

Effect of intraoperative blood loss on postoperative complications and prognosis of patients with colorectal cancer: A meta-analysis

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Abstract. The purpose of the present study was to evaluate whether the amount of intraoperative blood loss (IBL) affects the complications and prognosis of patients with colorectal cancer (CRC). The PubMed, EMBASE and the Cochrane Library databases were used to search for eligible studies from inception to November 30, 2020. Hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled up. The overall survival (OS) and disease-free survival (DFS) were compared between the larger IBL group and the smaller IBL group. The present study was performed with RevMan 5.3 (The Cochrane Collaboration). A total of seven studies involving 1,540 patients with CRC were included in the present study. The smaller IBL group had a higher rate of OS (HR=1.45, 95% CI=1.17 to 1.8, P=0.0007) and a higher rate of DFS (HR=1.76, 95% CI=1.40 to 2.21, P<0.00001). Furthermore, the larger IBL group had a higher rate of postoperative complications than the smaller IBL group (odds ratio=2.06, 95% CI=1.72 to 2.15, P<0.00001). In conclusion, a smaller IBL was associated with better OS and DFS, and a lower risk of postoperative complications compared with a larger IBL in patients with CRC, suggesting that surgeons should pay more attention during perioperative management and surgical operation to reduce IBL.

Introduction

Colorectal cancer (CRC) has become the third most common cancer type and the second leading cause of cancer-related

death (1). In the past 10 years, the incidence and mortality rate of CRC in China have increased (2). The treatment of CRC includes surgery, chemotherapy, radiotherapy and immunotherapy (3-5). Surgery is still the main treatment for CRC and radical resection is the key to cure (6,7).

At the same time, it is particularly important to reduce the incidence of postoperative complications. It was reported that postoperative complications of CRC may worsen the prognosis and increase the risk of recurrence (8). This has led to increased resource utilization, readmission and decreased patient satisfaction (9). Therefore, it was important to determine the prognostic factors of CRC, as it may help patients benefit from more active treatment. Although surgery has been the key treatment, it is also important for surgeons to control intraoperative blood loss (IBL). Previous studies reported that blood transfusion may increase the risk of complications as well (10). In recent years, due to the popularity of laparoscopic surgery and the development of surgical equipment, such as ultrasound systems, the average amount of IBL has decreased and the demand for perioperative blood transfusion has also decreased (11).

Previous studies reported the value of IBL in predicting the prognosis and complications of patients with CRC. However, the predictive effect of IBL on complications and prognosis has been controversial. Tamagawa *et al* (7) reported that the reduction of IBL may improve the overall survival (OS) and disease-free survival (DFS) of patients with CRC. However, Egenvall *et al* (12) indicated that major IBL increases the risk of postoperative complications, but may not affect OS. Thus, the purpose of the present meta-analysis study was to evaluate whether postoperative complications and prognosis were affected by the amount of IBL in patients with CRC.

Materials and methods

Study registration. The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13). The registration ID of the present meta-analysis on PROSPERO is CRD42022309536 (https://www.crd.york.ac.uk/prosperto/display_record.php?ID=CRD42022309536).

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Search strategy. The PubMed, EMBASE and Cochrane Library databases were searched from inception up to November 30, 2020. To find eligible studies, two key words were used: IBL and CRC. The search strategy was limited to the English language. For IBL, the search items were as follows: 'blood loss' OR 'intraoperative blood loss'. For CRC, the search terms were as follows: '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'. Subsequently, 'AND' was used to combine the two search items.

Inclusion and exclusion criteria. Studies were included in the present meta-analysis if they met the following criteria: i) The study included patients with CRC who underwent radical surgery; ii) the studies reported the comparison between a larger IBL group and a smaller IBL group; iii) postoperative complications and prognosis were reported. The exclusion criteria for this study were as follows: i) Conference abstracts, reviews, letters, comments or case reports, and duplicated publication data; ii) insufficient data for analysis. Data were extracted from graphs if required/possible. The lists of references of eligible studies were searched to retrieve any further articles missed in the original search. Any disagreements regarding inclusion and exclusion were resolved by discussion among all authors.

Study selection. The databases were searched by two authors (FL and XRL) independently. After removing duplicate records, the titles and abstracts were screened by QL, ZLW and XPS. Full texts were then evaluated for eligibility according to the inclusion and exclusion criteria by DP and ZWL. The final decision was made through discussion among all authors.

Definitions of outcomes. Postoperative complications were classified according to the Clavien-Dindo classification and severe postoperative complications were defined as grades \geq III (14). OS was defined as the time from diagnosis to death from any cause. DFS was defined as the time from diagnosis to the time of recurrence, death or last follow-up.

Data extraction. The following data of the present study were extracted: i) Publication year, first author's name, country, sample size, study design, and definition of larger IBL and smaller IBL; ii) baseline information, including sex, tumor location, tumor stage, tumor size and surgical approach; iii) surgery-related information, including IBL, operation time and operation approach; iv) postoperative complications; and v) survival outcomes (OS and DFS).

Quality assessment. The Newcastle-Ottawa scale (NOS), which has a score ranging from 0-9 points, was used to assess the quality of the enrolled studies (15). A study with a score of 9 points was considered to be of high quality, a study with a score of 7-8 points was considered of medium quality and a study with \leq 6 points was considered to be of low quality.

Statistical analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the OS and DFS of patients

with CRC. Odds ratios (ORs) and 95% CIs were calculated for the postoperative complications. Statistical heterogeneity was assessed by using the value of I^2 and the result of the chi-squared test. If $I^2 > 50\%$, the random-effects model was used and $P < 0.1$ was considered statistically significant. The fixed-effects model was used in this study if $I^2 \leq 50\%$ and $P < 0.05$ was considered statistically significant (16). The present study was performed with RevMan 5.3 (The Cochrane Collaboration).

Results

Study selection. A total of 5,398 studies were identified from the database, including 1,845 studies in PubMed, 3,261 studies in Embase and 292 studies in the Cochrane Library. After removing duplicate studies, 4,417 were left for record screening. After browsing the titles and abstracts, 42 studies were left for full-text scanning. Finally, 7 studies (7,12,17-21) were included in this study (Fig. 1).

Characteristics of the included studies. A total of seven studies (7,12,17-21) involving 10,540 patients were included in the present study. These studies selected were published from 2006 to 2021, including six retrospective studies and one prospective study. In two studies, the cutoff for the larger and smaller IBL groups was 200 ml, while it was 250 ml in two studies, 450 ml in one study, 200 ml in one study and one study did not include specific values. A total of four studies were assigned an NOS score of 8, one study scored 7 and two studies scored 6. The NOS scores are presented in Table I.

Comparison of characteristics between the larger and smaller IBL groups. Sex, tumor location, tumor stage and surgical approach were included in the baseline information. By comparing the baseline information, it was found that male sex (OR=1.47, 95% CI=1.30 to 1.66, $P < 0.00001$) and tumor location in the rectum (OR=2.98, 95% CI=1.36 to 6.53, $P = 0.006$) were associated with larger IBL. However, T1-T3 stage (OR=0.59, 95% CI=0.34 to 1.02, $P = 0.06$), T4 stage (OR=1.69, 95% CI=0.97 to 2.92, $P = 0.06 > 0.05$) and surgical approach ($P = 0.91$) had no statistically significant association with the amount of IBL (Table II).

Comparison of survival outcomes between the larger and smaller IBL groups. A total of seven studies (7,12,17-21) reported on OS and two studies (7,19) reported on DFS of patients with CRC who underwent radical CRC surgery. The random-effects model was used to calculate the HR values. It was found that the smaller IBL group had better OS (HR=1.45, 95% CI=1.17 to 1.80, $P = 0.0007$; Fig. 2) and better DFS (HR=1.76, 95% CI=1.40 to 2.21, $P < 0.00001$; Fig. 3A) than the larger IBL group.

Comparison of complications between the larger and smaller IBL groups. There were two studies (12,20) reporting postoperative complications. After pooling up the data, it was found that the larger IBL group had a higher rate of postoperative complications than the smaller IBL group (OR=2.06, 95% CI=1.72 to 2.45, $P < 0.00001$; Fig. 3B).

Table I. Characteristics of the studies included in the meta-analysis.

| Author, year | Country | Study design | Study date | Sample size | | Total | Definition of larger and smaller IBL | | NOS score | (Refs.) |
|-----------------|---------|----------------------------|------------|------------------|-------------------|-------|--------------------------------------|-------------------|-----------|---------|
| | | | | Larger IBL group | Smaller IBL group | | Larger IBL group | Smaller IBL group | | |
| Tamagawa, 2021 | Japan | Retrospective | 2000-2019 | 489 | 1108 | 1597 | ≥200 | <200 | 8 | (7) |
| Shibutani, 2021 | Japan | Retrospective | 2012-2016 | 66 | 211 | 277 | >100 | ≤100 | 7 | (21) |
| Okamura, 2016 | Japan | Retrospective | 2003-2007 | 412 | 1142 | 1554 | ≥200 | <200 | 8 | (20) |
| Egenvall, 2014 | Sweden | Retrospective | 1997-2003 | 1398 | 445 | 1843 | ≥450 | <450 | 8 | (12) |
| Jiang, 2013 | China | Retrospective | 2005-2011 | 52 | 87 | 139 | >250 | ≤250 | 6 | (24) |
| Mörner, 2012 | Sweden | Prospective | 1997-2003 | 1588 | 1474 | 3062 | ≥250 | <250 | 8 | (18) |
| McArdle, 2006 | UK | Retrospective+ prospective | 1991-1994 | NA | NA | 2068 | NA | NA | 6 | (17) |

IBL, intraoperative blood loss, ml; NOS, Newcastle-Ottawa scale.

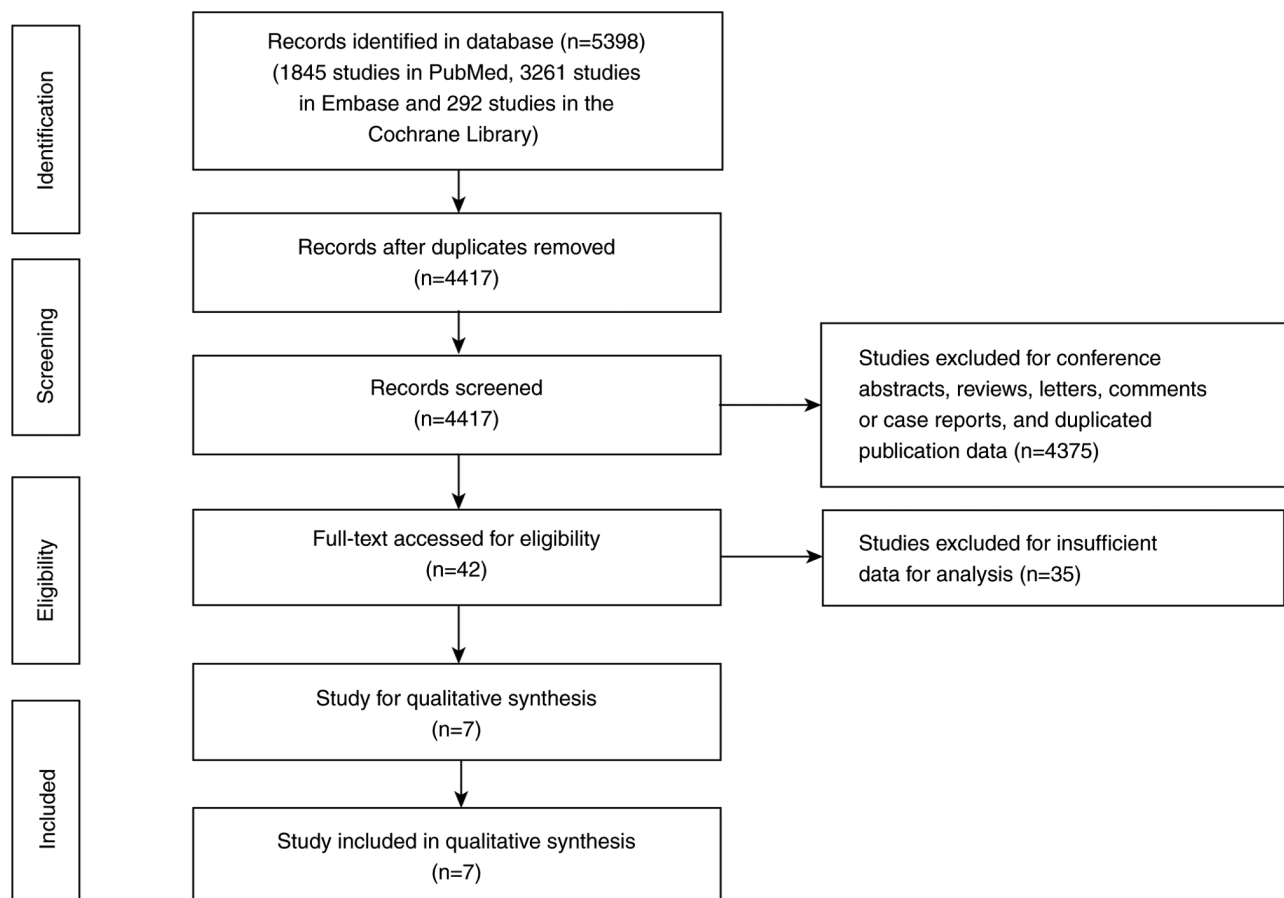


Figure 1. Flowchart of study selection.

Factor analysis of HRs for OS and DFS. There were further factors that affected OS and DFS. Thus, a subgroup analysis of factors, including age, sex, lymph node metastasis (LNM), surgical approach, tumor location, tumor stage and body mass index was conducted. It was indicated that LNM (HR=1.64,

95% CI=1.16-2.31, P=0.005; Fig. 4A) and higher tumor stage (HR=2.25, 95% CI=1.98-2.56, P<0.00001; Fig. 4B) were related to poor OS. However, no significant influence on DFS was found for age (P=0.66) or sex (P=0.66). The results of the subgroup analysis are presented in Table III.

Table II. Association of the different features with larger and smaller IBL groups.

| Characteristic | Studies, n | Participants, n (larger/smaller IBL) | Mean difference/odds ratio (95% CI); P-value | Heterogeneity |
|-----------------|------------|---|---|---------------------------------|
| Sex | | | | |
| Male | 5 | 2417/2993 | 1.47 (1.30, 1.66); P<0.00001 | I ² =45%; P=0.12 |
| Female | 5 | 2417/2993 | 0.72 (0.64, 0.82); P<0.00001 | I ² =0%; P=0.50 |
| Tumor location | | | | |
| Rectum | 2 | 901/2250 | 2.98 (1.36, 6.53); P=0.006 | I ² =95%; P<0.0001 |
| Colon | 2 | 901/2250 | 0.27 (0.19, 0.39); P<0.00001 | I ² =76%; P=0.04 |
| Tumor stage | | | | |
| T1-T3 | 2 | 555/1319 | 0.59 (0.34, 1.02); P=0.06 | I ² =65%; P=0.09 |
| T4 | 2 | 555/1319 | 1.69 (0.97, 2.92); P=0.06 | I ² =66%; P=0.09 |
| Type of surgery | | | | |
| Laparoscopic | 2 | 1631/1520 | 0.83 (0.03, 24.16); P=0.91 | I ² =100%; P<0.00001 |
| Open | 2 | 1631/1520 | 1.20 (0.04, 34.75); P=0.91 | I ² =100%; P<0.00001 |

IBL, intraoperative blood loss, ml; T, tumor.

Table III. Factor analysis of HRs for OS and DFS.

| A, Factors for OS | | | | |
|---------------------------------------|------------|-------|------------------------------|--------------------------------|
| Factor | Studies, n | Model | HR (95% CI); P-value | Heterogeneity |
| Age | 5 | RE | 1.14 (0.74, 1.77); P=0.55 | I ² =98%; P<0.00001 |
| Sex (male/female) | 2 | RE | 1.12 (0.95, 1.33); P=0.17 | I ² =69%; P=0.003 |
| LNM | 3 | FE | 1.64 (1.16, 2.31); P=0.005 | I ² =0%; P=0.45 |
| Surgical approach (laparoscopic/open) | 2 | FE | 0.80 (0.63, 1.03); P=0.08 | I ² =0%; P=0.47 |
| Tumor location (rectum/colon) | 2 | FE | 1.12 (0.86, 1.45); P=0.41 | I ² =0%; P=0.96 |
| Tumor stage (III/II/I) | 2 | RE | 2.25 (1.98, 2.56); P<0.00001 | I ² =72%; P=0.06 |
| BMI (≥25/<25 kg/m ²) | 2 | RE | 1.5 (0.37, 6.13); P=0.57 | I ² =88%; P=0.004 |
| B, Factors for DFS | | | | |
| Factor | Studies, n | Model | Hazard ratio (95% CI) | Heterogeneity |
| Age | 2 | RE | 0.88 (0.51, 1.52); P=0.66 | I ² =60%; P=0.12 |
| Sex (male/female) | 2 | FE | 0.82 (0.67, 1.01); P=0.06 | I ² =0%; P=0.90 |

HR, hazard ratio; OS, overall survival; DFS, disease-free survival; LNM, lymph node metastasis; BMI, body mass index; FE, fixed effects; RE, random effects.

Discussion

Despite the improvement of the treatment level in recent years, the five-year survival rate of patients with metastatic CRC is still poor (6). It has been determined that risk factors such as age, type 2 diabetes mellitus, lymph node status and tumor stage may predict the postoperative survival rate of patients with CRC (8). In the present study, it was found that LNM and tumor stage were prognostic factors for patients with CRC. These results were similar to those of previous studies (7,12).

Various previous studies have discussed the relationship among IBL, postoperative complications and prognosis; however, the effect of IBL on complications and prognosis remains controversial. McArdle *et al* (17) reported that the mortality rate was higher and OS was worse after massive bleeding during CRC surgery. Mörner *et al* (18) supported the hypothesis that the degree of bleeding during colon cancer surgery affected long-term survival. However, Egenvall *et al* (12) indicated that larger IBL increases the risk of postoperative complications, but does not affect OS. Thus, in the present study, the effect of IBL on the

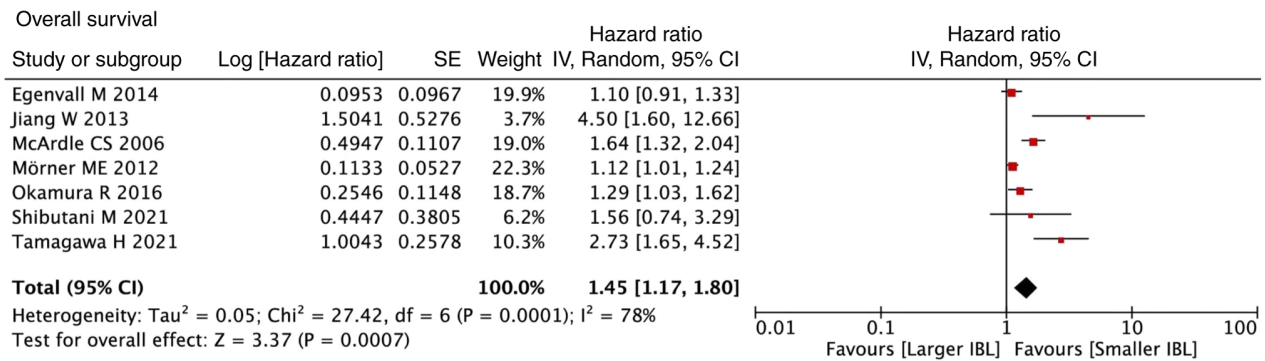
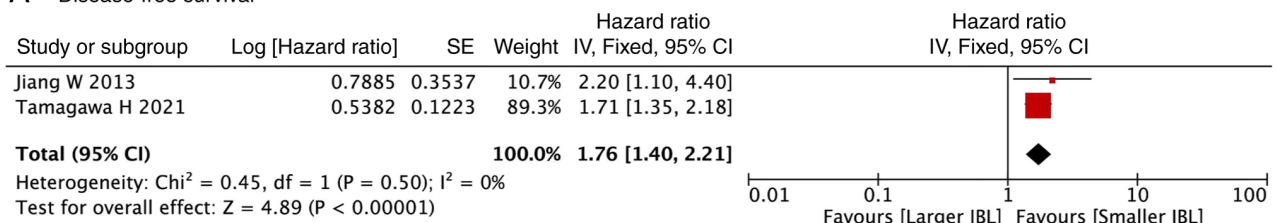


Figure 2. Overall survival analysis between larger IBL group and smaller IBL group. IBL, intraoperative blood loss; SE, standard error; IV, inverse variance; df, degrees of freedom.

A Disease-free survival



B Complications

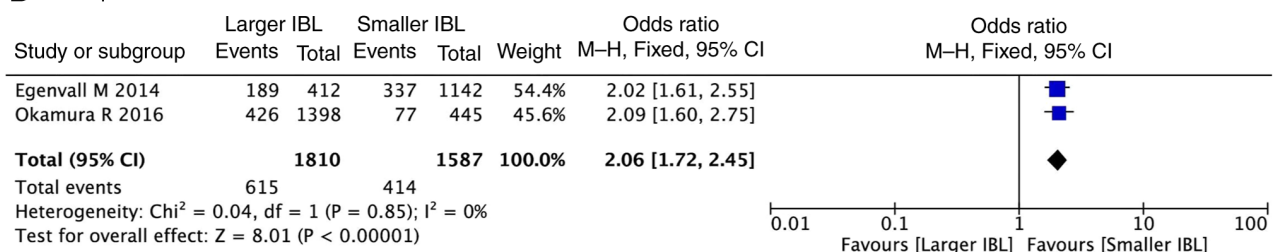
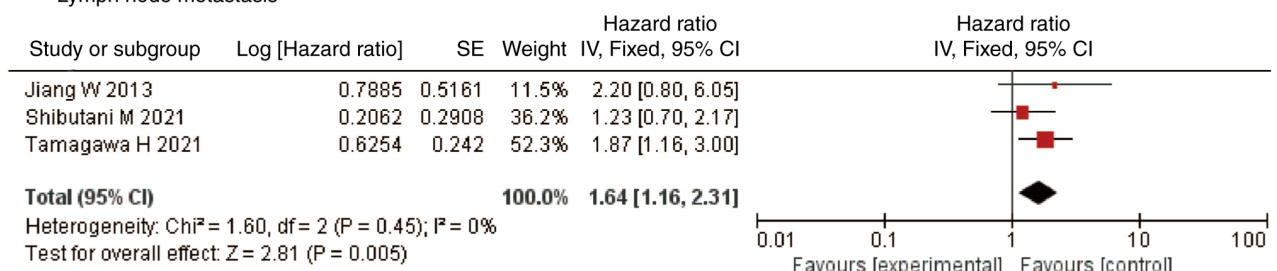


Figure 3. (A) Disease-free survival analysis between larger IBL group and smaller IBL group. (B) Forest plot showing complications between larger and smaller IBL group. IBL, intraoperative blood loss; SE, standard error; IV, inverse variance; df, degrees of freedom.

A Lymph node metastasis



B Tumor stage

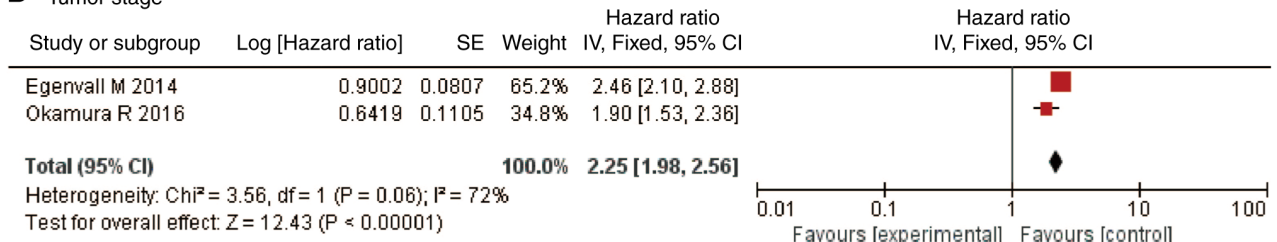


Figure 4. (A) Forest plot showing the association between lymph node metastasis and overall survival. (B) Forest plot showing the association between tumor stage and overall survival.

postoperative complications and prognosis of patients with CRC was explored.

Patients with early CRC have no obvious symptoms and they are already in the intermediate and late stages of the disease at the time of diagnosis (22). Previous studies demonstrated that in the late T-stage, the amount of IBL may be increased (7). Patients with advanced T-stage receive systemic chemoradiotherapy before the operation and may require more extensive anatomy for surrounding blood vessels and tissues during the operation (12). Furthermore, preoperative radiotherapy may increase IBL (23). In addition, metastasis was reported to be the main characteristic of advanced CRC (24), and the liver was the most common organ of CRC metastasis and liver metastasis was the main cause of death from CRC (25). Patients with advanced CRC were determined to have a 40-50% probability of secondary liver metastasis, which reduces OS (26). In addition, Jiang *et al* (19) found that the number of CRC liver metastases was a predictor of larger IBL, which was associated with worse OS in patients with CRC liver metastasis resection. However, in the present study, it was not found that the T-stage was associated with large IBL. Therefore, more data are needed for further research.

The incidence rate of CRC is higher in the elderly (27,28). Advanced age is an important risk factor for postoperative mortality and the elderly had poor performance status, recovery ability and comorbid diseases. Okamura *et al* (20) reported that elderly patients with CRC were more suitable for laparoscopic surgery. Compared with traditional open surgery, laparoscopic surgery had a smaller incision, less IBL, a shorter postoperative hospital stay and lower postoperative complications and postoperative mortality (29,30). However, in the present study, no significant difference in surgical approach was found between the larger and the smaller IBL groups. A high volume of IBL significantly affected the postoperative complication incidence rate, OS and recurrence in elderly patients with CRC (20). Furthermore, certain studies reported that men had higher IBL than women among patients undergoing CRC surgery (7,12,17). The reason may be that men have a narrower pelvis, making the operation more difficult. In the present study, it was found that male sex was associated with larger IBL.

A larger IBL increases the probability of blood transfusion and a blood transfusion would in turn increase the risk of postoperative mortality (10). The mechanism behind the effect of a larger IBL on prognosis remains elusive. The potential causes may be as follows: i) The amount of IBL indirectly represents the degree of tumor progression (21), and this would increase the scope of intraoperative anatomy; ii) a large amount of IBL would accelerate tumor overflow and hematogenous dissemination (31); iii) larger IBL leads to systemic hypoperfusion and insufficient oxygenation, promotes systemic inflammatory response and hinders antitumor immunity (32). Inflammation may increase the risk of postoperative infection, leading to poor prognosis.

Of note, there are some limitations to this study. First, the seven articles included in the present study were observational and most of these studies came from Asia, which may introduce bias into the analysis. Furthermore, the present study did not assess the potential impact of confounding variables and postoperative treatment on the relationship between

IBL and outcomes. In addition, the amount of blood loss during the operation was an estimated amount, which may have some bias. As another limitation, the definition of IBL was inconsistent and different studies had different cut-offs for high and low IBL. In addition, the present study did not include the impact of other factors on postoperative complications. In addition, this study did not assess the potential impact of different surgical techniques or treatment regimens on the relationship between IBL and outcomes. Finally, no publication bias was assessed, and no sensitivity analysis was performed by excluding one study to determining the impact on the pooled effect. Therefore, comprehensive, prospective and high-quality randomized controlled trials should be performed in the future.

In conclusion, a smaller IBL was associated with higher OS and DFS and lower risk of postoperative complications compared with a larger IBL in patients with CRC, which reminded us that surgeons should pay more attention to the perioperative management and surgical operation to reduce IBL.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Data extraction, ZWL, QL, XYL, DP and ZLW; quality assessments, XRL, XPS, DP and FL; data analysis, XPS, DP and WZ; writing-original draft, ZWL; writing-review and editing, ZWL, DP and XPS. Confirmation of the authenticity of the raw data, DP and ZWL. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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