhang L, He Y, Tu X, Wang C, Ding X, Ye R, Shi J, Xie Y, Jiang Y and Deng X (2022) FOXC2 as a prognostic marker and a potential molecular target in patients with human solid tumors. Front. Surg. 9:960698. doi: 10.3389/fsurg.2022.960698

FOXC2 as a prognostic marker and a potential molecular target in patients with human solid tumors

Long Zhang[1†], Yong He[1†], Xiaohong Tu[2], Chao Wang[3], Xiaojun Ding[1], Rongqiang Ye[1], Jiayu Shi[3,4], Yuancai Xie[1*], Yufen Jiang[5*] and Xiaohong Deng[1*]

[1]Department of Hepatopancreatobiliary Surgery, Ganzhou People's Hospital of Jiangxi Province (Ganzhou Hospital Affiliated to Nanchang University), Ganzhou, China, [2]Department of Physical Education, Ganzhou Teachers College, Ganzhou, China, [3]Hepatic Surgery Center, Institute of Hepato-pancreato-biliary Surgery, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [4]Department of Hepato-pancreato-biliary Surgery, Wuhan University of Science and Technology, Wuhan, China, [5]Department of Gastroenterology, Kezhou People's Hospital, Atushi, China

Background: Forkhead Box Protein C2 (FOXC2) belongs to the Forkhead/Wing-helix family. The regulatory role of this transcription factor in physiological function and carcinogenic activity has been proven in subsequent investigations. However, there is still scarcity of evidence on the relationship between FOXC2 expression and prognosis in human solid tumors. We conducted this meta-analysis to evaluate the role of FOXC2 as a prognosis factor and a possible target marker in human solid tumors.

Methods: PubMed, Web of Science, Embase, and the Cochrane library database were all searched methodically. Eligible publications on FOXC2 in human solid tumors were gathered and reviewed. The effect sizes were calculated using pooled hazard ratios (HRs) or odds ratios (ORs) with the corresponding 95% confidence interval (CI). Statistical analysis was conducted with Stata SE12.0.

Results: This meta-analysis comprised 3,267 patients from 20 studies covering a variety of solid tumors. Increased FOXC2 expression was related to shorter overall survival (OS) (HR = 2.05, 95% CI: 1.73–2.42). High expression of FOXC2 is associated with lymph node metastases (OR = 3.33, 95% CI: 2.65–4.19), TNM stage (OR = 3.09, 95% CI: 2.00–4.78), and age (OR = 1.26, 95% CI: 1.06–1.50), according to the pooled ORs. However, no significant association was observed between the high expression of FOXC2 and sex, tumor size or tumor differentiation.

Conclusion: Increased expression of FOXC2 is associated with unfavored OS, lymph node metastases, TNM stage, and age. FOXC2 is a promising prognostic marker and a novel target marker in human solid tumors.

KEYWORDS

FOXC2, solid tumor, prognosis, survival, tumor biomarker

Introduction

The transcription factor forkhead box (FOX) is a family with a highly conserved winged-helix DNA-binding domain (1, 2). FOX family members are involved in cell growth, differentiation, aging and carcinogenesis, and various regulatory and functional activities (3, 4). From FOXA to FOXR, there are 17 gene subfamilies of FOX and more than 14 have been identified in humans (5). FOXC2, also known as the mesenchyme forkhead-1 (MHF1), consists of a single exon located on the chromosomal band 16p24.1 (6). FOXC2 is necessary for the development of the lungs (7), bone (8), cardiovascular system (9), adipose tissue in adults (10), and various other organs or tissues. In addition to physiologic functions as cellular metabolism, angiogenesis and wound healing, dysregulated FOXC2 contributes to tumorigenesis and malignancy progression in cell proliferation, metabolic reprogramming, lymph-angiogenesis, epithelial-mesenchymal transition (EMT), and drug resistance (11–16). Recent studies have reported that FOXC2 is dysregulated in malignancies, including breast cancer (13), gastric cancer (17), esophageal carcinoma (18).

Currently, there is an increasing interest on the oncogenic role of FOXC2 both *in vivo* and *in vitro*. FOXC2 has also merged as a potential molecular target in preclinical/clinical studies due to the dysregulated expression level and nuclear localization. Previous studies have associated expression levels of FOXC2 with clinical and pathological characteristics including tumor size, differentiation, metastasis, and stage (19, 20). However, there is still lack of proof that FOXC2 expression in human solid tumors has significant predict value. This analysis was carried out in order to systematically assess the potential prognostic significancy of FOXC2.

Methods

Literature search

A systematic literature search was undertaken in PubMed, Web of Science, Embase, and Cochrane library databases before April, 2022. The following keywords and search terms were used to find potentially eligible studies: ("Forkhead box protein C2" OR "*FOXC2*" OR "*MHF1*" OR "mesenchyme forkhead1") AND ("cancer" OR "carcinoma" OR "neoplasm" OR "tumor" OR "malignancy") AND ("prognosis" OR "survival"). Additional research was found by looking through the references of the selected articles. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used in this analysis (21).

Study selection

The following were the selection criteria of this analysis: (1) patients with solid tumors diagnosed pathologically; (2) the expression FOXC2 in tissue were determined by immunohistochemistry (IHC) or quantitative real-time polymerase chain reaction (q-PCR); (3) available data for calculating odds ratio (OR) with 95% CIs were depicted; (4) only the study with the most extensive or recent data was considered, if multiple publications used employed overlapping samples from the same institution; (5) patients were categorized into groups based on high and low FOXC2 expression levels. Exclusion criteria in this meta-analysis were as follows: (1) duplicate publications; (2) research with no data or data from animal or cellular experiments; (3) only serum levels of FOXC2 expression were detected; (4) studies only provided Kaplan-Meier curves but no multivariate data; (5) reviews, letters, case reports, or expert opinions.

Date extraction and quality assessment

The two independent investigators screened the all publications, classified and sorted out the titles and abstracts of the literature retrieved from reading, excluded duplicate literatures and literature failed inclusion criteria, contacted the original author for relevant information for the literature with incomplete information report, and determined whether it could be included in the final study after obtaining the full text. The research team shall assist in solving any dispute. The following information was retrieved from eligible articles: name of first author; publication year; sample size; cancer kind; criteria for increased expression of FOXC2; detecting methodology; outcome measuring; patient follow-up; HRs with corresponding 95% CI; and clinical characteristics (age, sex, tumor size, lymph node metastases, distant metastases, TNM stage). We preferred multivariate analysis in research with both univariate and multivariate analyses because it is better at explaining confounding factors. If there was a disagreement, a compromise was sought through debate until everyone agreed. The quality evaluation for eligible studies was undertaken by 2 independent investigators (CW and LZ), and any discrepancies were handled by consensus among all authors. The Newcastle-Ottawa Scale (NOS) tool was used to evaluate the quality of all eligible studies (22). The NOS scores ranged from 0 to 9. High quality was assigned to studies with NOS score ≥ 6.

Statistical analysis

Stata SE12.0 was applied to conduct this meta-analysis (Stata Corp., College Station, USA). The heterogeneity of the included studies used Chi-square-based Q test and I^2 statistic (23). $P < 0.05$ for the Q test and an $I^2 > 50\%$ indicates significant heterogeneity. For studies with no obvious heterogeneity ($P_h > 0.05$, $I^2 < 50\%$), the fixed-effects model was adopted, and the random-effects model was used for others ($P_h \leq 0.05$, $I^2 \geq$

50%). The sensitivity analysis was conducted to check the stability of results. Begg's and Egger's tests were conducted to investigate potential publication bias (24). Differences with $P < 0.05$ were considered as statistically significant.

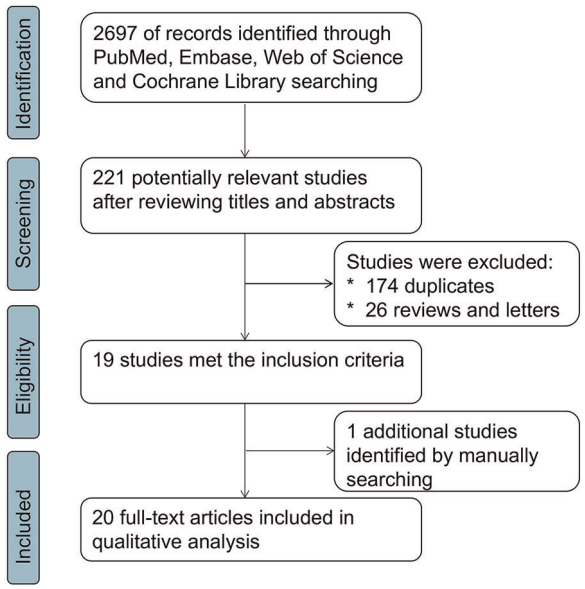

FIGURE 1
Literature search and selection flowchart.

Results

Study characteristics

The procedure of literature retrieval was depicted in Figure 1. A total of 3,267 patients with solid tumors were included in eligible articles published between 2011 and 2021 (17–19, 25–40). These studies were conducted in China ($n = 12$), Japan ($n = 5$), Singapore ($n = 1$), Spain ($n = 1$), and Norway ($n = 1$). Mean of patient sample size was 163 (from 61 to 338). In this meta-analysis, 15 varying solid tumor kinds were summarized, including 2 non–small-cell lung cancer, 2 breast cancers, 2 esophageal squamous cell carcinoma, 2 colorectal cancer, 2 cervical cancer, and 1 each of glioma, oral squamous cell carcinoma, pulmonary neuroendocrine tumors, extrahepatic cholangiocarcinoma, hepatocellular carcinoma, gastric cancer, oral tongue squamous cell carcinoma, ovarian cancer, prostate cancer, and phyllodes tumor of the breast. All of the specimens were well preserved, and diagnosis was made based on pathological findings. The main characteristics of enrolled studies are summarized in Supplementary Table S1. Eligible studies included in this meta-analysis had NOS scores ranging from 5 to 9, with a mean of 6.5.

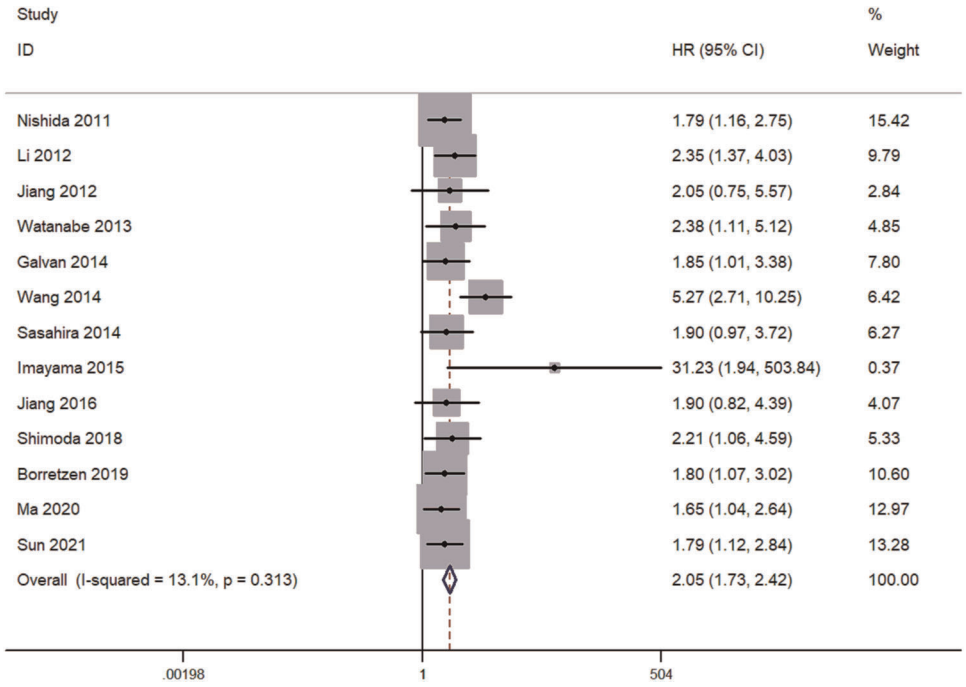

FIGURE 2
Forest plots for the relationship between high FOXC2 expression and OS.

Prognostic value of FOXC2 in patients with solid tumors

In 13 articles, the overall survival (OS) was reported. The pooled hazard ratios (HRs) and corresponding 95% CI were estimated by the fixed-effects model. The results indicated a mild heterogeneity in studies ($I^2 = 13.1\%$, $P_h = 0.313$). HRs for the increased FOXC2 expression against the low FOXC2 expression were 2.31 (95% CI: 1.73–2.42) (**Figure 2**). Patients with increased expression of FOXC2 presented significantly shorter OS, indicating that increased FOXC2 expression was associated with unfavored OS.

Clinical and pathological characteristics associated with FOXC2 expression

The pooled results (**Supplementary Table S2**) showed that elevated expression of FOXC2 was significantly related with lymph node metastases (OR = 3.33, 95% CI: 2.65–4.19, $P < 0.05$) (**Figure 3A**), TNM stage (OR = 3.09, 95% CI: 2.00–4.78, $P < 0.05$) (**Figure 3B**), and age (OR = 1.26, 95% CI: 1.06–1.50, $P < 0.05$) (**Figure 3D**). However, no significant correlation was observed between increased expression of FOXC2 and tumor differentiation (**Figure 3C**), sex, or tumor size (data not shown). Due to a lack of data, we were unable to detect the relationship between FOXC2 overexpression and other clinical and pathological characteristics.

Sensitivity analysis

Sensitivity analysis was conducted to assess the FOXC2 expression and OS by gradually deleting each individual research from the pooled analysis. The purpose of this approach is to evaluate the impact of the deleted data set on

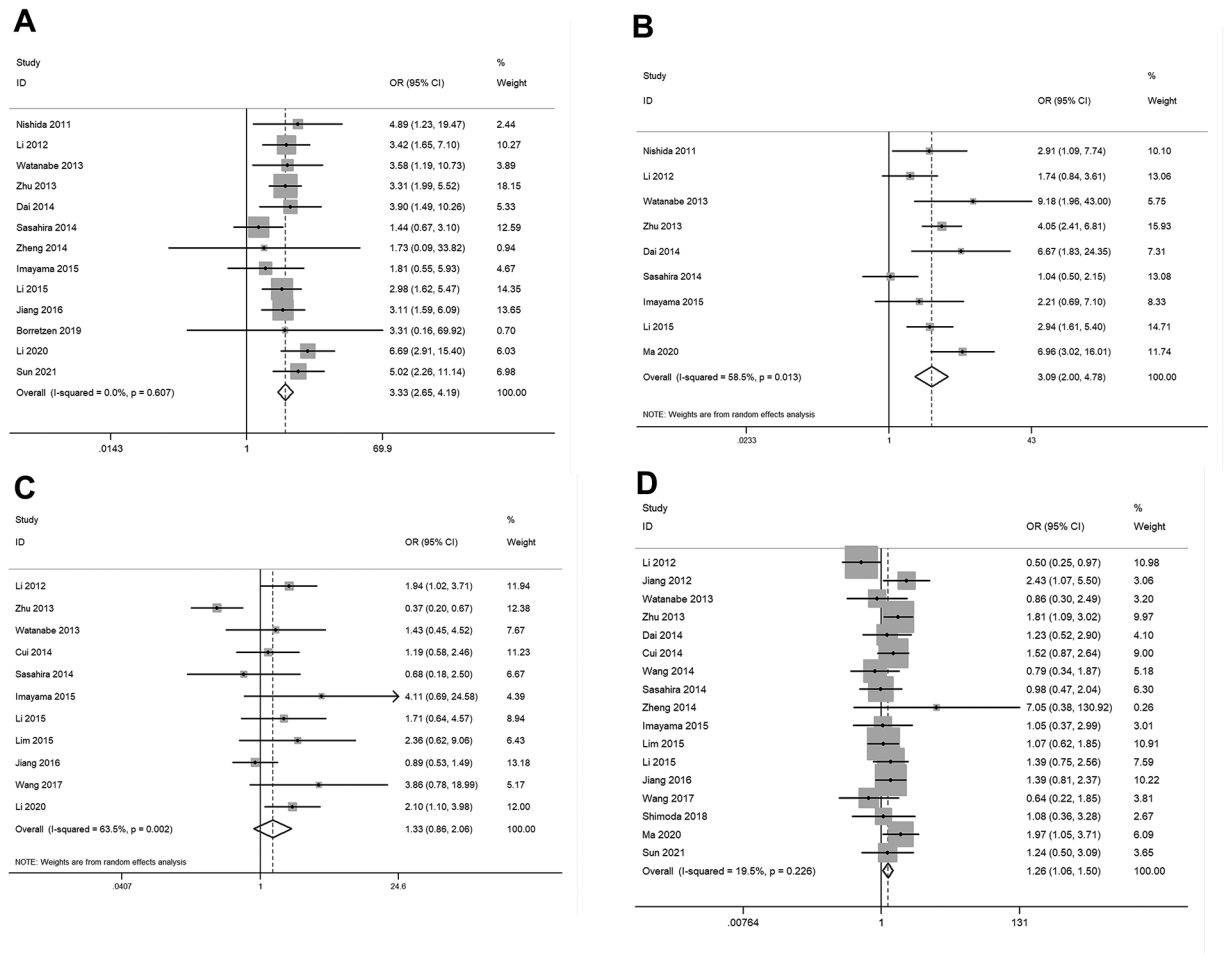

FIGURE 3
Forest plots for the relationship between FOXC2 overexpression and clinical and pathological characteristics. (A) Lymph node metastases, (B) TNM stage, (C) tumor differentiation, (D) patient age.

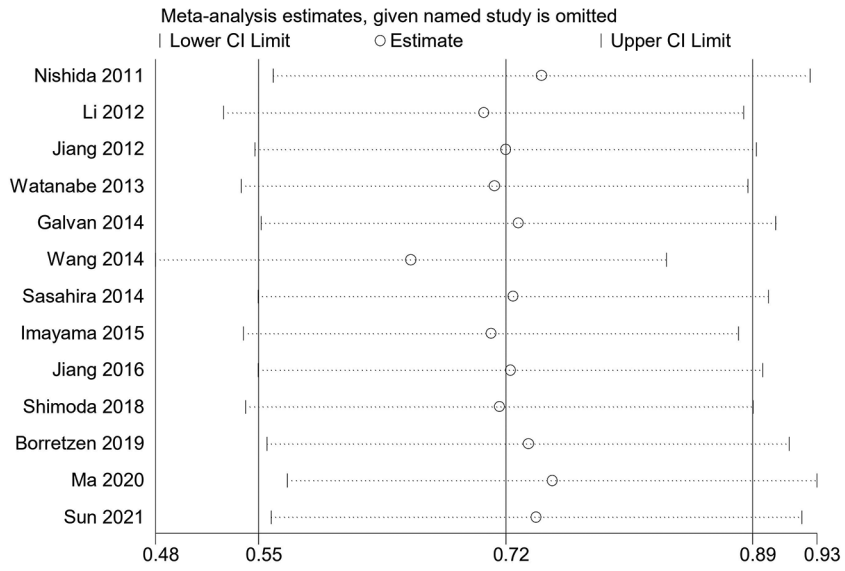

FIGURE 4
Sensitivity analysis regarding overall survival.

the overall HRs. The fingdings were reliable, and the exclusion of any study had no effect on the results (Figure 4).

Publication bias

Begg's Test and Egger's tests were conducted to evaluate the publication bias. Findings revealed that there was no publication bias between FOXC2 expression and OS in the included studies (Figure 5).

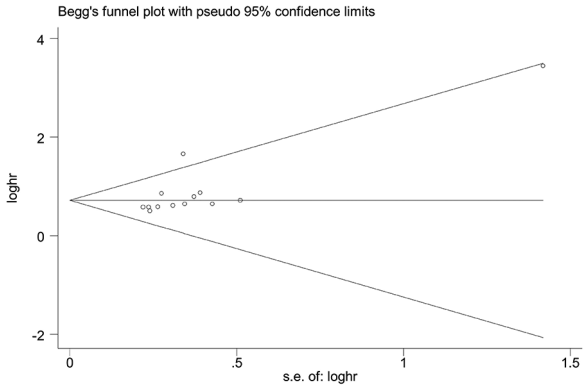

FIGURE 5
Publication bias in this meta-analysis.

Discussion

As a kind of genomic disease, lots of somatic mutations, structural mutations and gene recombination occur during the carcinogenesis process (41). There were 19.3 million new cancer cases and 10.0 million cancer deaths estimated in 2020 worldwide, with cancer burden anticipated to rise to 28.4 million by 2040 (42). Despite advancements in cancer surveillance enrollment, surgical techniques, systematic therapy and palliative care, the survival of individuals with solid tumors still remains unsatisfactory. Finding novel tumor markers is critical in order to provide accurate diagnosis and prospective therapeutic targets.

FOXC2 acts as a key mediator of tumor initiation and progression, involving tumor proliferation, migration, invasion, metastasis, and EMT (3). FOXC2 overexpression has been reported in a range of tumor kinds, including lung cancer (19), colorectal cancer (15), gastric cancer (16), ovarian cancer (40) and glioma (32). Furthermore, FOXC2 overexpression was associated with clinical characteristics and a poor prognosis (43, 44). FOXC2 is a novel independent biological marker for predicting tumor progression and survival because of its prognostic significancy and association with clinicopathological features. The prognosis effect of elevated FOXC2 expression was assessed in patients with solid tumors. The findings indicated that elevated FOXC2 expression was related with shorter OS in solid tumors. Additionally, increased FOXC2 was closely associated with age, TNM stage and lymph node metastasis, suggesting that FOXC2 could be a useful biomarker for predicting prognosis in human solid tumors based on clinical pathology. Targeting FOXC2 might be a viable approach for these patients.

The limitations of this analysis were as follows: first, in this meta-analysis, the majority of the studies were conducted among Asian population. Other ethnic groups, such as Europeans, Africans and Americans, are relatively under-studied, which may limit the global applicability of the results discussed. Further high-quality studies from diverse ethnical origins are necessary to investigate the therapeutic importance of FOXC2. Second, despite the fact that FOXC2 overexpression was associated with patient age, tumor differentiation, lymph node metastasis and TNM stage, we were unable to evaluate the association between FOXC2 overexpression and other clinical and pathological characteristics due to insufficient data. Third, the number of studies included in this analysis could restrict its statistical power. Although no publication bias was found, potential publication bias may still exist due to the insufficient studies available for assessments. Then, inconsistencies in detecting platforms, methodologies, and criteria for IHC or RT-PCR, and distinct tumor kinds with varying prognostic differences may lead to skewed results. Furthermore, the mean of NOS scores is 6.5, implying that the quality of studies in this analysis is acceptable but not supreme, which might be inevitable in meta-analysis. Finally, the combined predictive significance of FOXC2 and other tumor markers was not assessed. As a result, higher quality multicenter studies with larger population, as well as consistent criteria for assessing the expression of FOXC2, are necessary for validation of the findings.

Conclusion

In this analysis, increased expression level of FOXC2 is associated with poor prognosis, as well as TNM stage, lymph node metastases, and age. FOXC2 could serve as a novel prognostic marker in solid tumors. For these patients, targeting FOXC2 could be a feasible treatment option. To corroborate the findings, further well-designed pre-clinical/clinical studies with high-quality data are needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LZ, YH, XHT, and CW participated in the date collection and manuscript drafting. LZ, YH, XJD, RQY, YCX, and JYS performed the data analysis. LZ, YFJ, and XHD conceived the study and designed the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The research was supported by the Natural Science Foundation of Jiangxi Province (NO. 20202BABL206076) and the Doctoral Research Fund of Ganzhou People's Hospital (NO. BSQD2020008) to LZ, and Chen Xiao-ping Foundation for the Development of Science and Technology of Hubei Province (NO. CXPJJH12000002-2020058) and Scientific Research Funding of Tongji Hospital (NO. 2021A11) to CW.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.960698/full#supplementary-material.

References

1. Hargadon KM, Győrffy B, Strong EW. The prognostic significance of FOXC2 gene expression in cancer: a comprehensive analysis of RNA-seq data from the cancer genome atlas. *Cancer Genet.* (2021) 254–255:58–64. doi: 10.1016/j.cancergen.2021.02.005

2. Herman L, Todeschini AL, Veitia RA. Forkhead transcription factors in health and disease. *Trends Genet.* (2021) 37:460–75. doi: 10.1016/j.tig.2020.11.003

3. Xu J, Wang K, Zhang Z, Xue D, Li W, Pan Z. The role of forkhead box family in bone metabolism and diseases. *Front Pharmacol*. (2021) 12:772237. doi: 10.3389/fphar.2021.772237

4. Koch S. Regulation of wnt signaling by FOX transcription factors in cancer. *Cancers*. (2021) 13. doi: 10.3390/cancers13143446

5. Myatt SS, Lam EW. The emerging roles of forkhead box (fox) proteins in cancer. *Nat Rev Cancer*. (2007) 7:847–59. doi: 10.1038/nrc2223

6. Kume T. Foxc2 transcription factor: a newly described regulator of angiogenesis. *Trends Cardiovasc Med*. (2008) 18:224–8. doi: 10.1016/j.tcm.2008.11.003

7. Tsuji M, Morishima M, Shimizu K, Tsuji M, Morishima M, Shimizu K, Morikawa S, Heglind M, Enerbäck S, et al. FOXC2 influences alveolar epithelial cell differentiation during lung development. *Dev Growth Differ*. (2017) 59:501–14. doi: 10.1111/dgd.12368

8. Kim SH, Cho KW, Choi HS, Kim SH, Cho KW, Choi HS, Park SJ, Rhee Y, Jung HS, et al. The forkhead transcription factor FOXC2 stimulates osteoblast differentiation. *Biochem Biophys Res Commun*. (2009) 386:532–6. doi: 10.1016/j.bbrc.2009.06.071

9. Seo S, Kume T. Forkhead transcription factors, FOXC1 and FOXC2, are required for the morphogenesis of the cardiac outflow tract. *Dev Biol*. (2006) 296:421–36. doi: 10.1016/j.ydbio.2006.06.012

10. Cederberg A, Gronning LM, Ahren B, Tasken K, Carlsson P, Enerback S. FOXC2 Is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell*. (2001) 106:563–73. doi: 10.1016/S0092-8674(01)00474-3

11. Seo S, Fujita H, Nakano A, Kang M, Duarte A, Kume T. The forkhead transcription factors, FOXC1 and FOXC2, are required for arterial specification and lymphatic sprouting during vascular development. *Dev Biol*. (2006) 294:458–70. doi: 10.1016/j.ydbio.2006.03.035

12. Hader C, Marlier A, Cantley L. Mesenchymal-epithelial transition in epithelial response to injury: the role of FOXC2. *Oncogene*. (2010) 29:1031–40. doi: 10.1038/onc.2009.397

13. Li W, Fu X, Liu R, Li W, Fu X, Liu R, Wu C, Bai J, Xu Y, et al. FOXC2 often overexpressed in glioblastoma enhances proliferation and invasion in glioblastoma cells. *Oncol Res*. (2013) 21:111–20. doi: 10.3727/096504013X13814233062171

14. Lin F, Li X, Wang X, Sun H, Wang Z, Wang X. Stanniocalcin 1 promotes metastasis, lipid metabolism and cisplatin chemoresistance via the FOXC2/ITGB6 signaling axis in ovarian cancer. *J Exp Clin Cancer Res*. (2022) 41:129. doi: 10.1186/s13046-022-02315-3

15. Cui YM, Jiao HL, Ye YP, Cui YM, Jiao HL, Ye YP, Chen CM, Wang JX, Tang N, et al. Retraction note to: FOXC2 promotes colorectal cancer metastasis by directly targeting MET. *Oncogene*. (2022) 41:2529. doi: 10.1038/s41388-022-02287-w

16. Liu H, Zhang Z, Han Y, Liu H, Zhang Z, Han Y, Fan A, Liu H, Zhang X, et al. The FENDRR/FOXC2 axis contributes to multidrug resistance in gastric cancer and correlates with poor prognosis. *Front Oncol*. (2021) 11:634579. doi: 10.3389/fonc.2021.634579

17. Zhu JL, Song YX, Wang ZN, Zhu JL, Song YX, Wang ZN, Gao P, Wang MX, Dong YL, et al. The clinical significance of mesenchyme forkhead 1 (FOXC2) in gastric carcinoma. *Histopathology*. (2013) 62:1038–48. doi: 10.1111/his.12132

18. Nishida N, Mimori K, Yokobori T, Nishida N, Mimori K, Yokobori T, Sudo T, Tanaka F, Shibata K, et al. FOXC2 Is a novel prognostic factor in human esophageal squamous cell carcinoma. *Ann Surg Oncol*. (2011) 18:535–42. doi: 10.1245/s10434-010-1274-y

19. Jiang W, Fan H, Qian C, Ding J, Wang Q, Pang X. Prognostic value of high FOXC2 expression in resectable non-small cell lung cancer, alone or in combination with E-cadherin expression. *BMC Cancer*. (2016) 16:16. doi: 10.1186/s12885-016-2056-0

20. Chen J, Rong X, Liu X, Chen J, Rong X, Liu X, Zheng D, Rong X, Chen F, et al. FOXC2 is a prognostic biomarker and contributes to the growth and invasion of human hepatocellular carcinoma. *Cancer Cell Int*. (2020) 20:196. doi: 10.1186/s12935-020-01265-0

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Br Med J*. (2009) 339:b2535. doi: 10.1136/bmj.b2535

22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. (1994) 50:1088–101. doi: 10.2307/2533446

25. Dai J, Wang JY, Yang LL, Dai J, Wang JY, Yang LL, Xiao Y, Qu ZL, Qin SH, et al. Correlation of forkhead box C2 with subtypes and invasive ability of invasive breast cancer. *J Huazhong Univ Sci Technolog Med Sci*. (2014) 34:896–901. doi: 10.1007/s11596-014-1370-5

26. Imayama N, Yamada S, Yanamoto S, Imayama N, Yamada S, Yanamoto S, Naruse T, Matsushita Y, Takahashi H, et al. FOXC2 Expression is associated with tumor proliferation and invasion potential in oral tongue squamous cell carcinoma. *Pathol Oncol Res*. (2015) 21:783–91. doi: 10.1007/s12253-014-9891-6

27. Jiang W, Pang XG, Wang Q, Shen YX, Chen XK, Xi JJ. Prognostic role of twist, slug, and FOXC2 expression in stage I non-small-cell lung cancer after curative resection. *Clin Lung Cancer*. (2012) 13:280–7. doi: 10.1016/j.cllc.2011.11.005

28. Li Y, Yang W, Yang Q, Zhou S. Nuclear localization of GLI1 and elevated expression of FOXC2 in breast cancer is associated with the basal-like phenotype. *Histol Histopathol*. (2012) 27:475–84. doi: 10.14670/HH-27.475

29. Li Q, Wu J, Wei P, Li Q, Wu J, Wei P, Xu Y, Zhuo C, Wang Y, et al. Overexpression of forkhead box C2 promotes tumor metastasis and indicates poor prognosis in colon cancer via regulating epithelial-mesenchymal transition. *Am J Cancer Res*. (2015) 5:2022–34. PMID: 26269761

30. Lim JC, Koh VC, Tan JS, Tan WJ, Thike AA, Tan PH. Prognostic significance of epithelial-mesenchymal transition proteins twist and FOXC2 in phyllodes tumours of the breast. *Breast Cancer Res Treat*. (2015) 150:19–29. doi: 10.1007/s10549-015-3296-4

31. Sasahira T, Ueda N, Yamamoto K, Sasahira T, Ueda N, Yamamoto K, Kurihara M, Matsushima S, Bhawal UK, et al. PROX1 and FOXC2 act as regulators of lymphangiogenesis and angiogenesis in oral squamous cell carcinoma. *PLoS One*. (2014) 9:e92534. doi: 10.1371/journal.pone.0092534

32. Wang YW, Yin CL, Zhang HY, Wang YW, Yin CL, Zhang HY, Hao J, Yang YY, Liao H, et al. High expression of forkhead box protein C2 is related to poor prognosis in human gliomas. *Asian Pac J Cancer Prev*. (2014) 15:10621–5. doi: 10.7314/APJCP.2014.15.24.10621

33. Wang J, Yue X. Role and importance of the expression of transcription factor FOXC2 in cervical cancer. *Oncol Lett*. (2017) 14:6627–31. doi: 10.3892/ol.2017.7004

34. Watanabe A, Suzuki H, Yokobori T, Watanabe A, Suzuki H, Yokobori T, Altan B, Kubo N, Araki K, et al. Forkhead box protein C2 contributes to invasion and metastasis of extrahepatic cholangiocarcinoma, resulting in a poor prognosis. *Cancer Sci*. (2013) 104:1427–32. doi: 10.1111/cas.12249

35. Zheng CH, Quan Y, Li YY, Deng WG, Shao WJ, Fu Y. Expression of transcription factor FOXC2 in cervical cancer and effects of silencing on cervical cancer cell proliferation. *Asian Pac J Cancer Prev*. (2014) 15:1589–95. doi: 10.7314/APJCP.2014.15.4.1589

36. Shimoda Y, Ubukata Y, Handa T, Shimoda Y, Ubukata Y, Handa T, Yokobori T, Watanabe T, Gantumur D, et al. High expression of forkhead box protein C2 is associated with aggressive phenotypes and poor prognosis in clinical hepatocellular carcinoma. *BMC Cancer*. (2018) 18:597. doi: 10.1186/s12885-018-4503-6

37. Børretzen A, Gravdal K, Haukaas SA, Beisland C, Akslen LA, Halvorsen OJ. FOXC2 expression and epithelial-mesenchymal phenotypes are associated with castration resistance, metastasis and survival in prostate cancer. *J Pathol Clin Res*. (2019) 5:272–86. doi: 10.1002/cjp2.142

38. Galván JA, Astudillo A, Vallina A, Crespo G, Folgueras MV, González MV. Prognostic and diagnostic value of epithelial to mesenchymal transition markers in pulmonary neuroendocrine tumors. *BMC Cancer*. (2014) 14:855. doi: 10.1186/1471-2407-14-855

39. Ma L, Yang R, Gu J, Jiang H, Li H. The expression of AGGF1, FOXC2, and E-cadherin in esophageal carcinoma and their clinical significance. *Medicine*. (2020) 99:e22173. doi: 10.1097/MD.0000000000022173

40. Sun Y, Wang X, Wen H, Zhu B, Yu L. Expression and clinical significance of the NCAPH, AGGF1, and FOXC2 proteins in serous ovarian cancer. *Cancer Manag Res*. (2021) 13:7253–62. doi: 10.2147/CMAR.S329688

41. Bird A. Genetic determinants of the epigenome in development and cancer. *Swiss Med Wkly*. (2017) 147:w14523. doi: 10.4414/smw.2017.14523

42. Sung H, Ferlay J, Siegel RL, Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

43. Cui YM, Jiang D, Zhang SH, Cui YM, Jiang D, Zhang SH, Wu P, Ye YP, Chen CM, et al. FOXC2 promotes colorectal cancer proliferation through inhibition of FOXO3a and activation of MAPK and AKT signaling pathways. *Cancer Lett*. (2014) 353:87–94. doi: 10.1016/j.canlet.2014.07.008

44. Wang T, Zheng L, Wang Q, Hu YW. Emerging roles and mechanisms of FOXC2 in cancer. *Clin Chim Acta*. (2018) 479:84–93. doi: 10.1016/j.cca.2018.01.019

frontiers | Frontiers in Surgery

TYPE Review
PUBLISHED 06 January 2023
DOI 10.3389/fsurg.2022.1015884

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Sohan Lal Solanki,
Tata Memorial Hospital, India
David Morris,
University of New South Wales, Australia

*CORRESPONDENCE
Shuohui Gao
shgao@jlu.edu.cn

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 10 August 2022
ACCEPTED 09 November 2022
PUBLISHED 06 January 2023

CITATION
Sun L, Li C and Gao S (2023) Diffuse malignant peritoneal mesothelioma: A review.
Front. Surg. 9:1015884.
doi: 10.3389/fsurg.2022.1015884

Diffuse malignant peritoneal mesothelioma: A review

Luanbiao Sun, Chenguang Li and Shuohui Gao*

Gastrointestinal Colorectal and Anal Surgery, China-Japan Union Hospital, Changchun, China

Diffuse malignant peritoneal mesothelioma (DMPM) is an unusual and life-threatening locally invasive tumor. The morbidity and mortality of the disease are associated with progressive local effects in the abdominal cavity, such as abdominal distention, painful sensations, and early saturation with reduced oral intake, which eventually lead to intestinal obstruction and cachexia. Computed tomography (CT) has been widely used as a first-line diagnostic tool for DMPM. In addition, the most sensitive immunohistochemical markers of DMPM include WT 1, D2-40, and calmodulin. This paradigm has altered with the advancements in the immunohistochemical analysis of BRCA1-Associated Protein 1 (BAP1) the lack of BAP1 expression shows the diagnosis of malignancy. DMPM is resistant to conventional chemotherapies. Therefore, the gold standard for the treatment of DMPM is the combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The overexpression of the phosphatidylinositol 3-kinase (PI3K)/AKT serine/threonine kinase 1 (AKT)/mammalian target of rapamycin (mTOR) signaling pathway drives the malignant phenotype of DMPM, thereby showing promising potential for the treatment of DMPM. The coordinated activities among multiple RTKs are directly involved in the biological processes of DMPM, suggesting that the combined inhibition of the PI3K and mTOR signaling pathways might be an effective measure. This treatment strategy can be easily implemented in clinical practice. However, the combined inhibition of ERBB1(HER1)/ERBB2 (HER2) and ERBB3 (HER3) requires further investigations. Thus, based on these, the discovery of novel targeted therapies might be crucial to improving the prognosis of DMPM patients.

KEYWORDS

diffuse malignant peritoneal mesothelioma (DMPM), hyperthermic intraperitoneal chemotherapy (hipec), immunotherapy, targeted molecular therapy, signaling pathway

Introduction

Malignant peritoneal mesothelioma (MPM) is an unusual and invasive primary malignancy of the peritoneum, which is characterized by the widespread multiple meta-static nodules, originating from the peritoneum. MPM has been conventionally classified into diffuse MPM (DMPM) and border-line forming MPM, including multi-cystic PM (MCPM) and well-differentiated papillary PM (WDPPM). DMPM is a rare type of primary malignancy, originating from the mesothelial cells in the peritoneum, and is characterized by a diffused and invasive growth of the tumor along the peritoneal surface.

Incidence and epidemiology

DMPM accounts for 7%–30% of mesotheliomas (1). Wynn and Miller first reported DMPM for the first time in 1908 (2). The global epidemiological data of DMPM varies due to differences in geographical locations, genetic susceptibilities, and exposure levels of environmental and occupational carcinogens. The United Kingdom, Australia, and New Zealand have the highest incidence rates, while Japan, Slovenia, and other central European countries have the lowest incidence rates. The median age at the time of DMPM diagnosis is earlier than other peritoneal surface malignancies (63 71 years). Males are more likely to develop pleural mesothelioma, while females are more likely to develop DMPM. Moreover, DMPM occurs in younger females more likely as compared to the DMPM, occurring in male patients. The incidence rates of DMPM in the United States are 19.4 million and 4.1 million among the male and females populations, respectively, with about 15,000 new confirmed cases each year; the median age at the time of diagnosis is 63.3 years with a latency period of about 40–50 years from asbestos exposure to disease development (3, 4). There are limited epidemiological studies conducted on DMPM in China. Zhao et al. reported that the overall incidence and mortality rates increased from 2.14 to 3.14 million and 1.24 to 2.44 million, respectively, in the asbestos-exposed population at the time of DMPM diagnosis in China from 2000 to 2013. The mean ages at the time of DMPM diagnosis were 55.2 years in the exposed population and 47.3 years in the non-exposed population (5).

Etiology and pathogenesis

Asbestos is believed to be the most frequent carcinogen, causing pleural mesothelioma. Although it has a weak correlation, it is considered one of the high-risk factors for DMPM. Approximately, one-third of the DMPM patients have a history of previous asbestos exposure (4). The timing and duration of asbestos exposure are not directly correlated with the disease progression, suggesting that long-term asbestos exposure might not cause DMPM. On the contrary, the short-term exposure might cause a substantial tumor burden. Numerous randomized and observational studies, including the National Lung Screening Trial (NLST) and International Early Lung Cancer Action Program (IELCAP), screened asbestos-exposed workers using chest computed tomography (CT) for lung screening programs. Although there is a moderately consistent epidemiological correlation between the DMPM and asbestos exposure, no screening program or plan has been proposed for the early detection of DMPM. Therefore, researchers have recommended annual abdominal ultrasonography for individuals with a history of asbestos exposure to improve early detection (6). Other physicochemical carcinogens include gross zeolite, xylene, mica, and talcum powder. The other physical factors associated with DMPM include chronic peritonitis and therapeutic radiation. In addition, DMPM is also associated with genetic susceptibility and simulated jejunum 40 (7).

Clinical presentation

Most DMPM cases are asymptomatic or non-specific in their early stages. However, DMPM has an insidious onset and is diagnosed in the middle to late stages with a median time from the onset of symptoms to diagnosis of approximately four months. The diversified clinical presentations mainly depend on the degree of intra-abdominal spread. The most common symptoms include abdominal distention (41%–86%) and abdominal pain (31%–87%). Other clinical manifestations include weight loss (32%), abdominal masses (30%), fever (22%), diarrhea (17%), vomiting (15%), and new hernias (12%). In addition, about 8% of the cases are incidentally diagnosed. The typical growth of DMPM is characterized by an extensive growth along the peritoneal surface with little involvement of the extra-abdominal organs. The enlargement of the local lymph node might obstruct the superior vena cava or compress the vital organs, thereby showing the corresponding signs and symptoms. In some patients, the acute abdominal disease is the primary clinical manifestation, such as malignant intestinal obstruction or gastrointestinal perforation. During its progression, DMPM might also be accompanied by paraneoplastic syndromes, such as fever, thrombocytopenia, malignancy-associated thrombosis, hypoglycemia, Coombs-positive hemolytic anemia, and nephrotic syndrome.

Staging

Due to the inconsistent occurrence of lymph nodes and spread of metastasis, DMPM does not fit into the typical Tumor-Node-Metastasis (TNM) staging system for tumors. Yan et al. [2011] presented a staging system based on the degrees of peritoneal disease burden (T), intraperitoneal lymph node metastasis (N), and extraperitoneal metastasis (M) (8). The T stage was determined based on the calculation of the peritoneal carcinoma index (PCI) (**Figure 1**) (9). The Peritoneal Surface Oncology Group International(PSOGI) classified DMPM into three stages, including Stages I, II, and III, based on this TNM principle (**Table 1**).

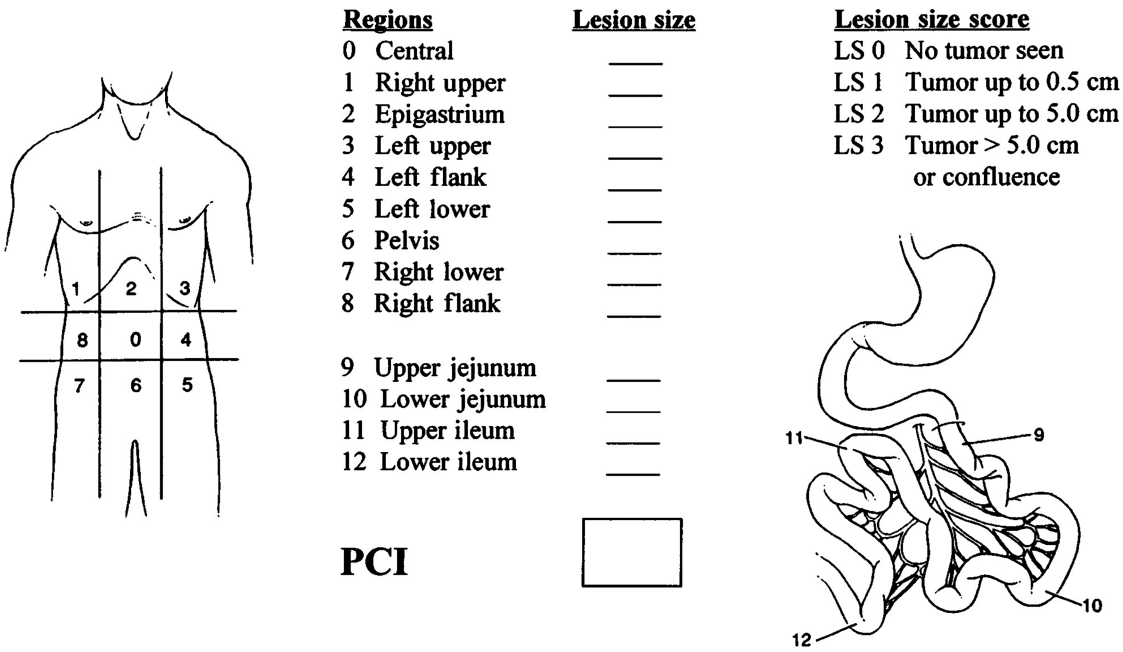

FIGURE 1
Peritoneal cancer Index (PCI) scoring system (9). Lesion size (LS) should be considered. The absence of malignant deposits is indicated by an LS-0 score: the tumor nodules less than 0.5 cm are indicated by an LS-1 score (the number of tumor nodules is not scored; only the size of the largest nodule is calculated); tumor nodules between 0.5 cm and 5.0 cm are indicated by an LS-2 score; and tumor nodules of more than 5.0 cm in either direction are indicated by LS-3 score. The confluence of stratification of tumors also indicates a score of LS-3 in the abdominal or pelvic areas. Each of the 13 areas received an LS score. The patient's peritoneal cancer index was calculated as the average lesion size score for each of the 13 abdominal-pelvic areas. The highest score was 39 or 13*3.

TABLE 1 TNM staging system for diffuse malignant peritoneal mesothelioma (DMPM).

Stage	PCI	T	N	M	5-year survival rates
I	1–10	T_1	N_0	M_0	87%
II	11–30	T_{2-3}	N_0	M_0	53%
III	≥30	T_4 T_{1-4} T_{1-4}	N_{0-1} N_1 N_{0-1}	M_{0-1} M_{0-1} M_1	29%

T refers to PCI: T_1 (PCI 1–10), T_2 (PCI 11–20), T_3 (PCI 21–30), and T_4 (PCI 30–39), which were significantly associated with the patient survival rates. N refers to lymph node status: N_0 without lymph node metastasis and N_1 with lymph node metastasis. M refers to extra-abdominal metastasis: M_0 without extra-abdominal metastasis and M_1 extra-abdominal metastasis.

Diagnosis and pathology

Diagnostic imaging/preoperative work-ups

Computed tomography (CT)

Currently, for the preoperative evaluation of DMPM, the CT scan is the preferred radiological method (10). This might be due to the feasibility, cost, short acquisition time, and relative ease of interpretation by non-trained radiologists. In addition, a CT scan can detect peritoneal diseases either malignant disease or plaques, and can identify asbestos exposure. In general, a CT scan can show mesenteric thickening, peritoneal effusion, greater omental thickening, peritoneal thickening, abdominal masses, and extra-abdominal metastases (11). Recent studies suggested that CT scans might help in diagnosing DMPM and other peritoneal surface malignancies (PSM) (12, 13). A meta-analysis showed that the CT scan tended to under-value the disease burden, regarding the small-volume diseases of the small intestine; these results were similar to the imaging analyses of the peritoneal diseases (14–16). However, these results might not indicate a restriction of CT scans in determining the surgical resectability of the preoperative workup for DMPM, given that high PCI is not one of the exclusion criteria for the surgical treatment of DMPM.

Magnetic resonance imaging (MRI)

MRI can be used as an imaging method for the diagnosis and preoperative evaluation of DMPM. It can more accurately assess the tumor progression, quantify PCI scores, diagnose peritoneal effusion, and determine disease stage (17, 18).

Fluorine-18 fluorodeoxyglucose (18F-FDG)-positron emission tomography-contrast-enhanced CT (PET/CT)

PET/CT has been recently introduced for the diagnosis of DMPM and has shown a promising potential due to the significant differences in the standardized uptake value (SUV) of 18F-FDG. PET/CT can be used to differentiate benign peritoneal lesions from malignant mesothelioma. Additionally, PET/CT can more accurately determine the preoperative staging lymph node status as compared to the CT alone and can also more sensitively detect the potential recurrent lesions with specificity accuracy and sensitivity of 89%, 87%, and 86%, respectively (19). These data, although heartening, require further verification by additional studies to highlight the importance of PET/CT in the preoperative evaluation of DMPM.

Laparoscopy

Laparoscopy is an effective method used for the diagnosis of DMPM due to its minimal invasiveness and clear visualization of the abdominal cavity. Laparoscopy can more accurately assess the resectability of DMPM, avoid ineffective open surgery, and has lower complications and mortality. Laparoscopy can better assess the small peritoneal metastatic lesions as compared to CT. The sensitivity, specificity, positive prediction value, negative prediction value, and accuracy of the laparoscopic preoperative evaluation are 100%, 75%, 96.6%, 100%, and 96.9%, respectively (20). However, for patients with poor abdominal conditions, such as previous surgery or high tumor load, laparoscopy might not achieve a comprehensive preoperative evaluation. The laparoscopic incision has a risk of implanting metastases as well (21, 22). The preoperative laparoscopy should be performed during subsequent surgery for the prevention of port site recurrence, thorough assessment of the abdominal cavity, and evaluation of serum, mesentery, and PCI (23). The biopsy of the diaphragmatic peritoneum is associated with local inflammatory reactions and adhesions, which limit the subsequent diaphragmatic peritoneal resection; therefore, surgery should be performed with caution or even avoided. The procedure of laparoscopy can be videotaped for repeated evaluation by the subsequent specialist (20).

Diagnostic histopathology

Most DMPM cases can be easily detected or strongly suspected based on immunohistochemical (IHC) staining and routine hematoxylin and eosin (H&E) staining. The results of H&E staining for the detection of DMPM can be classified as micropapillary clear cell, tubular papillary, solid, mucinous, pleomorphic sarcomatous, and biphasic. The sarcomatous type is characterized by the presence of closely spaced spindle-shaped cells. Moreover, few sarcomatous mesotheliomas are also observed with scattered malignant bony, muscle-like, or cartilage-like structures. The biphasic type includes both the sarcomatous and epithelial subtypes and accounts for at least 10% of the DMPM cases (24). In clinical practice, IHC staining is indispensable for the pathological diagnosis of DMPM. The histological diagnosis of DMPM should be performed by an expert pathologist, because the treatment recommendations are based on the specific assessment of histological subtypes and aggressiveness, including high Ki-67 index and high mitotic rate (25). DMPM can be differentiated from adenocarcinoma and peritoneal plasmacytoma based on the IHC analysis and specific biomarkers. The IHC markers include positive markers, such as WT1(tumor suppressor gene), calretinin, and D2–40, which confirm the presence of mesothelial differentiation, and negative markers, such as carcinoembryonic antigen (CEA), thyroid transcription factor 1 (TTF-1), claudin-4, and polyclonal which confirm the presence of DMPM (26–28). Notably, no single IHC marker is completely sensitive and specific. Therefore, a combination of the positive and negative markers, including at least two mesothelial cell markers (D2-40, calretinin, WT1) and two cancer cell markers (TTF-1, CEA, polyclonal, claudin-4), is recommended for the diagnosis of DMPM (29). The most sensitive marker for sarcomatous mesothelioma is D2-40/Podoplanin (transmembrane mucoprotein) (30). The broad-spectrum keratins, such as MNF116 (pan-Cytokeratin antibody), AE1/AE3 (pan-Cytokeratin antibody), and pan-cytokeratin, are expressed in both mesothelioma and carcinoma and are not specific.

Treatment options

DMPM was once considered an end-stage disease with a median overall survival (OS) of only 6 to 12 months after diagnosis. Recently advancements have been made in the treatment of DMPM, including both single chemotherapy and multiple forms of combination therapies, such as a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), systemic chemotherapy, peritoneal chemotherapy, immunotherapy, and targeted molecular therapy.

Combination of CRS and HIPEC

DMPM is mostly disseminated in the abdominal cavity. PSOGI recently established a comprehensive treatment strategy by combining the CRS and HIPEC as its core treatments for the resection and control of tumor progression;

TABLE 2 Preoperative, intraoperative, and postoperative managements for the combined CRS-HIPEC treatment.

Item	Recommendation
Preoperative management	
Preoperative anaesthetic assessment	Preoperative anaesthetic assessment (including cardiac risk, obstructive sleep apnea and frailty screening)
Physical exercise/ prehabilitation	Prehab programme of physical exercise should be indicated routinely
Preoperative optimisation	Smoking and alcohol cessation (alcohol abusers) four weeks before surgery should be indicated routinely Anemia identification and correction preoperatively should be indicated routinely
Nutritional screening, supplementation	Preop nutritional screening using a validated tool and measuring serum albumin should be indicated routinel Nutritional and protein supplementation in cases of severe malnutrition should be indicated routinely Oral immunonutrition could be indicated
PONV prevention	At least 2 antiemetic drugs should be indicated routinely to prevent PONV TIVA could be indicated to prevent PONV
Preoperative bowel preparation	MBP alone for patients undergoing CRS ± HIPEC including probable colectomy should not be indicated MBP alone for patients undergoing CRS ± HIPEC including probable rectal resection could be indicated In patients undergoing CRS ± HIPEC, oral antibiotic decontamination with or without preoperative MBP could be indicated
Preoperative fasting and carbohydrate treatment	Preoperative fasting of 6 h for solids and 2 h for liquids should be indicated routinely Carbohydrate loading until 2 h before induction of anaesthesia could be indicated
Intraoperative management	
Antimicrobial prophylaxis and skin preparation	PrAntiseptic shower, shaving and adhesive drapes could be indicated Ophylactic antibiotics within 1 h before incision should be indicated routinely Antibiotic prophylaxis during the postoperative period should not be indicated
Standard anaesthetic protocol	Cricoid pressure during rapid sequence intubation could be indicated Epidural analgesia should be indicated routinely Multimodal analgesia with one or several agents could be indicated routinely Protective ventilation should be indicated routinely Cardiac output monitoring should be indicated routinely Deep neuromuscular block and reversal by specific antagonists could be indicated
Intraoperative normothermia	Prevention of intraoperative hypothermia by use of active warming devices should be indicated routinely
Intraoperative normoglycaemia	Diabetes screening and intraoperative glycaemic control should be indicated routinely
Perioperative fluid management	Use of GDFT and catecholamines guided by advanced/invasive monitoring should be indicated routinely Substitution of losses (fluids and protein) by use of crystalloids could be indicated Limiting postop fluid-related weight gain is advised
Transfusion and management of coagulopathy	Restrictive transfusion should be performed routinely TXA alone or with cryoprecipitate could be administered Prothrombin complex concentrate could be administered
Early extubation	Early extubation should be done routinely
Postoperative management	
Nasogastric drainage	Prophylactic nasogastric drainage should not be done
Urinary indwelling catheter	Removal of urinary catheter as early as postoperative day 3 is recommended Removal of urinary catheter before removal of the epidural catheter could be indicated
Postoperative analgesia	Thoracic epidural analgesia containing local anaesthetics and short-acting opiates is recommended After TEA removal, analgesia with paracetamol (acetaminophen), NSAIDs and opioids is recommended

PONV, postoperative nausea and vomiting; TIVA, total intravenous anesthesia; MBP, mechanical bowel preparation; GDFT, goal directed fluid therapy; TXA, tranexamic acid.

this strategy is preferred for the treatment of DMPM. With a median OS of 38.4 to 63.2 months, a five-year survival rate of 39.0% to 91.3%, and a perioperative mortality rate of 0 to 6%, the death risk among the patients with serious adverse events in the perioperative period is more than twice that of the patients without serious adverse events. Effective management, including preoperative, intraoperative, and postoperative management, in the perioperative period for the combined CRS and HIPEC might effectively reduce perioperative mortality (Table 2) (31–33). The combined CRS and HIPEC treatment strategy can completely resect the visible tumor, which can be seen with the naked eye. The supplementation of high-dose HIPEC can enhance treatment efficacy under hyperthermia. The most effective HIPEC regimen is the platinum-based combination of HIPEC with high-dose chemotherapeutic agents, circulating in all the regions of abdominal and pelvic cavities, under sustained hyperthermia (43°C), which enhances the cytotoxicity of the chemotherapeutic agents (Figure 2). The adverse events of combined CRS and HIPEC mainly include pulmonary infection, biliary leakage, abdominal abscess, deep vein thrombosis, anastomotic leakage, congestive heart failure,

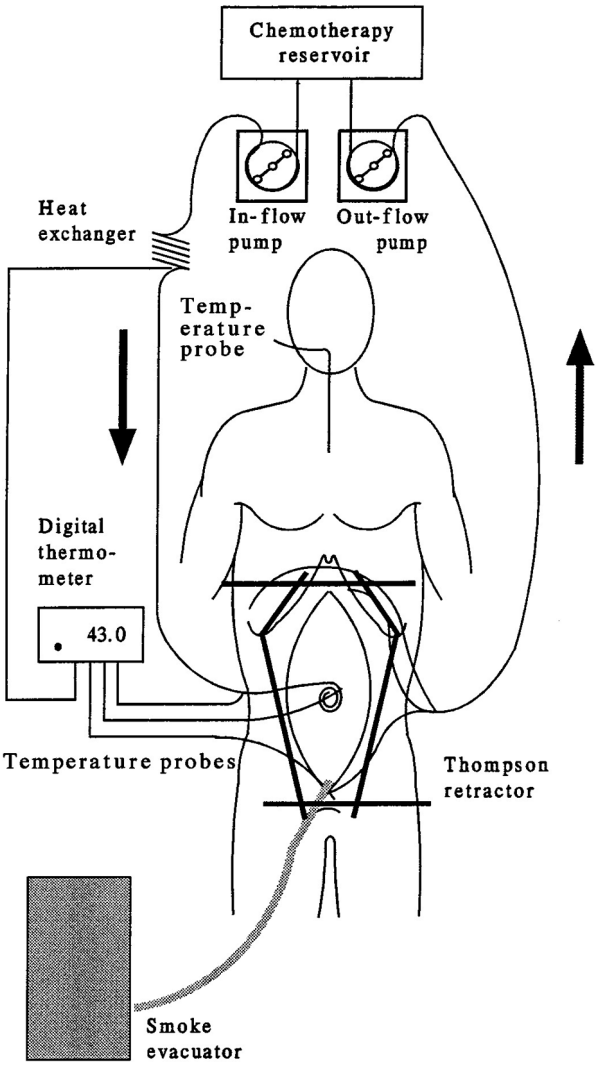

FIGURE 2
Equipment required for hyperthermic intraperitoneal chemotherapy (HIPEC) (9).

intestinal leakage, intestinal obstruction, incision dehiscence, hematological toxicity, cerebral infarction, pleural effusion, and moderate to severe hypoalbuminemia. These adverse events are correlated with the duration of surgery, PCI score, number of anastomoses, and organs or peritoneum resected (33). The adverse events are graded based on the PSOGI study (6) and consist of 48 adverse events, which are divided into 9 categories; each of which is classified as grade I-V. Grade I adverse events do not require intervention; grade II adverse events require drug therapy; grade III adverse events can be cured by conservative treatment and usually require intervention by auxiliary examinations, such as imaging; grade IV adverse events require intervention in the operation theater; and grade V adverse events are the patients' deaths. Among these, grade III-V adverse events are defined as SAE (severe adverse events).

Systemic chemotherapy (SC)

Palliative systemic chemotherapy

Pleural mesothelioma and DMPM are two different types of tumors. The effects of chemotherapeutic agents are similar for both these tumor types. However, the clinical trials, evaluating systemic therapy for the treatment of DPMP are limited. This might be due to the less effectiveness of single-agent and combination chemotherapies against DMPM with remission rates below 15%–20%. In phase III clinical trial, Vogelzang et al. recommended the use of pemetrexed in combination with cisplatin as a first-line chemotherapy regimen for the treatment of malignant pleural mesothelioma (34, 35). Two more studies reported that pemetrexed alone or in combination with cisplatin could effectively treat DMPM (median OS rates of 8.7 months and 13.1 months, respectively) (36, 37). The results showed that pemetrexed was well-tolerated with a low incidence of grade III/IV adverse events, among which, hematologic toxic reactions (2%) and non-hematologic toxic reactions, such as dehydration (7%), nausea (5%), and vomiting (5%), were the most common. A phase II clinical trial (38) showed that the combination of pemetrexed with gemcitabine could extend the median OS of DMPM patients to 26.8 months. However, the combined treatment regimen showed a higher incidence rate of serious adverse events. This combination is the first-line chemotherapy regimen for inoperable patients. The alternative second-line regimens include the combination of cisplatin with irinotecan or gemcitabine and tremelimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA4). However, the current second-line regimens have not shown any survival advantage in the relapsed or refractory cases.

Perioperative chemotherapy

Adjuvant chemotherapy combined with a drug regimen is recommended for DMPM patients, receiving the combination of CRS and HIPEC and having at least one poor prognostic factor, such as sarcomatous or biphasic type, involvement of lymph node, Ki-67 > 9%, PCI >17, adjuvant chemotherapy combined with a drug regimen is advised. The patients, receiving CRS + HIPEC and having a good prognosis, such as complete CRS, epithelial type, no lymph node involvement, Ki-67 ≤ 9%, PCI ≤17, require regular follow-up. It is unclear whether the patients will be benefitted from the adjuvant chemotherapy. The most preferred chemotherapy regimen is a combination of platinum and pemetrexed.

Peritoneal chemotherapy (PC)

PC can be used to treat malignant tumors on the peritoneal surface. The administration of high-dose chemotherapeutic drugs into the peritoneal cavity can reduce their systemic adverse effects. Studies on the intraperitoneal chemotherapy for DMPM have recommended postoperative intraperitoneal chemotherapy to enhance the efficacy of CRS and HIPEC combination therapy (39). There are two types of intraperitoneal chemotherapies. For the patients with DMPM, receiving CRS and HIPEC combination therapy, local adjuvant therapy (EPIC and/or NIPEC) can be recommended in combination with systemic chemotherapy if the postoperative clinical conditions are adequate. Long-term regional chemotherapy can improve the survival rates of DMPM patients (40). However, there is no definitive intraperitoneal chemotherapy regimen. An *in-vitro* study (41) suggested that the cisplatin and gemcitabine or cisplatin and pemetrexed combination therapies were more effective as compared to the single-agent cisplatin in thoracic chemotherapy; this study can serve as a basis for further studies on the abdominal chemotherapy regimens.

Immunotherapy

Malignant mesothelioma is sensitive to immunotherapy. Currently, preclinical studies and small sample clinical trials have been conducted on immunotherapy of mesothelioma. Tumor necrosis factor-α (TNFα), interferon (IFN), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-6 (IL-6) are effective immunotherapeutic agents for mesothelioma (42). Tani et al. (43) also reported that the combination of activated cytotoxic T lymphocytes (CTL) and chemotherapy was effective for DMPM patients. A phase II clinical trial (44) used tremelimumab, an anti-CTLA4 antibody, as a second-line treatment for mesothelioma, showing a disease control rate of 31% and progression-free survival (PFS) of 6 months. In addition, an animal study (45) showed that the pulse-treated dendritic cells could inhibit mesothelioma growth and control the local recurrence of mesothelioma. The immune-related drugs can kill tumor cells by blocking the negative costimulatory signaling pathways and activating the effector T cells. Simultaneously, the activated T cells can attack normal tissues and induce inflammatory cascades or even inflammatory storms by releasing cytokines, such as ILs and IFNs, resulting in various degrees of immunotherapy-related adverse reactions (irAEs). The irAEs can spread to various organ systems throughout the body, causing numerous toxicities, such as immunotherapy-related skin toxicity, gastrointestinal toxicity, liver toxicity, endocrine adverse reactions, pulmonary toxicity, bone and muscle toxicity, and rare immunotherapy-related toxicities, including neurotoxicity, cardiotoxicity, ocular toxicity, and nephrotoxicity (**Figure 3**) (46). The diagnosis and treatment of malignancy by a multidisciplinary team (MDT) approach through multidimensional discussions and analyses of irAEs can diagnose malignancy as early as possible, formulate a reasonable diagnosis, develop a reasonable treatment pathway and strategy, improve the efficiency of diagnosis and treatment plan, and improve the prognosis and quality of life of the patients (47). Further studies are needed to explore the efficacy of immunotherapy on DMPM.

Targeted molecular therapy

In most DMPM patients, strong ERBB1 (HER1) activation is associated with the co-activation of ERBB2 (HER2), ERBB3 (HER3), Axl receptor tyrosine kinase (Axl), and c-Met/hepatocyte growth factor receptor (MET); this activation is mediated mainly by the heterodimerization of receptors and by an autocrine-paracrine loop, which is induced by the expression of its cognate ligand. miRNA34a can downregulate the expression of Axl (48). Mutations were found in the structural domain of MET Sema in two "progressive" DMPM patients. The combined targeted molecular therapy of Axl and MET could inhibit the cellular motility in the DMPM cell line obtained from "progressive" DMPM. A study (49) also suggested that the coordinated activity of multiple crosstalk receptor tyrosine kinases (RTKs) was directly involved in the biological processes of DMPM. These results strongly recommend that the combined inhibition of ERBB1/ERBB2 and ERBB3, MET and Axl, or PI3K/AKT/mTOR signaling pathway might be a valid therapeutic strategy, which requires further clinical investigations.

Conclusions

DMPM is an unusual primary malignancy of the peritoneal mesothelial cell origin. The etiology and pathogenesis of DMPM are unknown. It might be caused by the interaction of carcinogenic environmental factors and the genetic susceptibility of the patients. Most early-stage patients are asymptomatic or have non-specific symptoms, thereby having a high misdiagnosis rate and poor prognosis. Some patients might benefit from the combination therapy of CRS and HIPEC. Complete CRS is an indicator of a good prognosis. The combination of pemetrexed and cisplatin is the first-line chemotherapy regimen for patients, who cannot undergo surgery. Adjuvant chemotherapy with the combination of pemetrexed and cisplatin is recommended for DMPM patients, receiving the combination of CRS and HIPEC and having at least one poor prognostic factor. The optimal

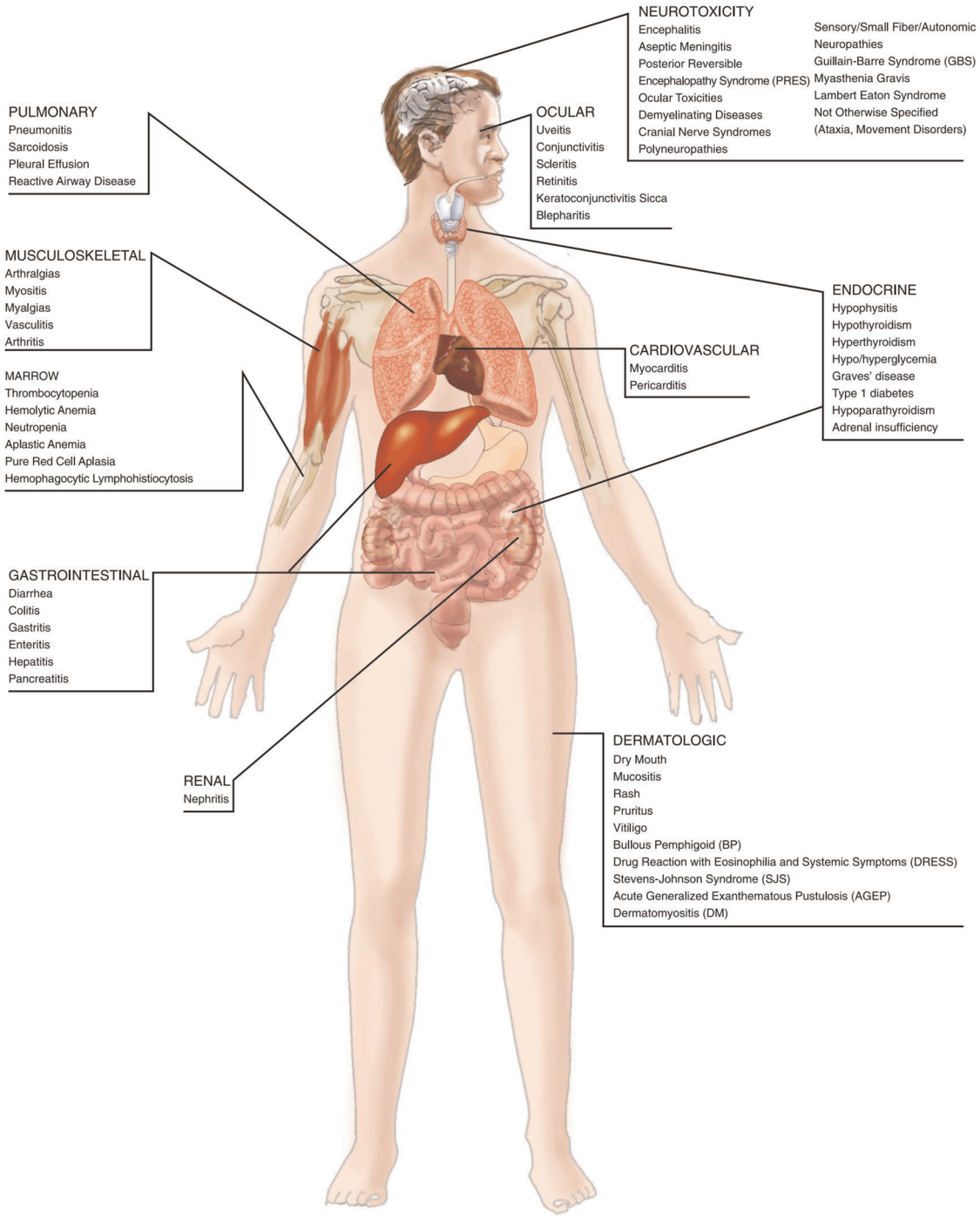

FIGURE 3
Diagram of immune checkpoint inhibitor-related toxicities (46).

outcome after combination therapy is determined by the pathological and biological markers of disease aggressiveness, such as proliferative activity and podoplanin expression. The patients, receiving the combination of CRS and HIPEC and having a favorable prognosis, require regular follow-up. Moreover, the effectiveness of adjuvant chemotherapy is needed to be further evaluated. This includes a physical examination, CT scan of the chest/abdomen/pelvis, laparoscopy, and serum cancer markers. The best practice for managing DMPM is the peritoneal surface malignancy-

multidisciplinary team (PSM-MDT). PSM-MDT might significantly change the evaluation and management of DMPM. The phosphatidylinositol 3-kinase (PI3K)/AKT serine/threonine kinase 1 (AKT)/mammalian target of rapamycin (mTOR) signaling pathway is overactivated or altered in many cancer types, thereby regulating a wide range of cellular processes, such as the cellular survival, proliferation, growth, metabolism, angiogenesis, and metastasis. The overexpression of this signaling pathway also drives the malignant phenotype of DMPM, showing promising potential for developing novel interventional strategies. Further research and understanding of the molecular biology and immunology of this disease might enhance the therapeutic strategies for the long-term survival and quality of life of DMPM patients.

Author contributions

SHG and LBS conceived and designed the study and helped to draft the manuscript. CGL performed the data collection. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to thank all the reviewers who participated in the review and MJEditor (www.mjeditor.com) for their linguistic assistance during the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973–2005. *Cancer Causes Control.* (2009) 20:935–44. doi: 10.1007/s10552-009-9328-9

2. Miller J, William H. A malignant tumor arising from the endothelium of peritoneum, and producing mucoid ascetic fluid. *J Pathol Bacteriol.* (1908) 12:267–78. doi: 10.1002/path.1700120212

3. Bianchi C, Bianchi T. Global mesothelioma epidemic: trend and features. *Indian J Occup Environ Med.* (2014) 18:82–8. doi: 10.4103/0019-5278.146897

4. Bridda A, Padoan I, Mencarelli R, Frego M. Peritoneal mesothelioma: a review. *MedGenMed.* (2007) 9:32.

5. Carbone M, Guo Z, Mao W. Improving the accuracy of mesothelioma diagnosis in China. *J Thorac Oncol.* (2017) 12:e132. doi: 10.1016/j.jtho.2017.04.020

6. Kusamura S, Kepenekian V, Villeneuve L, Lurvink RJ, Govaerts K, De Hingh IHJT, et al. Peritoneal mesothelioma: PSOGI/EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol.* (2021) 47:36–59. doi: 10.1016/j.ejso.2020.02.011

7. Gazdar AF, Carbone M. Molecular pathogenesis of malignant mesothelioma and its relationship to simian virus 40. *Clin Lung Cancer.* (2003) 5:177–81. doi: 10.3816/CLC.2003.n.031

8. Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, et al. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database*. *Cancer.* (2011) 117:1855–63. doi: 10.1002/cncr.25640

9. Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol.* (1999) 43:S15–25. doi: 10.1007/s002800051093

10. Park JY, Kim KW, Kwon HJ, Park MS, Kwon GY, Jun SJ, et al. Peritoneal mesotheliomas: clinicopathologic features, CT findings, and differential diagnosis. *AJR Am J Roentgenol.* (2008) 191:814–25. doi: 10.2214/AJR.07.3628

11. Baratti D, Kusamura S, Deraco M. Circulating CA125 and diffuse malignant peritoneal mesothelioma. *Eur J Surg Oncol.* (2009) 35:1198–9. doi: 10.1016/j.ejso.2009.04.007

12. Liang YF, Zheng GQ, Chen YF, Song H, Yin WJ, Zhang L. CT Differentiation of diffuse malignant peritoneal mesothelioma and peritoneal carcinomatosis. *J Gastroenterol Hepatol.* (2016) 31:709–15. doi: 10.1111/jgh.13260

13. Kato K, Gemba K, Fujimoto N, Aoe K, Takeshima Y, Inai K, et al. Computed tomographic features of malignant peritoneal mesothelioma. *Anticancer Res.* (2016) 36:1067–72. doi: 10.21873/anticanres.11205

14. Low RN, Barone RM, Lucero J. Comparison of MRI and CT for predicting the peritoneal cancer Index (PCI) preoperatively in patients being considered for cytoreductive surgical procedures. *Ann Surg Oncol.* (2015) 22:1708–15. doi: 10.1245/s10434-014-4041-7

15. de Bree E, Koops W, Kröger R, van Ruth S, Verwaal VJ, Zoetmulder FAN. Preoperative computed tomography and selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol.* (2006) 32:65–71. doi: 10.1016/j.ejso.2005.09.016

16. Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol.* (2009) 16:327–33. doi: 10.1245/s10434-008-0234-2

17. Low RN, Barone RM, Rousset P. Peritoneal MRI in patients undergoing cytoreductive surgery and HIPEC: history, clinical applications, and implementation. *Eur J Surg Oncol.* (2021) 47:65–74. doi: 10.1016/j.ejso.2019.02.030

18. Laghi A, Bellini D, Rengo M, Accarpio F, Caruso D, Biacchi D, et al. Diagnostic performance of computed tomography and magnetic resonance imaging for detecting peritoneal metastases: systematic review and meta-analysis. *Radiol Med.* (2017) 122:1–15. doi: 10.1007/s11547-016-0682-x

19. Dubreuil J, Giammarile F, Rousset P, Rubello D, Bakrin N, Passot G, et al. The role of 18F-FDG-PET/ceCT in peritoneal mesothelioma. *Nucl Med Commun.* (2017) 38:312–8. doi: 10.1097/MNM.0000000000000649

20. Laterza B, Kusamura S, Baratti D, Oliva GD, Deraco M. Role of explorative laparoscopy to evaluate optimal candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal mesothelioma. *In Vivo.* (2009) 23:187–90. doi: 10.1016/j.poly.2004.04.009

21. Nunez MF, Sardi A, Jimenez W, Nieroda C, Sittig M, MacDonald R, et al. Port-site metastases is an independent prognostic factor in patients with

peritoneal carcinomatosis. *Ann Surg Oncol*. (2015) 22:1267–73. doi: 10.1245/s10434-014-4136-1

22. Garofalo A, Valle M. Laparoscopy in the management of peritoneal carcinomatosis. *Cancer J*. (2009) 15:190–5. doi: 10.1097/PPO.0b013e3181a58e93

23. Passot G, Dumont F, Goéré D, Arvieux C, Rousset P, Regimbeau JM, et al. Multicentre study of laparoscopic or open assessment of the peritoneal cancer index (BIG-RENAPE). *Br J Surg*. (2018) 105:663–7. doi: 10.1002/bjs.10723

24. Marchevsky AM. Application of immunohistochemistry to the diagnosis of malignant mesothelioma. *Arch Pathol Lab Med*. (2008) 132:397–401. doi: 10.5858/2008-132-397-AOITTD

25. Turkcu G, AlabalIk U, Keles AN, Ibiloglu I, Küçüköner M, Sen HS, et al. Comparison of SKIP expression in malignant pleural mesotheliomas with ki-67 proliferation index and prognostic parameters. *Pol J Pathol*. (2016) 67:108–13. doi: 10.5114/PJP.2016.61445

26. Ordonez NG. Immunohistochemical diagnosis of epithelioid mesothelioma: an update. *Arch Pathol Lab Med*. (2005) 129:1407–14. doi: 10.5858/2005-129-1407-IDOEMA

27. Facchetti F, Gentili F, Lonardi S, Bercich L, Antin AS. Claudin-4 in mesothelioma diagnosis. *Histopathology*. (2007) 51:261–3. doi: 10.1111/j.1365-2559.2007.02743.x

28. Anttila S. Epithelioid lesions of the serosa. *Arch Pathol Lab Med*. (2012) 136:241–52. doi: 10.5858/arpa.2010-0216-RA

29. Husain AN, Colby TV, Ordóñez NG, Allen TC, Attanoos RL, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 update of the consensus statement from the international mesothelioma interest group. *Arch Pathol Lab Med*. (2018) 142:89–108. doi: 10.5858/arpa.2017-0124-RA

30. Chirieac LR, Pinkus GS, Pinkus JL, Godleski J, Sugarbaker DJ, Corson JM. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. *Am J Cancer Res*. (2011) 1:14–24.

31. Ren H, Wan X, Wei C, Yang G. Spatiotemporal variations in cardiovascular disease mortality in China from 1991 to 2009. *BMC Cardiovasc Disord*. (2019) 19:159. doi: 10.1186/s12872-019-1128-x

32. Solanki SL, Mukherjee S, Agarwal V, Thota RS, Balakrishnan K, Shah SB, et al. Society of onco-anaesthesia and perioperative care consensus guidelines for perioperative management of patients for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). *Indian J Anaesth*. (2019) 63:972–87. doi: 10.4103/ija.IJA_765_19

33. Li J, Wang AR, Chen XD, Zhang YX, Pan H, Li SQ. Effect of hyperthermic intraperitoneal chemotherapy in combination with cytoreductive surgery on the prognosis of patients with colorectal cancer peritoneal metastasis: a systematic review and meta-analysis. *World J Surg Oncol*. (2022) 20:200. doi: 10.1186/s12957-022-02666-3

34. Li Y, Zhou YF, Liang H, Wang HQ, Hao JH, Zhu ZG, et al. Chinese Expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies. *World J Gastroenterol*. (2016) 22:6906–16. doi: 10.3748/wjg.v22.i30.6906

35. Ryan CW, Herndon J, Vogelzang NJ. A review of chemotherapy trials for malignant mesothelioma. *Chest*. (1998) 113:66S–73S. doi: 10.1378/chest.113.1_Supplement.66S

36. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. (2003) 21:2636–44. doi: 10.1200/JCO.2003.11.136

37. Janne PA, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer*. (2005) 7:40–6. doi: 10.3816/CLC.2005.n.020

38. Carteni G, Manegold C, MartinGarcia G, Siena S, Zielinski CC, Amadori D, et al. Malignant peritoneal mesothelioma-results from the international expanded access program using pemetrexed alone or in combination with a platinum agent. *Lung Cancer*. (2009) 64:211–8. doi: 10.1016/j.lungcan.2008.08.013

39. Simon GR, Verschraegen CF, Jänne PA, Langer CJ, Dowlati A, Gadgeel SM, et al. Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. *J Clin Oncol*. (2008) 26:3567–72. doi: 10.1200/JCO.2007.15.2868

40. Sugarbaker PH, Welch LS, Mohamed F, Glehen O. A review of peritoneal mesothelioma at the Washington cancer institute. *Surg Oncol Clin N Am*. (2003) 12:605–21. doi: 10.1016/S1055-3207(03)00045-0

41. Sugarbaker PH, Chang D. Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival. *Eur J Surg Oncol*. (2017) 43:1228–35. doi: 10.1016/j.ejso.2017.01.009

42. Cameron RB, Hou D. Intraoperative hyperthermic chemotherapy perfusion for malignant pleural mesothelioma: an in vitro evaluation. *J Thorac Cardiovasc Surg*. (2013) 145:496–504. doi: 10.1016/j.jtcvs.2012.10.042

43. Soulie P, Ruffié P, Trandafir L, Monnet I, Tardivon A, Terrier P, et al. Combined systemic chemoimmunotherapy in advanced diffuse malignant mesothelioma. Report of a phase I-II study of weekly cisplatin/interferon alfa-2a. *J Clin Oncol*. (1996) 14:878–85. doi: 10.1200/JCO.1996.14.3.878

44. Tani M, Tanimura H, Yamaue H, Mizobata S, Yamamoto M, Iwahashi M, et al. Successful immunochemotherapy for patients with malignant mesothelioma: report of two cases. *Surg Today*. (1998) 28:647–51. doi: 10.1007/s005950050200

45. Calabro L, Morra A, Fonsatti E, Cutaia O, Amato G, Giannarelli D, et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncol*. (2013) 14:1104–11. doi: 10.1016/S1470-2045(13)70381-4

46. Hegmans JP, Hemmes A, Aerts JG, Hoogsteden HC, Lambrecht BN. Immunotherapy of murine malignant mesothelioma using tumor lysate-pulsed dendritic cells. *Am J Respir Crit Care Med*. (2005) 171:1168–77. doi: 10.1164/rccm.200501-057OC

47. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related adverse events (irAEs): diagnosis, management, and clinical pearls. *Curr Oncol Rep*. (2020) 22:39. doi: 10.1007/s11912-020-0897-9

48. Winters DA, Soukup T, Sevdalis N, Green J, Lamb BW. The cancer multidisciplinary team meeting: in need of change? History, challenges and future perspectives. *BJU Int*. (2021) 128:271–9. doi: 10.1111/bju.15495

49. Belfiore A, Busico A, Bozzi F, Brich S, Dallera E, Conca E, et al. Molecular signatures for combined targeted treatments in diffuse malignant peritoneal mesothelioma. *Int J Mol Sci*. (2019) 20:5817. doi: 10.3390/ijms20225817

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 06 January 2023
DOI 10.3389/fsurg.2022.1012897

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Dmitry Enikeev,
I.M. Sechenov First Moscow State Medical University, Russia
Ines Rivero Belenchon,
Virgen del Rocío University Hospital, Spain

*CORRESPONDENCE
Baolin Song
baolin_song@126.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 06 August 2022
ACCEPTED 02 November 2022
PUBLISHED 06 January 2023

CITATION
Li L, Zhu J, Shao H, Huang L, Wang X, Bao W, Sheng T, Chen D, He Y and Song B (2023) Long-term outcomes of radiofrequency ablation vs. partial nephrectomy for cT1 renal cancer: A meta-analysis and systematic review. Front. Surg. 9:1012897. doi: 10.3389/fsurg.2022.1012897

Long-term outcomes of radiofrequency ablation vs. partial nephrectomy for cT1 renal cancer: A meta-analysis and systematic review

Linjin Li[1], Jianlong Zhu[1], Huan Shao[2], Laijian Huang[1], Xiaoting Wang[2], Wenshuo Bao[1], Tao Sheng[2], Dake Chen[1], Yanmei He[2] and Baolin Song[2]*

[1]Department of Urology, the Third Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou People's Hospital, Wenzhou, China, [2]Department of Urology, Jiaxing Hospital of Traditional Chinese Medicine, Jiaxing, China

Background: Partial nephrectomy (PN) is one of the most preferred nephron-sparing treatments for clinical T1 (cT1) renal cancer, while radiofrequency ablation (RFA) is usually used for patients who are poor surgical candidates. The long-term oncologic outcome of RFA vs. PN for cT1 renal cancer remains undetermined. This meta-analysis aims to compare the treatment efficacy and safety of RFA and PN for patients with cT1 renal cancer with long-term follow-up of at least 5 years.

Method: This meta-analysis was performed following the PRISMA reporting guidelines. Literature studies that had data on the comparison of the efficacy or safety of RFA vs. PN in treating cT1 renal cancer were searched in databases including PubMed, Embase, Web of Science, and the Cochrane Library from 1 January2000 to 1 May 2022. Only long-term studies with a median or mean follow-up of at least 5 years were included. The following measures of effect were pooled: odds ratio (OR) for recurrence and major complications; hazard ratio (HR) for progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). Additional analyses, including sensitivity analysis, subgroup analysis, and publication bias analysis, were also performed.

Results: A total of seven studies with 1,635 patients were finally included. The treatment efficacy of RFA was not different with PN in terms of cancer recurrence (OR = 1.22, 95% CI, 0.45–3.28), PFS (HR = 1.26, 95% CI, 0.75–2.11), and CSS (HR = 1.27, 95% CI, 0.41–3.95) as well as major complications (OR = 1.31, 95% CI, 0.55–3.14) ($P > 0.05$ for all). RFA was a potential significant risk factor for OS (HR = 1.76, 95% CI, 1.32–2.34, $P < 0.001$). No significant heterogeneity and publication bias were observed.

Conclusion: This is the first meta-analysis that focuses on the long-term oncological outcomes of cT1 renal cancer, and the results suggest that RFA has comparable therapeutic efficacy with PN. RFA is a nephron-sparing technique with favorable oncologic efficacy and safety and a good treatment alternative for cT1 renal cancer.

KEYWORDS
radiofrequency ablation, partial nephrectomy, recurrence, survival, renal cancer

Introduction

For patients with localized cT1 renal cancer warranting curative therapy, nephron-sparing treatments are recommended by most guidelines (1–4). Particularly, partial nephrectomy (PN) has become the preferred therapeutic modality for small renal cancer because quite a few clinical observations reported similar oncologic outcomes to radical nephrectomy (5–7). On the other hand, radiofrequency ablation (RFA), a minimally invasive thermal ablation technique with curative potential for solid tumor, was once considered an alternative therapy predominately for patients not amenable to nephrectomy (8, 9).

With the clinical promotion of RFA application and increased number of studies, several meta-analysis further compared RFA and PN in treating renal cancer. A meta-analysis by Pan et al. included 16 studies and found that the local tumor recurrence rate in RFA group was higher than that in PN group [odds ratio (OR) = 1.81]. However, the distant metastasis rate was not statistically different between the two groups (OR = 1.63) (10). Yang et al. analyzed the outcome of radiofrequency ablation over partial nephrectomy for renal mass smaller than 4 cm and identified eight eligible studies for analyses from May 2007 to May 2015 (11). They observed no statistical differences between the two groups in 5-year disease-free survival [hazard ratio (HR) = 1.29, 95% CI, 0.71–2.32, $P = 0.4$], local recurrence rate (OR = 0.99, 95% CI, 0.38–2.58, $P = 0.98$), and surgical complications [relative risk (RR) = 0.82, 95% CI, 0.37, 1.80; $P = 0.62$] between RFA and PN. Overall, the oncologic efficacy of RFA vs. PN has been controversial and undetermined.

Previously, the long-term results comparing partial nephrectomy and radiofrequency ablation were very limited. Olweny et al. first reported the oncologic outcomes at a minimum of 5 years of follow-up and found that RFA yielded comparable 5-year overall survival (OS), cancer-specific survival (CSS), overall disease-free survival, local recurrence-free survival, and metastasis-free survival to PN in 74 patients (12). After that, the studies from China by Chang et al. also reported that RFA had comparable 5-year oncologic outcomes but better preservation of renal function than PN in clinical T1a renal cancer (13) as well as in T1b renal cancer (14). Ji et al. also reported 5-year overall, cancer-specific, and disease-free survival rates of 93.3% vs. 94.6%, 98.0% vs. 98.5%, and 97.1% vs. 97.3%, for RFA and PN, respectively (all P-value>0.05) (15). Notably, despite the nonsignificant difference in these statistics, there seem to be a trend of a lower oncologic efficacy for RFA. Therefore, the question of whether RFA and PN have similar efficacy for clinical T1 renal cancer remains unsettled. Now, with the increased data from long-term studies in recent years, we performed this meta-analysis and systematic review to further update our knowledge of the long-term outcomes of RFA and partial nephrectomy for cT1 renal cancer.

Materials and methods

Literature search

The meta-analysis and systematic review were conducted and reported following the PRISMA guidelines (16, 17). We searched all literature focusing on the comparison of RFA vs. PN in patients with renal cancer with long-term follow-up of at least 5 years in the following databases from 1 Jan 2000 to 1 May 2022: PubMed, Embase, Web of Science, and the Cochrane Library. The following key words were used for the literature search:

for searching literature focusing on renal cancer: renal, kidney, rcc, nephritic;
for searching literature focusing on RFA: ablation, RFA, or radiofrequency;
for searching literature focusing on PN: nephrectomy or surgical or surgery or resection.

In addition, an additional literature search was performed *via* checking the citation lists of the literature identified and recent meta-analysis reviews. Literature was managed by the software Endnotes (version X7). The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42022329446).

Literature screening

There were two authors who independently reviewed the literature and assessed its eligibility for inclusion. If there was dissonance with the result, further discussion with the third author was conducted. The human-based studies were considered suitable for inclusion according to the PICOS guideline:

P (Population): patients with clinical T1 renal cancer (either T1a or T1b);
I (Intervention): patients were treated by RFA;
C (Comparison): patients were treated by PN;
O (Outcome): at least one of the following main outcomes should be reported: rate of recurrence, progression (recurrence, metastases, or progression-free survival (PFS), CSS, and OS. Secondary outcome is the rate of major complication;
S (Study design): a long-term comparative study with median/mean follow-up time longer than 5 years in both the RFA and PN groups.

The following literatures were excluded during the screening of title, abstract and full text:

(1) duplicate literatures;
(2) non-English literatures;
(3) several types of literature that usually do not contain original data: review, meta-analysis, guideline, letter, comment, editorial, reply, and protocol;
(4) case report;
(5) nonrelevant topic; and
(6) no available data were found in the full text review.

Data extraction

Two authors independently extracted raw data from each study. The third author was responsible for checking the data extracted by the two authors and resolving divergences *via* discussion and literature review. The following raw data from included studies were extracted: study location, stage of renal cancer, ablation approach (percutaneous or laparoscopic), ablation navigation (computed tomography or ultrasound), surgical approach (open or laparoscopic), study sample size, number of the surgery group, number of the ablation group, average age of the entire population, follow-up duration of the surgery group, follow-up duration of the ablation group, and R.E.N.A.L. nephrometry score (18) of both groups. Furthermore, the following data were collected for further data synthesis: the incidence of recurrence in the whole follow-up period; the HR value and 95% CI of PFS, CSS, and OS; and the incidence of major complications. If the HR and 95% CI were unavailable but the Kaplan–Meier (K–M) curve were provided for PFS, CSS, or OS, then the statistics of time-to-event were extracted from the Kaplan–Meier curve by using the software Engauge, and the data were further used to calculate the HR and 95% CI *via* the method provided by Tierney et al. (19). All extracted data are collected in an Excel file, which can be found in the **Supplementary Material**.

Definitions

Recurrence

Local recurrence was defined as a new focal enhancement in the ablation bed or enlargement of the ablation defect on follow-up imaging for RFA and a new mass at or near the PN site for PN. Metastatic recurrence was defined as extrarenal disseminated disease, with or without pathologic confirmation. Tumor recurrence included local recurrence and metastatic recurrence.

Progression-free survival

PFS was defined as the period from the date of treatment start or the baseline assessment until objective disease progression, subjective disease deterioration, or death, whichever occurred first.

Cancer-specific survival

CSS was defined as the duration from the time of treatment start or the baseline assessment to the date of renal cancer-related death or the end of follow-up.

Overall survival

OS was defined as the duration from the time of treatment start or the baseline assessment to the date of death or censor of follow-up.

Major complication

Postoperative complications were categorized according to the Common Terminology Criteria Adverse Events (CTCAE) version 5.0:

(1) Grade 1: Mild adverse events (AEs); asymptomatic or mild symptoms; requiring no treatment;
(2) Grade 2: Moderate AEs; requiring less treatment; local or noninvasive treatment;
(3) Grade 3: Severe AEs but not immediately life-threatening; hospitalization or prolong of hospitalization;
(4) Grade 4: Life-threatening; requiring emergency treatment;
(5) Grade 5: Death due to AEs.

Major complications were considered CTCAE grade $\geq$3.

Study quality and risk of bias assessment

Based on the recommendations of Cochrane Collaborations, two independent authors evaluated the quality of the included studies using the ROBINS-I risk of bias assessment tool (20) which consists of seven domains, namely, bias due to confounding, bias in the selection of participants into the study, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of the outcome, and bias in the selection of the reported result (21). The dissonance of the results was resolved in a similar way as described in the Literature search section. The risk of overall bias was assessed according to the summary of the above items.

Effect measures and synthesis methods

In the synthesis and presentation of results, the following effect measures were obtained using the *metan* module of the STATA software, version 15 (Stata Corporation, College Station, TX, United States): OR and 95% CI for recurrence and major complications, HR and 95% CI for PFS, CSS, and

OS. The studies were eligible for each synthesis when the relative raw data were available following the random effects model. For missing values such as the HR for PFS, CSS, and OS, the statistics were extracted from the Kaplan–Meier curves as described above in the Data extraction section. The forest plots were used to visually display the results of individual studies and syntheses. Subgroup analysis was performed to explore possible causes of heterogeneity among the study results. The studies were divided into subgroups according to the following factors: study location (United States, China, and Korea), stage of renal cancer (T1a, T1b, and T1a/T1b), ablation approach (percutaneous and laparoscopic), ablation navigation (CT and ultrasound), surgical approach (open and laparoscopic), average age (≤60 and >60 years), and R.E.N.A.L. nephrometry score (available and not reported). Sensitivity analysis was conducted by omitting one literature at each analysis to evaluate the robustness of the synthesized results using the *metaninf* module of the STATA software.

Reporting bias assessment

To assess the risk of bias due to missing results in a synthesis, the *metabias* module of STATA was used to perform *Egger*'s test. The *P*-value of *Egger*'s test <0.05 was considered significant publication bias. The funnel plot for identifying the underreported articles was also performed by using the *metafunnel* module of STATA to visually display the results of the reporting bias assessment.

Results

Study selection and characteristics of included studies

As shown in **Figure 1**, a total of 2,640 and 35 studies were initially identified from database searching and citation searching, respectively. After screening by reviewing the title, abstract, and full text, seven studies were finally included in the meta-analysis (12–15, 22–24). As listed in **Table 1**, 1,635 patients with renal cancer (548 in the RFA group and 1,413 in the PN group) were included. Four studies were conducted in China, two in the United States, and one in Korea. Both T1a and T1b renal cancers were studied. RFA was performed either percutaneously or laparoscopically. Ultrasound was the most commonly used navigation technique for RFA ($n = 6$ out of 7) while PN was performed either open or laparoscopically.

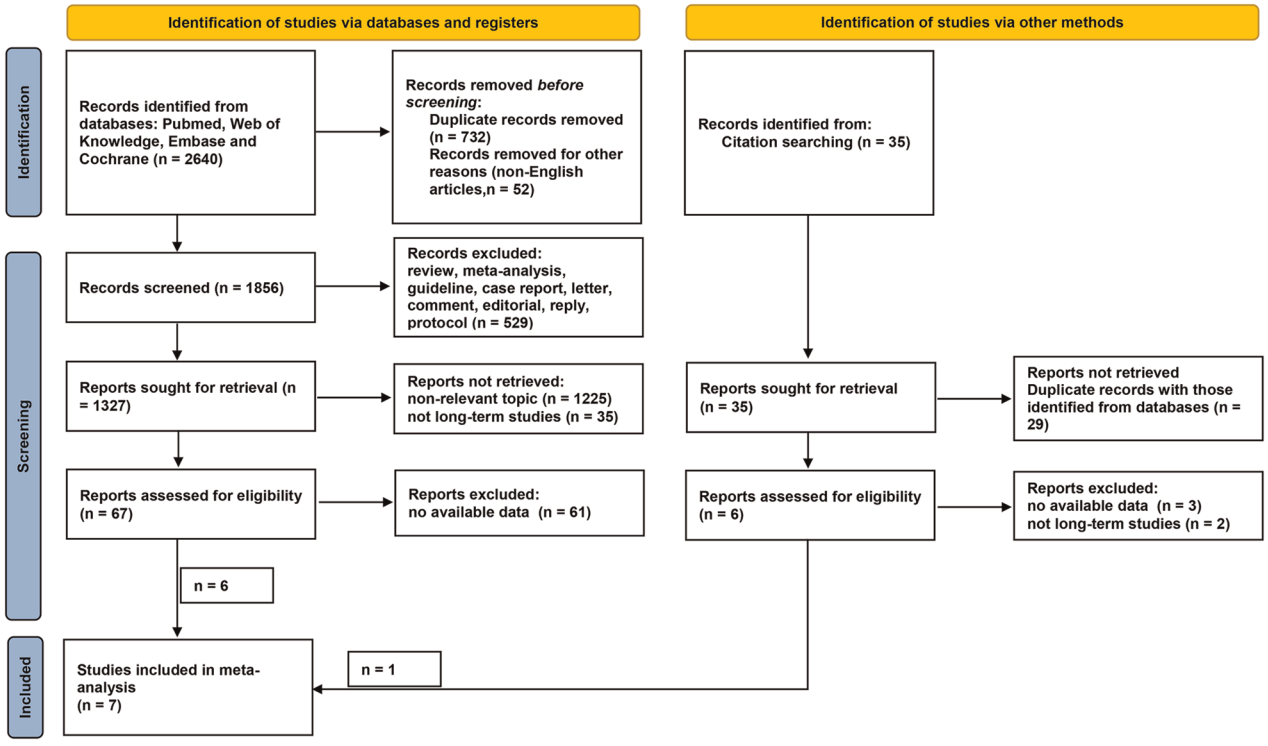

FIGURE 1
Flow diagram of literature selection. Records were identified *via* databases (n = 2,640) and other methods (citation searching, n = 35). After screening, a total of six and one records were considered eligible for inclusion from databases and other methods, respectively. Finally, seven studies were included in the present meta-analysis.

TABLE 1 Characteristics of included studies.

Study	Study location	Stage of RCC	RFA approach	RFA navigation	PN approach	Study sample size	No. of PN group	No. of ablation group	Average age	Follow-up of PN group	Follow-up of RFA group
Olweny (2012)	United States	T1a	P/L	CT	O/L	74	37	37	<60	66	61
Chang (2015)[a]	China	T1b	P/L	US	O/L	56	29	27	>60	71	73
Chang (2015)[b]	China	T1a	P/L	US	O/L	90	45	45	<60	69	67
Ji (2016)	China	T1a	L	US	L	179	74	105	>60	82	78
Liu (2017)	China	T1a/T1b	P	US	O/L	213	120	93	>60	80	77
Park (2019)	Korea	T1a	L	US	O	115	53	62	<60	68	60
Andrews (2019)	United States	T1a	P	US/CT	O	908	835	73	>60	113	90

RCC, renal cell carcinoma; RFA, radiofrequency ablation; PN, partial nephrectomy; P/L: percutaneous or laparoscopic; L, laparoscopic; P, percutaneous; CT, computed tomography; US, ultrasound; O/L, open or laparoscopic; O, open.
[a]Chang et al. in 2015 investigated the T1b stage RCC.
[b]Chang et al. in 2015 investigated the T1a stage RCC.

The median/mean follow-up duration ranged from 60 to 90 months for the RFA group and 66 to 113 months for the PN group. The characteristics of the PN and RFA groups were compared and listed in Table 2. The R.E.N.A.L. nephrometry scores of both groups were reported in three studies. In two studies, the nephrometry scores were similar between two groups (mean/median score = 8 in both groups). In another study, the

TABLE 2 Comparison of PN and RFA groups.

Study	R.E.N.A.L. nephrometry score (mean/median + range)		Mean/median age (year)		Mean/median ASA score		Choice of treatment approach	
	PN group	RFA group	PN group	RFA group	PN group	RFA group	Indication for PN	Indication for RFA
Olweny (2012)	N/A	N/A	54.8	63.8	1.9	2.3	Unspecified	Unspecified
Chang (2015)[a]	7.8 (5–11)	8.5 (6–11)	56.9	64	1.5	2.1	Unspecified	Unspecified
Chang (2015)[b]	8 (5–10)	8 (6–10)	52.8	52.9	1.7	1.7	Unspecified	Patients with significant comorbidities, a solitary kidney, or tumors in unresectable locations; patients unwilling to take the risk of PN
Ji (2016)	N/A	N/A	57.3	64.2	1.7	2.3	Unspecified	Older and comorbid patients; the presence of solitary kidney
Liu (2017)	8 (5–11)	8 (5–11)	58.5	68	1	2	Unspecified	Patients with smaller tumors (<4 cm) and peripheral tumors
Park (2019)	N/A	N/A	53	58	1.6	1.8	Unspecified	Unspecified
Andrews (2019)	N/A	N/A	62	72	N/A	N/A	Eligibility for PN was first determined by the urologist's discretion	Patients further interested in percutaneous ablation or deemed unfit for PN

PN, partial nephrectomy; RFA, radiofrequency ablation; R.E.N.A.L., radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, hilar tumor touching main renal artery or vein and location relative to polar lines; ASA, American Society of Anesthesiologists score; N/A, not available.
[a]Chang et al. in 2015 investigated the T1b stage RCC.
[b]Chang et al. in 2015 investigated the T1a stage RCC.

nephrometry scores were not different (8.5 in the PN group and 7.8 in the RFA group, $P = 0.698$). In most of the studies ($n = 6$ out of 7), the patients in RFA group were significantly older than PN group. Similarly, in five of the seven studies, the patients in RFA group had higher ASA scores. We have also collected the indication for the choice of treatment approach (PN and RFA) in these studies, and it turned out that RFA was commonly recommended in patients with significant comorbidities, a solitary kidney, or tumors in unresectable locations.

Risk of bias in studies

Figure 2 shows the results of the assessments of study risk by using the ROBINS-I tool for non-randomized controlled trial (RCT) studies. Overall, one study was of high quality with low risk of bias, five studies were of moderate quality, and the other one study was identified as having low quality. The most common confounding bias risk was due to the different ages in the RFA and PN groups. The confounding bias risk in the study by Andrews et al. was considered serious due to distinct baseline confounding factors including age, serum creatinine, histology, and size of tumor. The study by Chang et al. was evaluated as high quality because it was designed based on a propensity score-matched cohort, which reduced the risk of confounding factors.

Results of individual studies and syntheses, sensitivity analyses, and reporting biases

Recurrence

As shown in Figure 3A, RFA had a higher recurrence probability than PN but without statistical difference (OR = 1.22, 95% CI, 0.45–3.28, $P = 0.691$) with minor heterogeneity ($I^2 = 34.8\%$, $P = 0.189$). The sensitivity analysis (Figure 3B) showed that the study by Liu et al. (22) had a distinct impact on the pooled result while the other studies did not. After omitting the study by Liu et al., the pooled OR was 0.87 (95% CI, 0.39–1.95), which favors the treatment of RFA but still without significant difference. The funnel plot (Figure 3C) also suggested that that the study by Liu et al. was a potential source of publication bias, but this bias did not reach statistical significance (*P*-value of *Egger*'s test = 0.063).

Progression-free survival

RFA might be a potential risk factor for PFS (Figure 4A), with a pooled HR of 1.26 (95% CI, 0.75–2.11) but without significance ($P = 0.382$). There was no heterogeneity observed ($I^2 = 0\%$, $P = 0.\ 948$). The sensitivity analysis (Figure 4B) suggested that the result of pooled PFS was relatively stable. The funnel plot also showed good symmetry, and the *P*-value of *Egger*'s test was 0.443. Thus, no publication bias was considered.

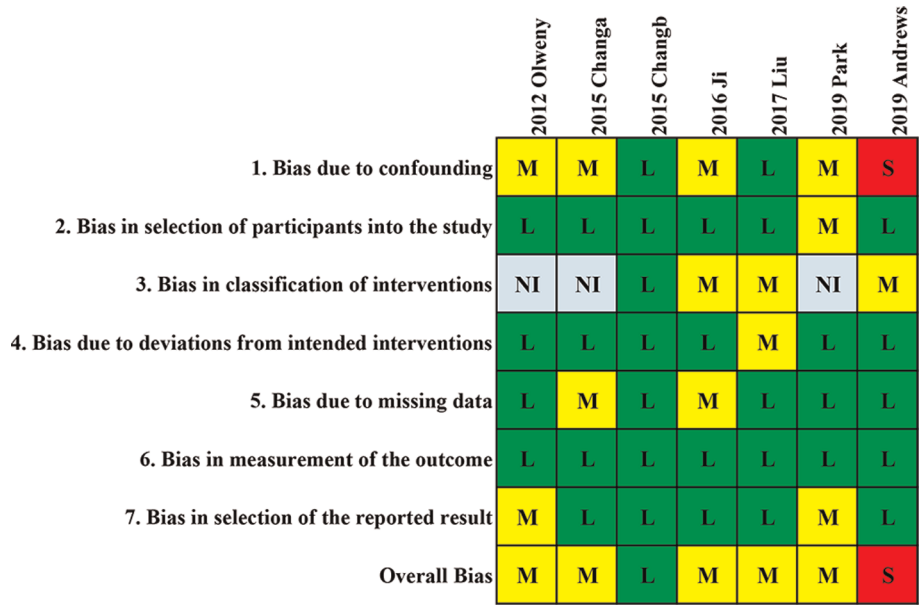

FIGURE 2
Quality assessment of included studies. Quality assessment of the involved studies with a ROBINS-I tool for non-RCT studies. L, low; M, moderate; S, serious; NI, no information.

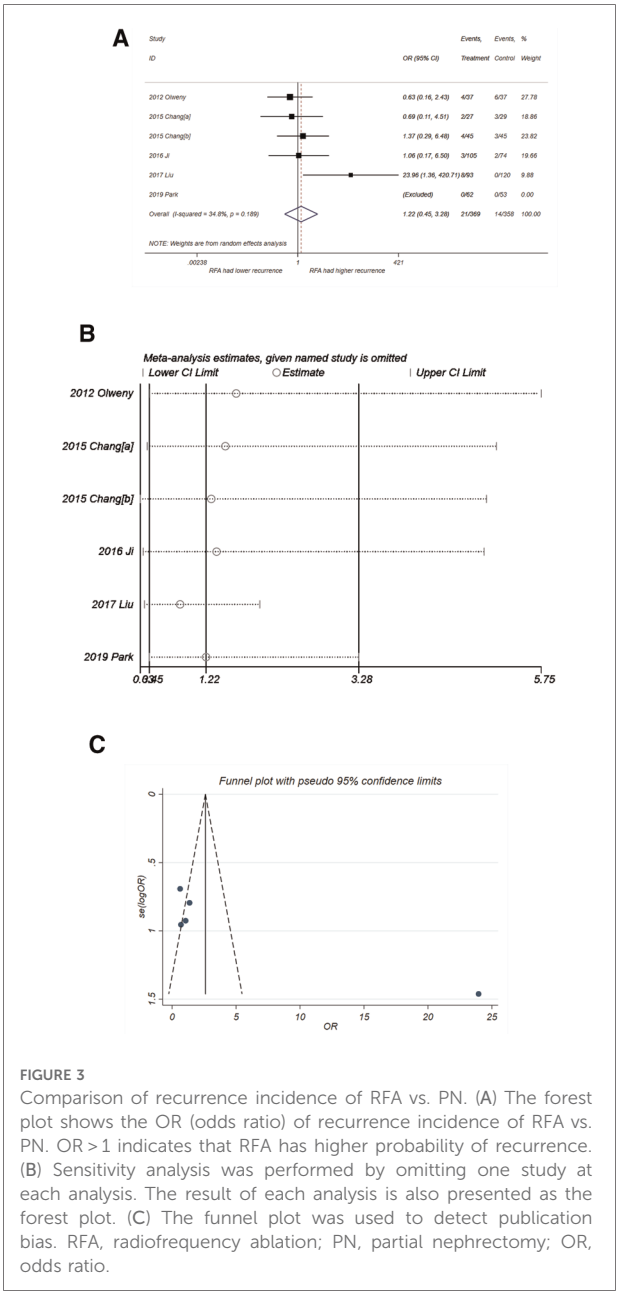

FIGURE 3
Comparison of recurrence incidence of RFA vs. PN. (**A**) The forest plot shows the OR (odds ratio) of recurrence incidence of RFA vs. PN. OR > 1 indicates that RFA has higher probability of recurrence. (**B**) Sensitivity analysis was performed by omitting one study at each analysis. The result of each analysis is also presented as the forest plot. (**C**) The funnel plot was used to detect publication bias. RFA, radiofrequency ablation; PN, partial nephrectomy; OR, odds ratio.

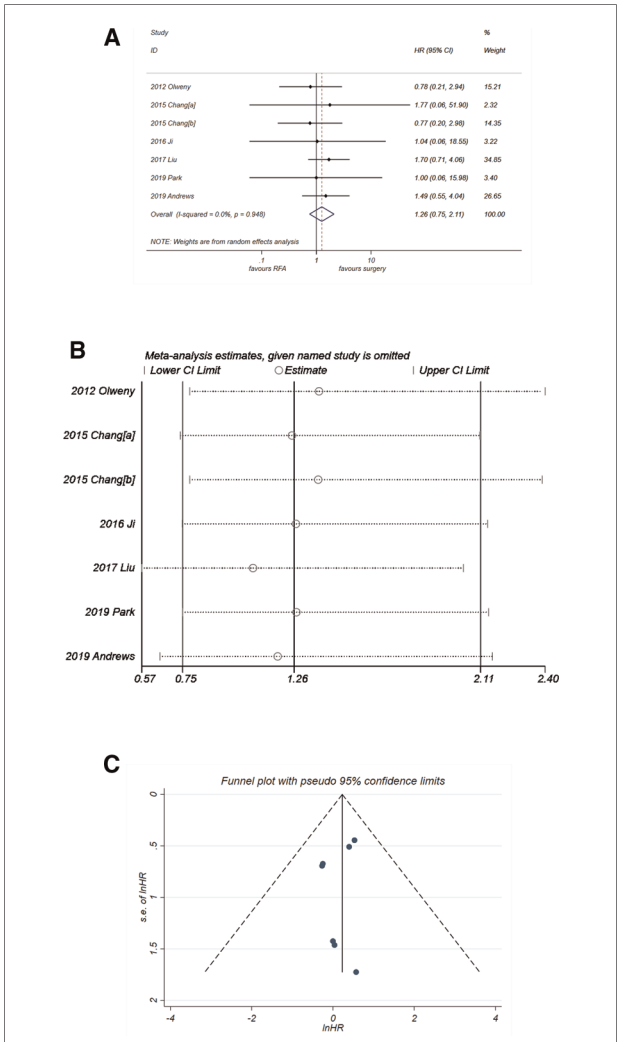

FIGURE 4
Comparison of PFS of RFA vs. PN. (**A**) The forest plot shows the HR of PFS of RFA vs. PN. HR > 1 indicates that RFA has higher risk for PFS. (**B**) Sensitivity analysis was performed by omitting one study at each analysis. The result of each analysis is also presented as the forest plot. (**C**) The funnel plot was used to detect publication bias. PFS, progression-free survival; RFA, radiofrequency ablation; PN, partial nephrectomy; HR, hazard ratio.

Cancer-specific survival

The results of CSS were consistent with those of PFS. The pooled HR (Figure 5A) was 1.27 (95% CI, 0.41–3.95) with $P = 0.679$. No heterogeneity was observed ($I^2 = 0\%$, $P = 0.997$). The forest plot in Figure 5B showed good robustness of the synthesized HR of CSS. Similarly, no publication bias was found in the funnel plot in Figure 5C (*P*-value of *Egger's* test was 0.262).

Overall Survival

Unlike PFS and CSS, analysis of OS (Figure 6A) suggested that RFA was a significant risk factor with synthesized HR = 1.76 (95% CI, 1.32–2.34, $P < 0.001$). No heterogeneity was observed ($I^2 = 0\%$, $P = 0.983$). The sensitivity analysis (Figure 6B) showed that the robustness of the synthesized HR of OS was fine. A good degree of symmetry was noticed *via* the funnel plot (Figure 6C) with a *P*-value of *Egger's* test = 0.099, indicating no significant publication bias.

Major complication

No significant difference in the incidence of major complication was observed for RFA and PN (Figure 7A) with OR = 1.31 (95% CI,0.55–3.14, $P = 0.545$). No heterogeneity was observed ($I^2 = 0\%$, $P = 0.901$). The sensitivity analysis (Figure 7B) showed good robustness of the result. No

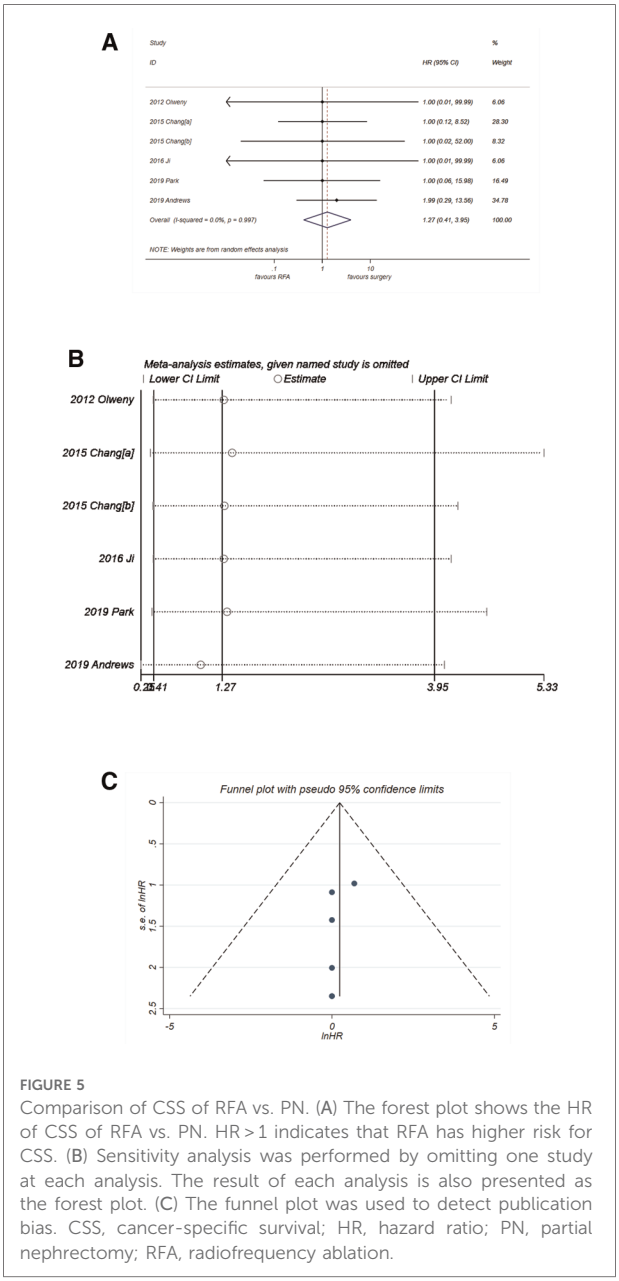

FIGURE 5
Comparison of CSS of RFA vs. PN. (**A**) The forest plot shows the HR of CSS of RFA vs. PN. HR > 1 indicates that RFA has higher risk for CSS. (**B**) Sensitivity analysis was performed by omitting one study at each analysis. The result of each analysis is also presented as the forest plot. (**C**) The funnel plot was used to detect publication bias. CSS, cancer-specific survival; HR, hazard ratio; PN, partial nephrectomy; RFA, radiofrequency ablation.

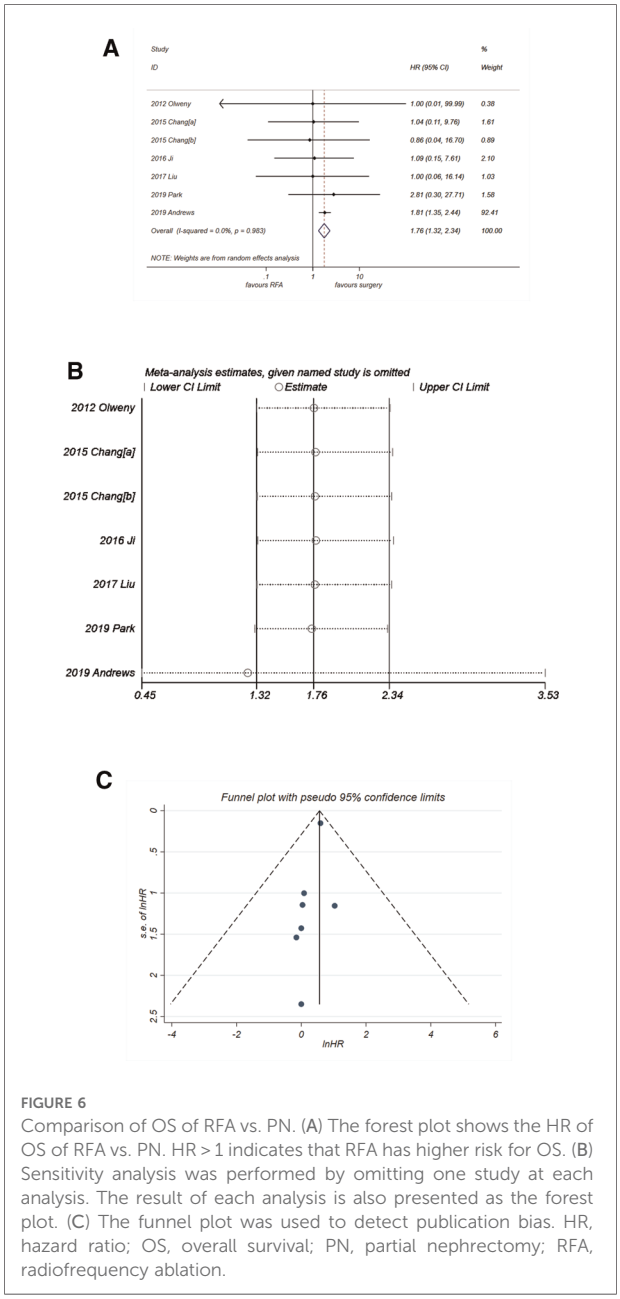

FIGURE 6
Comparison of OS of RFA vs. PN. (**A**) The forest plot shows the HR of OS of RFA vs. PN. HR > 1 indicates that RFA has higher risk for OS. (**B**) Sensitivity analysis was performed by omitting one study at each analysis. The result of each analysis is also presented as the forest plot. (**C**) The funnel plot was used to detect publication bias. HR, hazard ratio; OS, overall survival; PN, partial nephrectomy; RFA, radiofrequency ablation.

publication bias was observed in the funnel plot in Figure 7C (*P*-value of *Egger*'s test was 0.228).

Subgroup analysis

To investigate the potential source of heterogeneity for the result of recurrence, further subgroup analysis was performed. Because no heterogeneity was observed for PFS, CSS, OS, and major complication, subgroup analysis was performed only for recurrence. As shown in Table 3, because of the small number of included studies, the analysis was not valid in most of the subgroups. However, the values of I^2 in the subgroups of average age ≤60 and >60 years were 0.0% and 61.1%, respectively, indicating that the three studies with average population age >60 years might be the major source of heterogeneity for recurrence.

Discussion

In the present meta-analysis, RFA showed lower OS but similar recurrence, PFS, CSS, and major complications as compared with PN during the long-term follow-up over 5 years. This is currently the first meta-analysis focusing on the long-term outcomes of RFA

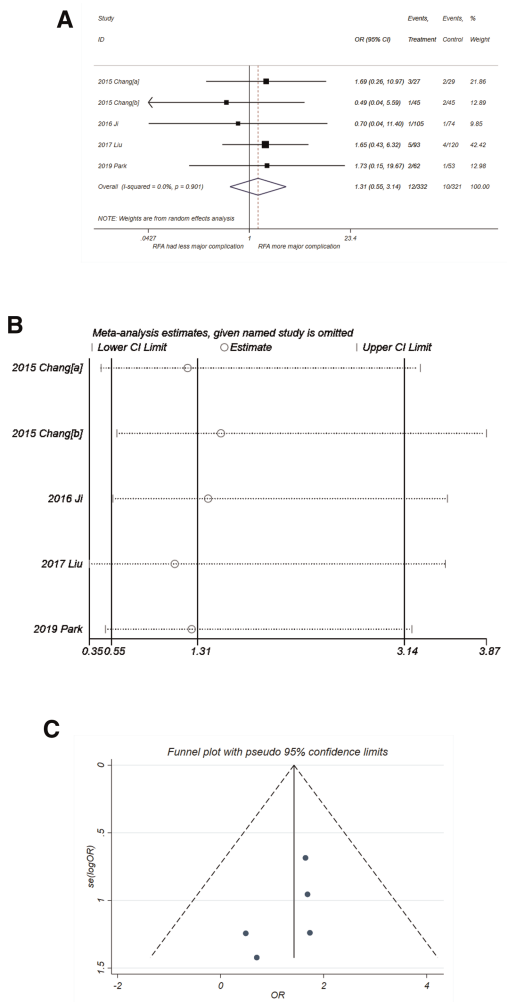

FIGURE 7
Comparison of major complication of RFA vs. PN. (**A**) The forest plot shows the OR of major complication of RFA vs. PN. OR > 1 indicates that RFA has higher probability of major complication. (**B**) Sensitivity analysis was performed by omitting one study at each analysis. The result of each analysis is also presented as the forest plot. (**C**) The funnel plot was used to detect publication bias. PN, partial nephrectomy; RFA, radiofrequency ablation; OR, odds ratio.

TABLE 3 Subgroup analysis for recurrence.

Subgroup	No. of studies	OR	Lower 95% CI	Upper 95% CI	I^2	*P* for I^2
Study location						
United States	1	0.626	0.161	2.432	—	—
China	4	1.629	0.461	5.748	40.7%	0.167
Korea	1	—	—	—	—	—
Stage of RCC						
T1a	4	0.918	0.376	2.237	0%	0.749
T1b	1	0.693	0.107	4.505	—	—
T1a/T1b	1	23.959	1.364	420.711	—	—
Ablation approach						
Percutaneous or laparoscopic	3	0.831	0.338	2.038	0%	0.743
Laparoscopic	2	1.059	0.173	6.499	—	—
Percutaneous	1	23.959	1.364	420.711	—	—
Ablation navigation						
CT	1	0.626	0.161	2.432	—	—
US	5	1.629	0.461	5.748	40.7%	0.167
Surgical approach						
Open or laparoscopic	4	1.363	0.374	4.976	51.6%	0.102
Laparoscopic	1	1.059	0.173	6.499	—	—
Open	1	—	—	—	—	—
Average age						
≤60	3	0.877	0.315	2.439	0%	0.459
>60	3	2.006	0.279	14.412	61.1%	0.077
R.E.N.A.L. nephrometry score						
Available	3	2.118	0.341	13.162	59%	0.087
Not reported	4	0.756	0.255	2.241	0	0.65

OR, odds ratio; CI, confidence interval; RCC, renal cell carcinoma; CT, computed tomography; US, ultrasound. R.E.N.A.L., radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, hilar tumor touching main renal artery or vein and location relative to polar lines.

and PN for renal cancer. It demonstrates the therapeutic efficacy as well as the safety of RFA for patients with renal cancer, especially for those not amenable to surgery.

Several guidelines have already recommended that thermal ablation should be considered in patients with small-size cancers who are poor surgical candidates (25–27). The puncture procedure of percutaneous RFA is similar to a needle biopsy and involves inserting a needle-like probe into the organ (28). Then, radiofrequency waves are produced by the probe and sent into the nearby tissue, which causes the necrosis of surrounding cells (29). Thereby, this relatively new technique has a remarkable advantage over PN, namely, RFA is better at preserving renal function as well as reducing other perioperative and postoperative complications (30, 31). Thereafter, many clinical trials and observations have reported favorable results with RFA when compared with PN. For instance, Bird et al. compared laparoscopic-guided RFA with laparoscopic PN in a retrospective study containing 69 patients and found no evidence of tumor recurrence in the follow-up period (32). In a large cohort study by Thompson et al., they reported that local recurrence-free survival and metastases-free survival were not significantly different between percutaneous RFA and PN (33). One of the shortcomings of most studies is the limited number of events (including local recurrence, distant metastases, death, and

cancer-specific death), which is mainly due to the short duration of follow-up (34). It is difficult to yield a statistically significant difference within short-term of follow-up; thus, a long-term study is needed to further determine the oncologic efficacy of RFA and PN. A recent meta-analysis by Rivero et al. (35) has a very alike theme with our meta-analysis. However, only 3 of the 15 studies included in the meta-analysis were with long-term follow-up more than 5 years. The results of the meta-analysis mainly reflect short/mid-term outcome of ablation vs. PN. There are several similar findings between the meta-analysis and ours. For instance, both meta-analyses yield a more favorable overall survival of PN. The results of cancer recurrence in both meta-analyses were similar between PN and ablation (HR= 1.32 and 1.22, $P = 0.22$ and 0.691, respectively). However, the cancer-specific survival was almost similar between RFA and PN in our study (HR = 1.27, $P = 0.679$), but in their meta-analysis, PN showed better efficacy for cancer-specific survival with HR of 3.84 ($P < 0.05$). Because ablation is usually applied to relatively older patients with more underlying diseases, this can lead to more noncancer-related death cases during the long-term follow-up. Therefore in our meta-analysis, the OS result favors PN, but the cancer-specific survival is similar between PN and RFA. The results of CSS might reflect a more objective comparison of RFA vs. PN.

An important interpretation for the results of the present meta-analysis is that although RFA shows an HR of 1.76 ($P < 0.001$), it does not necessarily mean that the efficacy of RFA is worse than PN. First, because the HR of OS in the six studies (**Figure 6A**) other than Andrews et al. (24) is extracted from the K–M curve, they all show large 95% CI range with a small weight in the synthesized data. On the other hand, the study by Andrews et al. with HR of 1.81 (95% CI, 1.32–2.34) holds a big weight of 92.4% in the synthesized data, as shown in **Figure 6A**. Thereby, the synthesized result is mainly affected by the study of Andrews et al., which leads to a final HR of 1.76 ($P < 0.001$). There might be more or less some bias in this figure, which is mainly due to the data extraction method and is hard to eliminate. Similarly, in the analysis of CSS (**Figure 5A**), the study by Andrews et al. holds a weight of 34.8%; this is way smaller than that in the analysis of OS (92.4%, **Figure 6A**). The final synthesized result of CSS suggests that the efficacy of RFA is not different with PN. Taken together, these results indicate that there might be some factors other than cancer-specific factors inducing a lower OS of RFA, such as age. As depicted in the characteristics of the seven included studies, six of them included an older population of the RFA group. Therefore, there might also be a potential selection bias, which can lead to the inconsistent results of OS and CSS.

Currently, PN is the treatment of choice for cT1 renal cancer, while RFA is considered an alternative therapy for patients with high surgical risk (2). The preference for PN might reflect the relative lack of clinical studies investigating the long-term oncological outcomes of RFA. Nevertheless, in this meta-analysis, with several recently published studies, we show that RFA and PN for cT1 renal cancer have comparable long-term oncological outcomes. There are several strengths of the present work: there is only minor heterogeneity in the analysis of recurrence and zero heterogeneity in other analysis, suggesting that the synthesis of data is more convincing; most of the results in the sensitivity analysis are quite stable, further demonstrating the robustness of the synthesized results; and lastly, the possibility of publication bias is extremely low, as demonstrated by the funnel plots and *Egger*'s tests.

There are also several limitations to this study. The number of included studies is relatively small, which is mainly due to the current clinical practice of renal cancer management. In addition, despite the fact that the choice of approach was usually based on tumor size, location, clinical judgment, and patient preference, it turned out that RFA was commonly recommended in patients with significant comorbidities, solitary kidney, or tumors in unresectable locations. Therefore, RFA was mainly performed in older patients with more preoperative risk factors who were not surgical candidates, which might contribute to the selection bias. A randomized controlled trial could be ideal and is expected to be performed in the future. Despite these limitations, the results in most studies have supported the clinical usefulness of RFA in appropriately selected patients with renal cell carcinoma (RCC).

Conclusion

This meta-analysis, which focuses on the long-term oncological outcomes of cT1 renal cancer, suggests that RFA has comparable therapeutic efficacy to PN. RFA is a safe, nephron-sparing, and oncologically effective technique for the treatment of cT1 renal cancer and also a potential treatment alternative for the young, healthy population. Nevertheless, a prospective randomized study with large number of patients and long-term follow-up could draw a further conclusion.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design: LL, JZ, and BS. Administrative support: DC, YH, and BS. Provision of study materials or patients: LL, JZ, LH, and XW. Collection and assembly of data: LL, WB, and TS. Data analysis and interpretation: LL, WB, and DC. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1012897/full#supplementary-material.

References

1. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. *J Urol.* (2017) 198(3):520–9. doi: 10.1016/j.juro.2017.04.100

2. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU Guidelines on renal cell carcinoma: the 2010 update. *Eur Urol.* (2010) 58(3):398–406. doi: 10.1016/j.eururo.2010.06.032

3. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU Guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* (2015) 67 (5):913–24. doi: 10.1016/j.eururo.2015.01.005

4. Finelli A, Ismaila N, Bro B, Durack J, Eggener S, Evans A, et al. Management of small renal masses: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* (2017) 35(6):668–80. doi: 10.1200/JCO.2016.69.9645

5. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol.* (2008) 179(2):468–71. doi: 10.1016/j.juro.2007.09.077

6. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol.* (2006) 7(9):735–40. doi: 10.1016/S1470-2045(06)70803-8

7. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc.* (2000) 75(12):1236–42. doi: 10.4065/75.12.1236

8. Gebauer B, Werk M, Lopez-Hanninen E, Felix R, Althaus P. Radiofrequency ablation in combination with embolization in metachronous recurrent renal cancer in solitary kidney after contralateral tumor nephrectomy. *Cardiovasc Intervent Radiol.* (2007) 30(4):644–9. doi: 10.1007/s00270-007-9012-y. PubMed PMID: 17436034

9. Iannuccilli JD, Dupuy DE, Beland MD, Machan JT, Golijanin DJ, Mayo-Smith WW. Effectiveness and safety of computed tomography-guided radiofrequency ablation of renal cancer: a 14-year single institution experience in 203 patients. *Eur Radiol.* (2016) 26(6):1656–64. doi: 10.1007/s00330-015-4006-7

10. Pan XW, Cui XM, Huang H, Huang Y, Li L, Wang ZJ, et al. Radiofrequency ablation versus partial nephrectomy for treatment of renal masses: a systematic review and meta-analysis. *Kaohsiung J Med Sci.* (2015) 31(12):649–58. doi: 10.1016/j.kjms.2015.09.007

11. Yang Y, Chen S, Chen F, Zhu K, Deng Q, Luo L, et al. Outcome of radiofrequency ablation over partial nephrectomy for small renal mass (<4 cm): a systematic review and meta-analysis. *Int J Clin Exp Med.* (2015) 8(11):20670–4.

12. Olweny EO, Park SK, Tan YK, Best SL, Trimmer C, Cadeddu JA. Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. *Eur Urol.* (2012) 61(6):1156–61. doi: 10.1016/j.eururo.2012.01.001

13. Chang X, Liu T, Zhang F, Ji C, Zhao X, Wang W, et al. Radiofrequency ablation versus partial nephrectomy for clinical T1a renal-cell carcinoma: long-term clinical and oncologic outcomes based on a propensity score analysis. *J Endourol.* (2015) 29(5):518–25. doi: 10.1089/end.2014.0864

14. Chang X, Zhang F, Liu T, Ji C, Zhao X, Yang R, et al. Radio frequency ablation versus partial nephrectomy for clinical T1b renal cell carcinoma: long-term clinical and oncologic outcomes. *J Urol.* (2015) 193(2):430–5. doi: 10.1016/j.juro.2014.07.112

15. Ji C, Zhao X, Zhang S, Liu G, Li X, Zhang G, et al. Laparoscopic radiofrequency ablation versus partial nephrectomy for cT1a renal tumors: long-term outcome of 179 patients. *Urol Int.* (2016) 96(3):345–53. doi: 10.1159/000443672

16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097

17. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Br Med J.* (2015) 350:g7647. doi: 10.1136/bmj.g7647

18. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol.* (2009) 182(3):844–53. doi: 10.1016/j.juro.2009.05.035

19. 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. doi: 10.1186/1745-6215-8-16

20. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Br Med J.* (2016) 355:i4919. doi: 10.1136/bmj.i4919

21. Schunemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE Guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol.* (2019) 111:105–14. doi: 10.1016/j.jclinepi.2018.01.012

22. Liu N, Huang D, Cheng X, Chong Y, Wang W, Gan W, et al. Percutaneous radiofrequency ablation for renal cell carcinoma vs. partial nephrectomy: comparison of long-term oncologic outcomes in both clear cell and non-clear cell of the most common subtype. *Urol Oncol.* (2017) 35(8):530 e1–e6. doi: 10.1016/j.urolonc.2017.03.014

23. Park JM, Yang SW, Shin JH, Na YG, Song KH, Lim JS. Oncological and functional outcomes of laparoscopic radiofrequency ablation and partial nephrectomy for T1a renal masses: a retrospective single-center 60 month follow-up cohort study. *Urol J.* (2019) 16(1):44–9. doi: 10.22037/uj.v0i0.4155

24. Andrews JR, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A, et al. Oncologic outcomes following partial nephrectomy and percutaneous ablation for

cT1 renal masses. *Eur Urol.* (2019) 76(2):244–51. doi: 10.1016/j.eururo.2019.04.026

25. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European association of urology guidelines on renal cell carcinoma: the 2022 update. *Eur Urol.* (2022) 82(4):399–410. doi: 10.1016/j.eururo.2022.03.006

26. Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. *J Urol.* (2021) 206(2):199–208. doi: 10.1097/JU.0000000000001911

27. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part II. *J Urol.* (2021) 206(2):209–18. doi: 10.1097/JU.0000000000001912

28. Luo M, Jiang H, Shi T. Multi-stage puncture path planning algorithm of ablation needles for percutaneous radiofrequency ablation of liver tumors. *Comput Biol Med.* (2022) 145:105506. doi: 10.1016/j.compbiomed.2022.105506

29. Zhang B, Moser MA, Zhang EM, Luo Y, Liu C, Zhang W. A review of radiofrequency ablation: large target tissue necrosis and mathematical modelling. *Phys Med.* (2016) 32(8):961–71. doi: 10.1016/j.ejmp.2016.07.092

30. Ofude M, Kitagawa Y, Koda W, Ueno S, Kadono Y, Konaka H, et al. Preserved renal function after percutaneous radiofrequency ablation for renal tumors: experience of a single institution. *Anticancer Res.* (2013) 33(10):4669–73.

31. Raman JD, Thomas J, Lucas SM, Bensalah K, Lotan Y, Trimmer C, et al. Radiofrequency ablation for T1a tumors in a solitary kidney: promising intermediate oncologic and renal function outcomes. *Can J Urol.* (2008) 15(2):3980–5.

32. Bird VG, Carey RI, Ayyathurai R, Bird VY. Management of renal masses with laparoscopic-guided radiofrequency ablation versus laparoscopic partial nephrectomy. *J Endourol.* (2009) 23(1):81–8. doi: 10.1089/end.2008.0087

33. Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol.* (2015) 67(2):252–9. doi: 10.1016/j.eururo.2014.07.021

34. O'Neal D, Cohen T, Peterson C, Barr RG. Contrast-enhanced ultrasound-guided radiofrequency ablation of renal tumors. *J Kidney Cancer VHL.* (2018) 5(1):7–14. doi: 10.15586/jkcvhl.2018.100

35. Rivero JR, De La Cerda J 3rd, Wang H, Liss MA, Farrell AM, Rodriguez R, et al. Partial nephrectomy versus thermal ablation for clinical stage T1 renal masses: systematic review and meta-analysis of more than 3,900 patients. *J Vasc Interv Radiol.* (2018) 29(1):18–29. doi: 10.1016/j.jvir.2017.08.013

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 24 March 2023
DOI 10.3389/fsurg.2023.1000522

OPEN ACCESS

EDITED BY
Cesare Ruffolo,
University Hospital of Padua, Italy

REVIEWED BY
Linhui Hu,
The Second Hospital of Anhui Medical University, China
Simona Ascanelli,
University Hospital of Ferrara, Italy

*CORRESPONDENCE
Guo-Cheng Du
guochengdu0011@163.com

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

RECEIVED 22 July 2022
ACCEPTED 14 February 2023
PUBLISHED 24 March 2023

CITATION
Yin J-M, Zhu K-P, Guo Z-W, Yi W, He Y and Du G-C (2023) Is red cell distribution width a prognostic factor in patients with breast cancer? A meta-analysis.
Front. Surg. 10:1000522.
doi: 10.3389/fsurg.2023.1000522

Is red cell distribution width a prognostic factor in patients with breast cancer? A meta-analysis

Jun-Ming Yin†, Ke-Peng Zhu†, Zhi-Wei Guo, Wen Yi, Ying He and Guo-Cheng Du*

Mastothyroid Vascular Surgery, The Second Clinical Medical College of North Sichuan Medical College Nanchong Central Hospital, Nanchong, China

Purpose: The current study aimed to investigate whether red blood cell distribution width (RDW) can predict the prognosis of patients with breast cancer (BC).

Methods: We searched four databases, including PubMed, Embase, Cochrane Library databases, and CNKI, from inception to Jun 13, 2022. The primary outcome was overall survival (OS), and the secondary outcome was disease-free survival (DFS). A subgroup analysis was conducted based on different treatments. This meta-analysis was performed with RevMan 5.3 (The Cochrane Collaboration, London, United Kingdom).

Results: A total of seven studies including 4,884 BC patients were identified. The high RDW group had a larger tumor size (OR = 2.12, 95% CI = 1.67 to 2.68, $P < 0.01$), higher proportions of advanced stage tumors (OR = 1.77, 95% CI = 1.38 to 2.27, $P < 0.01$), more lymph node metastases (OR = 2.00, 95% CI = 1.58 to 2.51, $P < 0.01$) and lower HER-2 expression (OR = 0.76, 95% CI = 0.61 to 0.95, $P = 0.02$). For prognosis, after pooling all the data, we found that the high RDW group was associated with worse OS (HR = 2.12, 95% CI = 1.47 to 3.08, $P < 0.01$) and DFS (HR = 1.77, 95% CI = 1.32 to 2.37, $P < 0.01$). The subgroup analysis found that RDW had prognostic significance but only for surgery-only patients (HR = 2.41, 95% CI = 1.67 to 3.49, $P < 0.01$).

Conclusion: High RDW was associated with worse OS and DFS. Therefore, RDW was a simple predictive factor for the prognosis of BC patients.

KEYWORDS

breast cancer, red blood cell distribution width, overall survival, disease-free survival, meta-analysis

Introduction

Breast cancer (BC) is one of the most common cancers and the second leading cause of cancer-related death in women worldwide (1, 2). Approximately 1.5 million women are diagnosed with BC each year, and this number is expected to increase to 2.2 million annually by 2025 (3). There are different treatments, including systemic therapy, surgery, and radiotherapy, depending on the stage of BC (4–6). Therefore, convenient preoperative predictive values for BC prognosis could help surgeons develop treatment strategies and improve surgical outcomes.

Red blood cell distribution width (RDW) is a simple and readily available parameter that represents the heterogeneity of red blood cell volume and is traditionally used in the differential diagnosis of anemia (7). Elevated RDW can predict mortality and morbidity in patients with benign diseases, including cerebral infarction (8), acute myocardial infarction (9), pancreatitis (10), pulmonary embolism (11), acute renal failure (12),

coronary artery disease, and heart failure (13, 14). It is also a marker for predicting the prognosis of tumors such as gastric cancer (15), esophageal cancer (16), hepatocellular carcinoma, and colorectal cancer (17, 18).

However, for BC, the effect of RDW on prognosis is controversial (19–25). Wang C et al. analyzed 443 BC patients and found that RDW was not a prognostic factor for OS (19). Similarly, Takeuchi H et al. analyzed 299 BC patients and found that RDW was not a predictor for DFS (20). However, Yoo YC et al. demonstrated that high RDW had high predictive power for OS and DFS (21). In another study reported by Yao D et al. high pretreatment RDW levels in BC patients were associated with poor OS and DFS; thus, RDW could be a potential predictive factor in determining poor prognosis in all from all patients (23). Therefore, it is necessary to identify the exact role of RDW in the prognosis of BC patients.

Materials and methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (26).

Literature search strategy

We searched four databases, including PubMed, Embase, Cochrane Library databases, and CNKI, from inception to Jun 13, 2022. The search strategy included two keywords: RDW and BC. For RDW, the search strategy was as follows: "red blood cell distribution width" OR "red cell distribution width" OR "RDW". In terms of BC, the search strategy was as follows: "Breast Neoplasms" OR "Breast Cancer" OR "Breast Tumor" OR "Breast Tumors" OR "Breast Carcinoma" OR "Breast Carcinomas". Then, we use "AND" to combine the two keywords. The languages were limited to English and Chinese.

Inclusion and exclusion criteria

Our meta-analysis aimed to analyze the effect of RDW on the prognosis of BC, therefore, the inclusion criteria for studies were as follows: (1) the patients included were diagnosed with primary BC; (2) the study included both a control group (the low RDW group) and an exercise group (the high RDW group); (3) the study reported the prognosis including overall survival (OS) or disease-free survival (DFS); and (4) the study was published in English or Chinese. The exclusion criteria for studies were as follows: (1) the article type was a case report, a review, a letter to the editor, comments, or conference literature; and (2) there was an absence of the full text. Two reviewers conducted the inclusion and exclusion criteria, separately. Disagreement was settled by group discussion.

Study selection

Two reviewers searched the four databases. The duplicated studies were eliminated first. Then, the titles and abstracts were screened to find eligible studies. After that, the full texts were checked to determine whether the studies were suitable for the final analysis. Two reviewers conducted the study selection, and the final judgment was made after a group discussion.

Data extraction

The data included the study information, baseline information, and prognostic information. The study information included the first author, publishing year, publishing country, and Newcastle-Ottawa Scale (NOS) score. The baseline information included the study data, patient information, sample size, and cutoff value of RDW. The prognostic information included OS and DFS. These data were extracted independently and cross-checked by two reviewers.

Definitions and outcomes

OS was defined as the time from diagnosis to death due to any cause. DFS was defined as the time from diagnosis to the time of recurrence, death, or last follow-up. The primary outcome was OS, and the secondary outcome was DFS.

Quality assessment

The NOS score was used to evaluate the quality of the included studies (27). A score of nine points represented high quality; a score of seven to eight points represented medium quality; and low-quality studies scored less than seven points.

Statistical analysis

In the current meta-analysis, dichotomous variables including tumor diameter, tumor stage, type of surgery, chemotherapy, lymph node metastases, peritumoral vascular invasion, and estrogen receptor (ER)/progesterone receptor (PR) positivity, were collected, and odds ratios (ORs) plus 95% confidence intervals (CIs) were calculated. For OS and DFS, hazard ratios (HRs) plus 95% CIs were calculated. A subgroup analysis was conducted according to the different treatments for patients. The I^2 value and the chi-squared test were used to assess the statistical heterogeneity (28, 29). When $I^2 > 50\%$, the random effects model was used, and $p < 0.1$ was considered statistically significant. The fixed effects model was used when $I^2 \leq 50\%$, and $p < 0.05$ was considered statistically significant. This meta-analysis was performed with RevMan 5.3 (The Cochrane Collaboration, London, United Kingdom).

Results

Study selection

A total of 71 studies were identified in the four databases (21 studies in PubMed, 32 studies in Embase, 0 studies in the Cochrane Library, and 18 studies in CNKI). There were 52 studies after removing the duplicated studies. Finally, seven studies were left for the final analysis (Figure 1).

Patient characteristics and quality assessment of the included studies

A total of seven studies including 4,884 BC patients were identified (19–25). The publishing year was from 2014 to 2021.

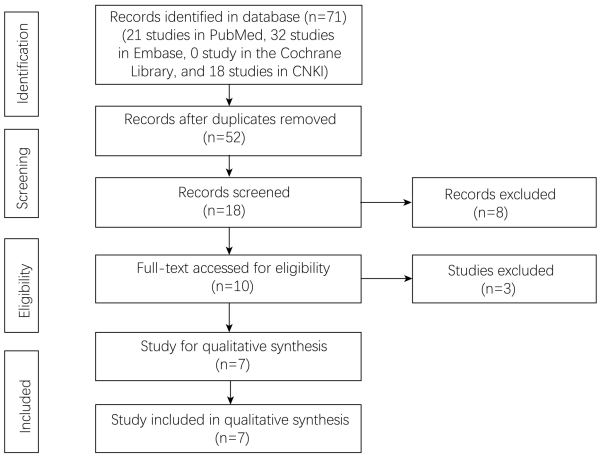

FIGURE 1
Flowchart of study selection.

Five studies were published in China, one study was published in Korea and one study was published in Japan. The study period was from 1996 to 2017. For the prognosis, six studies reported OS, and five studies reported DFS. The sample size, treatment, cutoff value, and NOS score of each included study are shown in Table 1.

Baseline information

The baseline information including tumor diameter, tumor stage, type of surgery, chemotherapy, lymph node metastases, peritumoral vascular invasion, ER/PR positivity, HER-2, and Ki-67, was compared between the high RDW group and the low RDW group. The high RDW group had a larger tumor size (OR = 2.12, 95% CI = 1.67 to 2.68, $P < 0.01$), a higher proportion of advanced stage tumors (OR = 1.77, 95% CI = 1.38 to 2.27, $P < 0.01$), more lymph node metastases (OR = 2.00, 95% CI = 1.58 to 2.51, $P < 0.01$) and lower HER-2 expression (OR = 0.76, 95% CI = 0.61 to 0.95, $P = 0.02$) (Table 2).

OS

Six studies with 4,585 patients reported OS data on BC patients. After pooling all the data, we found that the high RDW group was associated with worse OS than the low RDW group (HR = 2.12, 95% CI = 1.47 to 3.08, $P < 0.01$) (Figure 2).

DFS

Five studies with 3,390 patients reported data on DFS in BC patients. After pooling all the data, we found that the high RDW group was associated with worse DFS than the low RDW group (HR = 1.77, 95% CI = 1.32 to 2.37, $P < 0.01$) (Figure 3).

TABLE 1 Baseline characteristics of included studies.

Author	Year	Country	Study date	Sample size	Patients	Treatment	Survival volume	Cut-off volume	NOS
Takeuchi H	2019	Japan	2006–2017	299	M0 BC	Surgery	DFS	13.7%	7
Yoo YC	2021	Korea	2005–2010	1783	Invasive BC	Surgery, neoadjuvant therapy, chemotherapy or radiotherapy	OS/DFS	13.5%	9
Li F	2018	China	2010–2012	280	Invasive M0 BC	Surgery and chemotherapy (no neoadjuvant therapy before surgery)	OS/DFS	13.45%	7
Yao D	2019	China	2009–2014	825	Invasive M0 BC	Surgery (no neoadjuvant therapy, chemotherapy or radiotherapy)	OS/DFS	13.82%	9
Huang DP	2016	China	2008–2012	203	Invasive BC under 40 years old	Surgery or chemotherapy (no neoadjuvant therapy before surgery)	OS/DFS	13.75%	7
Yao M	2014	China	2009–2011	608	BC	no neoadjuvant therapy before surgery	OS	13.45%	8
Wang C	2014	China	1996–2011	886	Primary invasive BC	Any kind of clinical treatment, such as surgery, chemotherapy, radiation therapy, or hormone therapy	OS	14.5%	9

Abbreviations: NOS, newcastle-ottawa scales; BC, breast cancer; OS, overall survival; DFS, disease-free survival.

TABLE 2 Summary of characteristics between the high RDW group and the Low RDW group.

Characteristics	Studies	Participants (the High RDW/the Low RDW)	Odds Ratio/Mean Difference (95% CI)	Model	Heterogeneity
Tumor diameter					
≤5	3	546/762	Reference	Reference	Reference
>5	3	546/762	2.12 [1.67, 2.68]; $P < 0.00001$	FE	$I^2 = 3\%$; $P = 0.36$
TNM stage					
I	3	Reference	Reference	Reference	Reference
II	3	435/881	3.21 [0.23, 44.75]; $P = 0.39$	RE	$I^2 = 99\%$;
III	3	546/762	1.77 [1.38, 2.27]; $P < 0.00001$	FE	$P < 0.00001$
					$I^2 = 23\%$; $P = 0.27$
Type of surgery					
Conservation	3	546/362	Reference	Reference	Reference
Radical	3	546/352	0.81 [0.44,1.47]; $P = 0.48$	FE	$I^2 = 8\%$; $P = 0.30$
Chemotherapy					
FEC	3	Reference	Reference	Reference	Reference
TAC/TEC	3	500/684	0.80 [0.61, 1.06]; $P = 0.12$	FE	$I^2 = 29\%$; $P = 0.12$
Non	3	546/762	0.79 [0.54, 1.17]; $P = 0.25$	FE	$I^2 = 0\%$; $P = 0.25$
Lymph node metastases	3	546/762	2.00 [1.58, 2.51]; $P < 0.00001$	FE	$I^2 = 0\%$; $P = 0.83$
peritumoral vascular invasion	2	454/574	1.07 [0.45, 2.50]; $P = 0.88$	RE	$I^2 = 60\%$; $P = 0.12$
ER positive	4	756/1160	1.03 [0.85, 1.25]; $P = 0.76$	FE	$I^2 = 0\%$; $P = 0.72$
PR positive	4	756/1160	1.13 [0.94, 1.37]; $P = 0.19$	FE	$I^2 = 0\%$; $P = 0.80$
HER-2	4	756/1160	0.76 [0.61, 0.95]; $P = 0.02$	FE	$I^2 = 0\%$; $P = 0.82$
Ki-67	3	546/762	1.04 [0.83, 1.31]; $P = 0.72$	FE	$I^2 = 0\%$; $P = 1.00$

RDW, red blood cell distribution width; CI, confidence intervals.

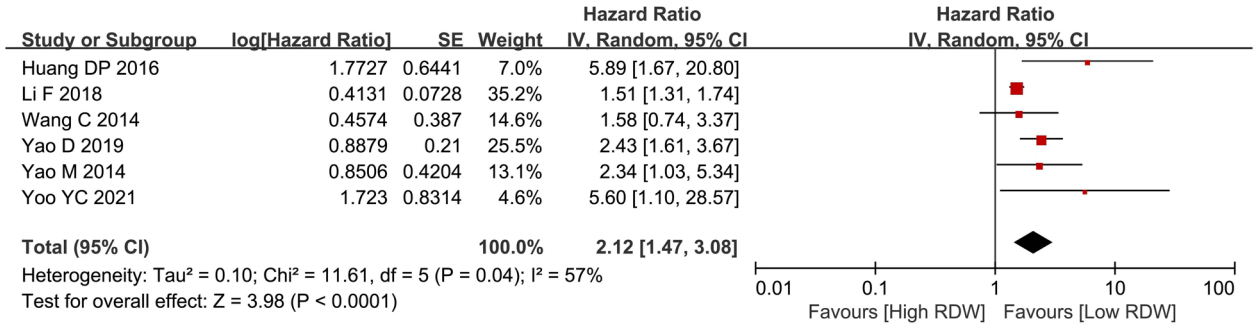

FIGURE 2
Os between the high RDW group and the low RDW group. Abbreviation: OS, overall survival; RDW, red blood cell distribution width.

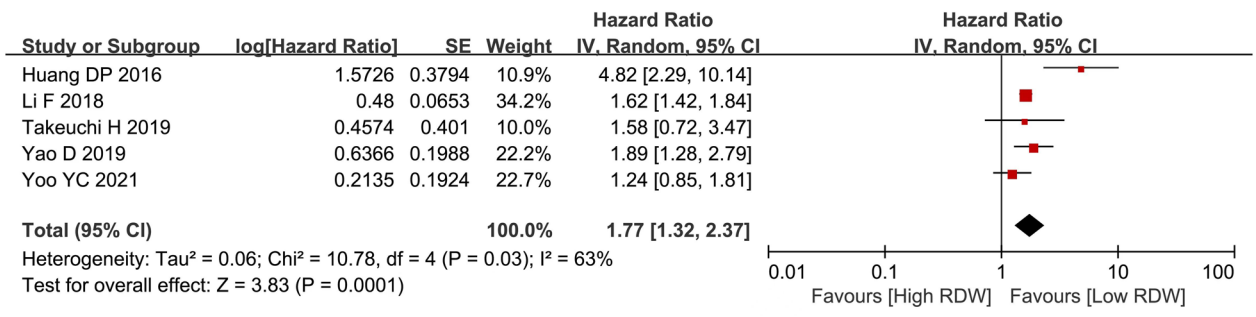

FIGURE 3
DFS between the high RDW group and the low RDW group. Abbreviation: DFS, disease-free survival; RDW, red blood cell distribution width.

Subgroup analysis for Os

According to the different treatments, the BC patients were divided into three groups. Two studies included patients who received surgery, neoadjuvant treatment or adjuvant treatment, two studies included patients who received surgery or adjuvant treatment, and two studies included patients who only underwent surgery. After subgroup analysis, RDW had prognostic significance only for the surgery-only patients (HR = 2.41, 95% CI = 1.67 to 3.49, $P < 0.01$) but not for the all-treatment groups (HR = 2.40, 95% CI = 0.75 to 7.72, $P = 0.14$) and the neoadjuvant treatment groups (HR = 2.57, 95% CI = 0.70 to 9.41, $P = 0.16$) (Figure 4).

Sensitivity analysis

A sensitivity analysis was conducted by excluding one study at a time to examine its impact on the result. In the current meta-analysis, the sensitivity analysis was performed based on the outcomes of OS and DFS, and the subgroup analyses of OS. After each study was successively removed, the omission of any of the studies did not change the conclusion. This suggested that the outcomes had a low level of sensitivity and produced reliable results.

Discussion

A total of seven studies including 4,884 BC patients were included in the current meta-analysis. For prognosis, after pooling all the data, we found that the high RDW group was associated with worse OS and DFS than the low RDW group, especially for BC patients who underwent only radical surgery. Therefore, we concluded that RDW could be widely used in the clinic as an easy preoperative prognostic predictor. Surgeons should pay more attention to patients with high preoperative RDW levels and take action in advance to prolong the survival time of BC patients.

Although many new prognostic markers have been explored and identified, the major problem with these biomarkers is that they heavily rely on complex molecular or genetic tests (30–32). Hematological parameters, including albumin, C-reactive protein (CRP), neutrophils, and lymphocytes, are readily available and inexpensive parameters for BC patients that could predict the prognosis (33–35). As a routinely available marker of the systemic inflammatory response, RDW predicts negative clinical outcomes in various tumors. However, there is a controversy regarding whether RDW has an impact on BC (19–25).

Of the seven included studies, two reported that RDW was a prognostic indicator (19, 20), but the other five studies reported that RDW did not affect BC (21–25). Therefore, the current study aims to investigate whether RDW can predict the prognosis of BC. If RDW could be used as an easy prognostic indicator, it would be a convenient clinical reference value. To our knowledge, our study is the first to pool all the prognostic data of RDW in BC. In our study, we found that high RDW was associated with worse OS and DFS than low RDW, which indicated that RDW was an important biomarker for BC.

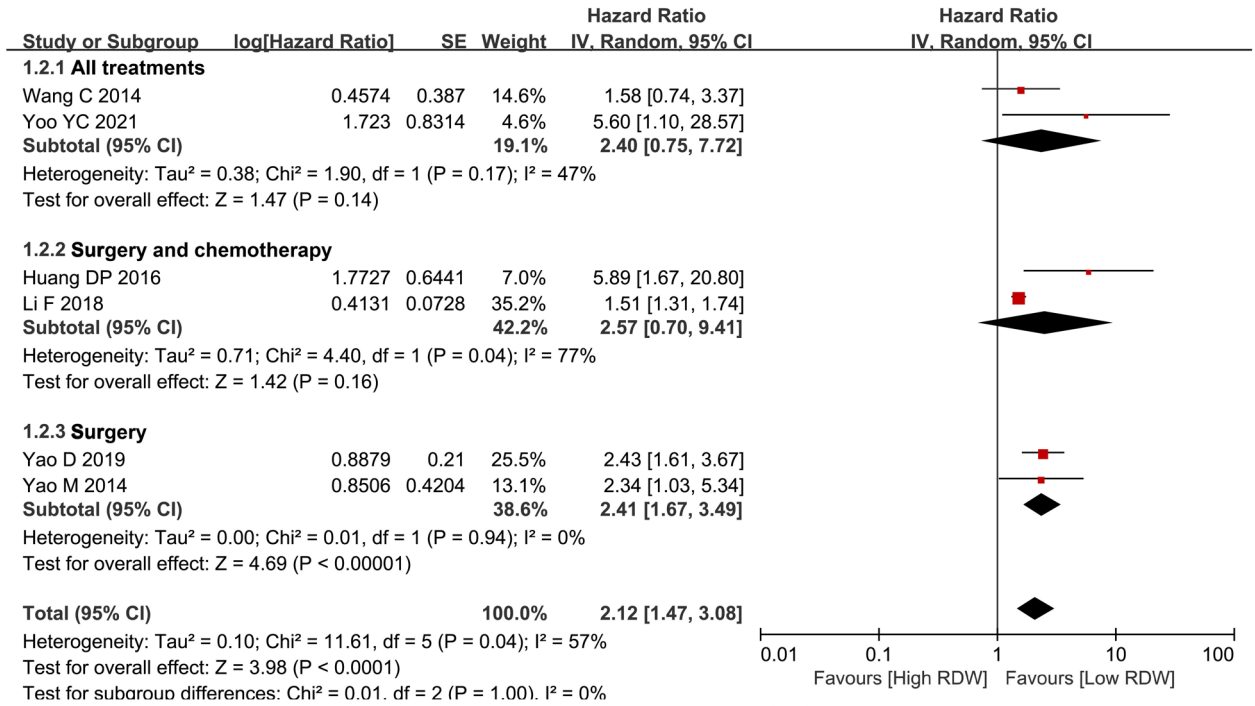

FIGURE 4
Subgroup analysis for OS based on treatment. Abbreviation: RDW, red blood cell distribution width.

The mechanisms for the relationship between RDW and poor prognosis remain complex and unclear. However, some hypotheses accounted for the mechanisms. One hypothesis was that oxidative stress (23, 36) might reduce the survival of red blood cells and lead to elevated RDW. Both endogenous and exogenous sources of reactive oxygen species (ROS) can lead to increased oxidative stress in cells (37). Moreover, excessive ROS can cause damage and modification of cellular macromolecules, thus mutating genomic DNA. Another hypothesis was that chronic inflammation (38) could induce an increase in RDW by disrupting the erythrocyte membrane, leading to changes in erythrocyte maturation. Inflammation in the microenvironment could promote tumor growth, invasion, angiogenesis, and ultimately metastasis of BC (39, 40). This was corroborated by our finding that patients with high RDW had larger tumor sizes, more advanced tumor stages, and were more likely to have lymph node metastases.

Thus, for clinicians, it is critical to pay more attention to monitoring patients with high preoperative RDW. Minimizing RDW before surgery and providing interventions such as nutritional support or anti-inflammatory drugs are necessary treatment strategies (21, 41).

There were some limitations in our meta-analysis. First, the seven included studies were relatively small with a small number of BC patients, which might cause bias; Second, the cut-off of RDW was inconsistent, which might cause heterogeneity; Third, all the included studies were from Asia, the lack of other regions might also lead to selection bias. Therefore, multicenter, multiregional, prospective, and high-quality RCTs should be carried out in the future.

In conclusion, high RDW was associated with worse OS and DFS. Therefore, RDW was a simple predictive factor for the prognosis of BC patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

GD and JY contributed to the conception and design of the study. JY organized the database. GD performed the statistical analysis. GD and JY wrote the first draft of the manuscript. KZ, ZG, WY, and YH wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by therapeutic effect and mechanism of ultrasound combined with neoadjuvant chemotherapy for breast cancer. (2022KFKT007)

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1000522/full#supplementary-material.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: gLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. Zujewski JA, Dvaladze AL, Ilbawi A, Anderson BO, Luciani S, Stevens L, et al. Knowledge summaries for comprehensive breast cancer control. *J Glob Oncol.* (2018) 4:1–7. doi: 10.1200/JGO.17.00141

3. Niu Y, Zhang F, Chen D, Ye G, Li Y, Zha Y, et al. A comparison of Chinese multicenter breast cancer database and SEER database. *Sci Rep.* (2022) 12(1):10395. doi: 10.1038/s41598-022-14573-4

4. Reis J, Boavida J, Tran HT, Lyngra M, Reitsma LC, Schandiz H, et al. Assessment of preoperative axillary nodal disease burden: breast MRI in locally advanced breast cancer before, during and after neoadjuvant endocrine therapy. *BMC Cancer.* (2022) 22(1):702. doi: 10.1186/s12885-022-09813-9

5. Curigliano G, Cardoso MJ, Poortmans P, Gentilini O, Pravettoni G, Mazzocco K, et al. Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic. *Breast.* (2020) 52:8–16. doi: 10.1016/j.breast.2020.04.006

6. Bel'skaya LV, Sarf EA. Prognostic value of salivary biochemical indicators in primary resectable breast cancer. *Metabolites.* (2022) 12(6):552. doi: 10.3390/metabo12060552

7. Ferrucci L, Guralnik JM, Woodman RC, Bandinelli S, Lauretani F, Corsi AM, et al. Proinflammatory state and circulating erythropoietin in persons with and without anemia. *Am J Med.* (2005) 118(11):1288. doi: 10.1016/j.amjmed.2005.06.039

8. Xie KH, Liu LL, Liang YR, Su CY, Li H, Liu RN, et al. Red cell distribution width: a novel predictive biomarker for stroke risk after transient ischaemic attack. *Ann Med.* (2022) 54(1):1167–77. doi: 10.1080/07853890.2022.2059558

9. Isik T, Uyarel H, Tanboga IH, Kurt M, Ekinci M, Kaya A, et al. Relation of red cell distribution width with the presence, severity, and complexity of coronary artery disease. *Coron Artery Dis.* (2012) 23(1):51–6. doi: 10.1097/MCA.0b013e32834e4f5c

10. O'Connell RM, Boland MR, O'Driscoll J, Salih A, Arumugasamy M, Walsh TN, et al. Red cell distribution width and neutrophil to lymphocyte ratio as predictors of outcomes in acute pancreatitis: a retrospective cohort study. *Int J Surg.* (2018) 55:124–7. doi: 10.1016/j.ijsu.2018.05.028

11. Xing X, Deng Y, Zhu Y, Xu S, Liu J, Zhang C, et al. Red cell distribution width for prognosis in patients with pulmonary embolism: a systematic review and meta-analysis. *Clin Respir J*. (2020) 14(10):901–7. doi: 10.1111/crj.13227

12. Yonemoto S, Hamano T, Fujii N, Shimada K, Yamaguchi S, Matsumoto A, et al. Red cell distribution width and renal outcome in patients with non-dialysis-dependent chronic kidney disease. *PLoS One*. (2018) 13(6):e0198825. doi: 10.1371/journal.pone.0198825

13. Latif A, Ahsan MJ, Lateef N, Kapoor V, Fazeel HM, Razzaq F, et al. Prognostic impact of red cell distribution width on the development of contrast-induced nephropathy, Major adverse cardiac events, and mortality in coronary artery disease patients undergoing percutaneous coronary intervention. *Curr Cardiol Rev*. (2021) 17(6):e051121191160. doi: 10.2174/1573403X17666210204154812

14. Hullin R, Barras N, Abdurashidova T, Monney P, Regamey J. Red cell distribution width and prognosis in acute heart failure: ready for prime time!. *Intern Emerg Med*. (2019) 14(2):195–7. doi: 10.1007/s11739-018-1995-7

15. Fu L, Li Q, Fan Q. Combination of preoperative red cell distribution width and neutrophil to lymphocyte ratio as a prognostic marker for gastric cancer patients. *J Gastrointest Oncol*. (2021) 12(3):1049–57. doi: 10.21037/jgo-21-271

16. Xu WY, Yang XB, Wang WQ, Bai Y, Long JY, Lin JZ, et al. Prognostic impact of the red cell distribution width in esophageal cancer patients: a systematic review and meta-analysis. *World J Gastroenterol*. (2018) 24(19):2120–9. doi: 10.3748/wjg.v24.i19.2120

17. Jing JS, Fu XL, Zhao W, Kong LB. Red cell distribution width as a prognostic factor in patients with hepatocellular carcinoma. *Clin Lab*. (2020) 66(7). doi: 10.7754/Clin.Lab.2019.191027

18. Song Y, Huang Z, Kang Y, Lin Z, Lu P, Lin Q, et al. Clinical usefulness and prognostic value of red cell distribution width in colorectal cancer. *Biomed Res Int*. (2018) 2018:9858943. doi: 10.1155/2018/9858943

19. Wang C, Civan J, Lai Y, Cristofanilli M, Hyslop T, Palazzo JP, et al. Racial disparity in breast cancer survival: the impact of pre-treatment hematologic variables. *Cancer Causes Control*. (2015) 26(1):45–56. doi: 10.1007/s10552-014-0481-4

20. Takeuchi H, Abe M, Takumi Y, Hashimoto T, Miyawaki M, Okamoto T, et al. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Sci Rep*. (2019) 9(1):3033. doi: 10.1038/s41598-019-40024-8

21. Yoo YC, Park S, Kim HJ, Jung HE, Kim JY, Kim MH. Preoperative routine laboratory markers for predicting postoperative recurrence and death in patients with breast cancer. *J Clin Med*. (2021) 10(12):2610. doi: 10.3390/jcm10122610

22. Li F, Zhong Y, Mo W, Zhang B. Predictive value of red blood cell distribution width on overall survival in breast cancer patients. *Guangdong Medical Journal*. (2018) 39(13):2034–9. doi: 10.13820/j.cnki.gdyx.2018.13.013

23. Yao D, Wang Z, Cai H, Li Y, Li B. Relationship between red cell distribution width and prognosis in patients with breast cancer after operation: a retrospective cohort study. *Biosci Rep*. (2019) 39(7):BSR20190740. doi: 10.1042/BSR20190740

24. Huang DP, Ma RM, Xiang YQ. Utility of red cell distribution width as a prognostic factor in young breast cancer patients. *Medicine (Baltimore)*. (2016) 95(17):e3430. doi: 10.1097/MD.0000000000003430

25. Yao M, Liu Y, Jin H, Liu X, Lv K, Wei H, et al. Prognostic value of preoperative inflammatory markers in Chinese patients with breast cancer. *Onco Targets Ther*. (2014) 7:1743–52. doi: 10.2147/OTT.S69657

26. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097

27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z

28. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract*. (2008) 14(5):951–7. doi: 10.1111/j.1365-2753.2008.00986.x

29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

30. Chen B, Tang H, Liu X, Liu P, Yang L, Xie X, et al. miR-22 as a prognostic factor targets glucose transporter protein type 1 in breast cancer. *Cancer Lett*. (2015) 356(2 Pt B):410–7. doi: 10.1016/j.canlet.2014.09.028

31. Zwart W, Flach KD, Rudraraju B, Abdel-Fatah TM, Gojis O, Canisius S, et al. SRC3 Phosphorylation at serine 543 is a positive independent prognostic factor in ER-positive breast cancer. *Clin Cancer Res*. (2016) 22(2):479–91. doi: 10.1158/1078-0432.CCR-14-3277

32. Luo P, Lu G, Fan LL, Zhong X, Yang H, Xie R, et al. Dysregulation of TMPRSS3 and TNFRSF11B correlates with tumorigenesis and poor prognosis in patients with breast cancer. *Oncol Rep*. (2017) 37(4):2057–62. doi: 10.3892/or.2017.5449

33. Zhou L, Ma S, Balde AI, Han S, Cai Z, Li Z. A retrospective propensity score matched study of the preoperative C-reactive protein to albumin ratio and prognosis in patients with resectable non-metastatic breast cancer. *Med Sci Monit*. (2019) 25:4342–52. doi: 10.12659/MSM.913684

34. Zeindler J, Angehrn F, Droeser R, Däster S, Piscuoglio S, Ng CKY, et al. Infiltration by myeloperoxidase-positive neutrophils is an independent prognostic factor in breast cancer. *Breast Cancer Res Treat*. (2019) 177(3):581–9. doi: 10.1007/s10549-019-05336-3

35. Al Jarroudi O, El Bairi K, Abda N, Zaimi A, Jaouani L, Chibani H, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of outcomes in inflammatory breast cancer. *Biomark Med*. (2021) 15(14):1289–98. doi: 10.2217/bmm-2020-0717

36. Ma YS, Wu SB, Lee WY, Cheng JS, Wei YH. Response to the increase of oxidative stress and mutation of mitochondrial DNA in aging. *Biochim Biophys Acta*. (2009) 1790(10):1021–9. doi: 10.1016/j.bbagen.2009.04.012

37. Klaunig JE. Oxidative stress and cancer. *Curr Pharm Des*. (2018) 24(40):4771–8. doi: 10.2174/1381612825666190215121712

38. Maurya PK, Kumar P, Chandra P. Biomarkers of oxidative stress in erythrocytes as a function of human age. *World J Methodol*. (2015) 5(4):216–22. doi: 10.5662/wjm.v5.i4.216

39. Sousa R, Gonçalves C, Guerra IC, Costa E, Fernandes A, do Bom Sucesso M, et al. Increased red cell distribution width in fanconi anemia: a novel marker of stress erythropoiesis. *Orphanet J Rare Dis*. (2016) 11(1):102. doi: 10.1186/s13023-016-0485-0

40. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J*. (2009) 158(4):659–66. doi: 10.1016/j.ahj.2009.07.024

41. Olafsson HB, Sigurdarson GA, Christopher KB, Karason S, Sigurdsson GH, Sigurdsson MI. A retrospective cohort study on the association between elevated preoperative red cell distribution width and all-cause mortality after noncardiac surgery. *Br J Anaesth*. (2020) 124(6):718–25. doi: 10.1016/j.bja.2020.02.009

Frontiers in Surgery

Explores and improves surgical practice and clinical patient management

A multidisciplinary journal which explores surgical practices - from fundamental principles to advances in microsurgery and minimally invasive techniques. It fosters innovation and improves the clinical management of patients.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact