Perioperative transfusion and the prognosis of colorectal cancer surgery: a systematic review and meta-analysis

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Abstract

Background: Perioperative transfusion can reduce the survival rate in colorectal cancer patients. The effects of transfusion on the short- and long-term prognoses are becoming intriguing.

Objective: This systematic review and meta-analysis aimed to define the effects of perioperative transfusion on the short- and long-term prognoses of colorectal cancer surgery.

Results: Thirty-six clinical observational studies, with a total of 174,036 patients, were included. Perioperative transfusion decreased overall survival (OS) (hazard ratio (HR), 0.33; 95% confidence interval (CI), 0.24 to 0.41; \(P < 0.0001\)) and cancer-specific survival (CSS) (HR, 0.34; 95% CI, 0.21 to 0.47; \(P < 0.0001\)), but had no effect on disease-free survival (DFS) (HR, 0.17; 95% CI, −0.12 to 0.47; \(P = 0.248\)). Transfusion could increase postoperative infectious complications (RR, 1.89; 95% CI, 1.56 to 2.28; \(P < 0.0001\)), pulmonary complications (RR, 2.01; 95% CI, 1.54 to 2.63; \(P < 0.0001\)), cardiac complications (RR, 2.20; 95% CI, 1.75 to 2.76; \(P < 0.0001\)), anastomotic complications (RR, 1.51; 95% CI, 1.29 to 1.79; \(P < 0.0001\)), reoperation (RR, 2.88; 95% CI, 2.05 to 4.05; \(P < 0.0001\)), and general complications (RR, 1.86; 95% CI, 1.66 to 2.07; \(P < 0.0001\)).

Conclusion: Perioperative transfusion causes a dramatically negative effect on long-term prognosis and increases short-term complications after colorectal cancer surgery.

Keywords: Transfusion, Colorectal cancer, Prognosis, Meta-analysis

Introduction

Patients with colorectal cancer often have accompanying anaemia or perioperative bleeding. Allogeneic transfusion becomes necessary in these cases. Some studies have found that perioperative transfusion could suppress the immune function and increase the recurrence and metastasis [1, 2], but others have not [3, 4]. One recent meta-analysis showed that perioperative transfusion could decrease the survival rate and increase the incidence rates of cancer recurrence and metastasis in colorectal cancer patients [5], but in that meta-analysis, low-quality studies were included, odds ratios (ORs) were used to extract the survival data, which was not appropriate, and the effects of censored data on the results were ignored. Until now, the effects of perioperative transfusion on the short- and long-term prognoses of the patients undergoing surgery for colorectal cancer are becoming increasingly intriguing. The effects of the volume and trigger of transfusion on the prognosis are unclear. Therefore, we conducted a systematic review and meta-analysis to address these issues and attempted to define the relationships between perioperative transfusion and short- or long-term prognosis in patients undergoing colorectal cancer surgery.
Methods
We conducted our systematic review and meta-analysis in accordance with the methods recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. There was no registered protocol.

Literature search
The PubMed, Cochrane library, and Embase databases (from January 1990 to June 2018) were searched. The reference lists of the research studies and previous meta-analysis articles were also checked to find any further eligible trials.

The key words for the electronic search strategy included intestinal, intestine, bowel, colonic, colon, rectal, rectum, colorectal, cancer, tumour, carcinoma, neoplasm, transfusion, and blood transfusion. The citations to be searched were restricted to clinical studies and were published in English, the participants of our study were patients undergoing surgery for colorectal cancer, and the intervening measure was perioperative allogeneic transfusion. The exclusion criteria were comparison between allogeneic and autogenous transfusion or comparison between autogenous transfusion and no transfusion.

Outcome parameters and data collection
The primary outcome of interest was overall survival (OS), while the secondary outcomes included disease-free survival (DFS), cancer-specific survival (CSS), and postoperative complications. OS was defined as the time from surgery to death from any cause. DFS was defined as the time from surgery to a recurrence or death from any cause. CSS was defined as the time from surgery to death from cancer recurrence or metastasis. Data were extracted and collected by two authors independently, and disagreements were resolved by discussion and consensus among all authors.

Quality assessment
The quality of publications was judged by the Newcastle-Ottawa Scale (NOS); a quality review of the data obtained from each study was performed on the basis of case selection, comparability, and outcome reporting. The highest score was 9 stars; a study with an NOS score greater than or equal to 7 stars was defined as a high-quality study, and if the NOS score was less than 7 stars, the study was excluded.

Statistical analysis
Meta-analysis was performed using Stata 12.0 software (StataCorp LP, US). The hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for OS, DFS, and CSS, and the risk ratios (RRs) with 95% CIs were calculated for postoperative complications. The HRs were extracted from the multivariable analysis when both univariable and multivariable analyses were available, and Engauge Digitizer 4.1 and Adobe Photoshop software were used for the extraction of HR [6]. Statistical heterogeneity was assessed using the chi-square test and $I^2$ statistics; $I^2 ≥ 50\%$ ($P < 0.1$) indicated significant heterogeneity, and the random-effects model was used, and the fixed-effects model was used when $I^2 < 50\%$ ($P > 0.1$) [7].

Subgroup and sensitivity analyses were performed to explore the source and size of heterogeneity among studies when necessary. Publication bias was evaluated by the Egger test, and $P ≥ 0.05$ represented no statistical significance in publication bias.

Results

Literature search and characteristics of eligible trials
We identified 5687 potential articles: 3749 articles from PubMed, 864 articles from Cochrane library, 1036 articles from Embase, and 38 articles from other sources. Sixty relevant articles were left after initial screening and reading the titles or abstracts, and 36 clinical observational studies with a total of 174,036 patients were ultimately included [1–4, 8–39]. The details of the screening process are presented in Fig. 1. These 36 studies were conducted in different countries and were published from 1990 to 2018. The characteristics and the qualities of these studies are presented in Table 1.

Results of meta-analysis

Overall survival (OS)
Data on OS were from 24 articles [1–4, 8, 9, 11, 13, 14, 16, 17, 19, 21, 22, 24, 28–30, 32–36, 38]. The random-effects model showed that transfusion could decrease OS significantly (HR, 0.33; 95% CI, 0.24 to 0.41; $I^2 = 61.9\%$; $P < 0.0001$; Fig. 2). There was no significant publication bias from the Egger test ($P = 0.297$).

Seven articles [2, 8, 10, 13, 17, 38, 39] reported the influence of transfusion volume ($> 3$ u and $≤ 3$ u) on OS. The fixed-effects model showed that OS was lower in the large transfusion volume group ($> 3$ u) compared with those in the small transfusion volume group ($≤ 3$ u) ($I^2 = 46.4\%$, $HR = 0.62$, 95% CI 0.48–0.77, $P < 0.0001$) (Fig. 3). There was no significant publication bias from the Egger test ($P = 0.072$).

Nine articles reported the trigger of transfusion. The comparison between transfusion and non-transfusion on OS was from five of these articles [8, 13, 14, 17, 32]; in the five articles, one [14] used intraoperative bleeding $> 1000$ ml as a trigger of transfusion, and the other four articles were included in the following meta-analysis. The triggers
were Hb ≤ 6 g/dl and Hb ≤ 7–10 g/dl, and the results showed that transfusion could reduce OS compared with non-transfusion if the trigger level was either Hb ≤ 6 g/dl ($I^2 = 0\%$, HR = 0.28, 95% CI 0.14–0.43, $P < 0.0001$) or Hb ≤ 7–10 g/dl ($I^2 = 0\%$, HR = 0.63, 95% CI 0.35–0.90, $P < 0.0001$) (Fig. 4). There was no significant publication bias from the Egger test ($P = 0.667$).

Disease-free survival (DFS) and cancer-specific survival (CSS) Data on DFS and CSS were from 7 [13, 14, 19, 21, 32, 33, 37] and 7 articles [3, 11, 12, 14, 24, 30, 33], respectively. The random-effects model showed that transfusion could decrease CSS significantly (HR, 0.34, 95% CI, 0.21 to 0.47, $I^2 = 62.9\%$; $P < 0.0001$) but did not affect DFS (HR, 0.17; 95% CI, −0.12 to 0.47; $I^2 = 54.6\%$; $P = 0.248$) (Fig. 5). There was no significant publication bias from the Egger test ($P = 0.912$).

Postoperative complications Data on 30- or 60-day postoperative infectious complications (wound and urinary infections), pulmonary complications (pneumonia, respiratory failure, and pulmonary embolism), cardiac complications (myocardial infarction, angina, cardiac arrest, and arrhythmia), anastomotic complications (anastomotic fistula and bleeding), reoperation, and general complications were from 9 [9, 13, 14, 16, 18, 23, 27, 28, 31], 6 [14, 16, 18, 23, 27, 28], 4 [14, 16, 18, 27], 6 [13, 14, 16, 23, 26, 27], 2 [11, 27], and 10 [8, 10, 12, 13, 16–18, 20, 26, 27] articles respectively. The meta-analysis showed that transfusion could increase infectious complications (RR, 1.89; 95% CI, 1.54 to 2.63; $I^2 = 42.4\%$; $P < 0.0001$), cardiac complications (RR, 2.20; 95% CI, 1.75 to 2.76; $I^2 = 0\%$; $P < 0.0001$), anastomotic complications (RR, 1.51; 95% CI, 1.29 to 1.79; $I^2 = 51.4\%$; $P < 0.0001$), reoperation (RR, 2.88; 95% CI, 2.05 to 4.05; $I^2 = 0\%$; $P < 0.0001$), and general complications (RR, 1.86; 95% CI, 1.66 to 2.07; $I^2 = 70.4\%$; $P < 0.0001$) (Fig. 6), and there was no significant publication bias from the Egger test ($P = 0.541$).

Subgroup and sensitivity analyses for OS Table 2 shows the subgroup analysis for OS. Publication dates, sample size, and study region did not influence the effects. However, data on OS in rectal cancer patients were only from two articles, and the subgroup analysis showed that transfusion had no significant effect on OS in rectal cancer patients, which was different from the finding for colorectal cancer or colon cancer patients. The sensitivity analysis showed that the results of the effect of transfusion on OS were not changed when any suspicious study was omitted.

Discussion Colorectal cancer is the most common human cancer. In the past few decades, many retrospective studies have focused on the effects of perioperative transfusion on short- and long-term prognoses in colorectal cancer patients, and a larger transfusion volume seems to have a poorer prognosis. It is very important to evaluate the trigger of transfusion and the influence of the volume of transfusion on prognosis to optimise perioperative transfusion and improve the outcome in colorectal cancer patients. Our
## Table 1 Characteristics of the trials

| ID | Country       | Tumour type | Sample size | Transfusion trigger | Type of blood products | Outcomes | NOS (stars) |
|----|---------------|-------------|-------------|---------------------|------------------------|----------|-------------|
| 1  | Switzerland   | Colonic     | 148         | BT+                 | –                      | OS       | 7           |
| 2  | Czech         | Colorectal  | 132         | BT−                 | –                      | OS       | 7           |
| 3  | USA           | Colonic     | 305         | Total               | –                      | OS, CSS  | 8           |
| 4  | Sweden        | Colorectal  | 199         | Total               | –                      | OS       | 8           |
| 5  | China         | Colorectal  | 803         | Total               | Hb < 6 g/dL, Hb 6–10 g/dL according to cardiopulmonary function | OS, postoperative complications | 7           |
| 6  | Japan         | Colorectal  | 35          | Total               | –                      | OS, postoperative complications | 8           |
| 7  | China         | Colonic     | 259         | Total               | Hb < 8 g/dL            | OS, postoperative complications | 7           |
| 8  | Australia     | Colorectal  | 423         | Total               | –                      | OS, DFS, CSS, postoperative complications | 8           |
| 9  | Australia     | Colorectal  | 151         | Total               | –                      | CSS, postoperative complications | 7           |
| 10 | Australia     | Rectal      | 471         | Total               | Preoperative Hb < 8 g/dL, intraoperative bleeding > 500 mL or Hb < 10 g/dL | OS, DFS, postoperative complications | 7           |
| 11 | Poland        | Colorectal  | 122         | Total               | Hb < 6 g/dL, Hb 6–10 g/dL according to cardiopulmonary function | OS, CSS, DFS | 8           |
| 12 | Japan         | Colorectal  | 23          | Total               | –                      | Allogeneic red blood cell | OS          | 8           |
| 13 | Turkey        | Colorectal  | 61          | Total               | –                      | Whole blood or RBC | OS          | 7           |
| 14 | China         | Colonic     | 614         | Total               | Hb < 6 g/dL, Hb 6–10 g/dL according to cardiopulmonary function | OS, postoperative complications | 7           |
| 15 | USA           | Colorectal  | 3815        | Total               | –                      | RBC      | OS, postoperative complications | 8           |
| 16 | Switzerland   | Rectal      | 217         | Total               | –                      | Prestored allogeneic blood | OS, DFS     | 7           |
| 17 | Germany       | Colorectal  | 135         | Total               | Hb 8–10 g/dL according to cardiopulmonary function | Postoperative complications | 7           |
| 18 | Italy         | Colorectal  | 68          | Total               | –                      | OS, DFS, postoperative complications | 7           |
| 19 | Sweden        | Colorectal  | 298         | Total               | –                      | LDB or RBC | OS          | 8           |
| 20 | Denmark       | Colorectal  | 288         | Total               | –                      | SAGM and/or FFP | Postoperative complications | 8           |
| 21 | Canada        | Colonic     | 2009        | Total               | –                      | OS, CSS  | 9           |
| 22 | Netherlands   | Colorectal  | 446         | Total               | –                      | LDB or RBC | OS          | 7           |
| 23 | England       | Colorectal  | 2073        | Total               | –                      | Whole blood or RBC | Postoperative complications | 7           |
| 24 | France        | Rectal      | 72          | Total               | Hb < 8 g/dL            | Postoperative complications | 7           |
| 25 | Denmark       | Colorectal  | 249         | Total               | –                      | LDB or RBC | OS, postoperative complications | 9           |
| 26 | Denmark       | Colorectal  | 452         | Total               | –                      | SAGM and/or FFP | OS          | 7           |
| 27 | USA           | Colorectal  | 6927        | Total               | –                      | OS, CSS, postoperative complications | 8           |
| 28 | USA           | Colonic     | 1845        | Total               | –                      | RBC      | Postoperative complications | 8           |
| 29 | USA           | Colorectal  | 110         | Total               | Postoperative Hb < 7 g/dL, preoperative Hb < 8.4 g/dL | OS, DFS, postoperative complications | 7           |
meta-analysis reviewed the current available literature on perioperative transfusion and the prognosis of colorectal cancer surgery and extracted the survival data by HR method, which is more precise than the OR or RR methods.

Our results showed that perioperative transfusion could reduce OS and CSS and could increase the incidence of postoperative complications. Inflammatory and immunosuppressive mediators were proved to be associated with the development of recurrence and metastasis.

| ID          | Country | Tumour type | Sample size | Transfusion trigger | Type of blood products | Outcomes | NOS (stars) |
|-------------|---------|-------------|-------------|---------------------|------------------------|----------|-------------|
| 30 Sánchez-Velázquez P 2018 [33] | Spain | Colonic | 363 | – | – | DFS, CSS | 8 |
| 31 Molland G 1995 [34] | Australia | Colorectal | 223, 210, 433 | – | All kinds of blood products | OS | 8 |
| 32 Cheslyn-Curtis S 1990 [35] | UK | Colorectal | 591, 370, 961 | – | – | OS | 7 |
| 33 Donohue JH 1995 [36] | USA | Colorectal | 446, 605, 1051 | – | Whole blood or RBC or plasma | OS | 8 |
| 34 Tartter PI 1992 [37] | USA | Colorectal | 110, 229, 329 | – | RBC | DFS | 7 |
| 35 Garau I 1994 [38] | Spain | Colorectal | 348, 338, 686 | – | Whole blood or RBC or plasma | OS | 7 |
| 36 Edna TH 1994 [39] | Norway | Colorectal | 236, 100, 336 | Hb < 9 g/dL or bleeding > 20% blood volume | SAGM | OS | 8 |

LDB leucocyte-depleted blood products, RBC packed red blood cells, SAGM buffy coat-depleted red cells suspended in saline, adenine, glucose, and mannitol, FFP fresh-frozen plasma

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Table 1 Characteristics of the trials (Continued)

![Fig. 2 Forest plot of overall survival after perioperative transfusion. SCC indicates sporadic colorectal cancer, HCC indicates hereditary colorectal cancer, group A in Miki C 2006 indicates the patient who received transfusion because of preoperative anaemia, and group B in Miki C 2006 indicates the patient who received transfusion because of excessive operative blood loss.](image)
Fig. 3 Forest plot of the effect of transfusion volume on overall survival

Fig. 4 Forest plot of the effect of transfusion trigger on overall survival
metastasis [40, 41], and transfusion could accelerate tumour progression by inducing an inflammatory response and immunosuppression [42]. In our meta-analysis, transfusion could reduce OS and CSS but had no effect on DFS. The possible reasons for this effect are that surgery, anaesthesia-related factors, and cancer staging can affect DFS, in addition to transfusion.

Allogeneic blood products release inflammatory factors during storage and can cause immunosuppression, including inhibiting NK cell activity and decreasing the Th1/Th2 ratio; eventually, infectious complications are increased after transfusion [42–46]. It has been reported that postoperative intra-abdominal infection is an independent prognostic factor of DFS and disease-specific survival in patients with colon cancer [33]. In our meta-analysis, transfusion also increased the incidence of cardiopulmonary complications, anastomotic complications, and reoperation, which suggested that postoperative complications might have a negative impact on oncologic outcome. There are only two articles (1582 patients) included that addressed the incidence of reoperation; thus, more studies are needed to confirm the result.

Our meta-analysis showed that the poor overall survival was closely related with the transfusion volume. Large amounts of blood products can generate more active biochemical substances, including vascular endothelial growth factors and plasminogen activator inhibitors, and are more likely to promote the tumour angiogenesis and tumour cell proliferation and migration [47]; together with surgical stress, large-volume transfusions may cause more immunosuppression [18]. One study showed that restrictive transfusion (transfusion trigger: Hb < 8 g/dl) could not improve the survival rate, especially in a high-risk group of elderly patients with cardiovascular disease [48], and our meta-analysis showed that restrictive (transfusion trigger: Hb ≤ 6 g/dl) or liberal transfusion (transfusion trigger: Hb ≤ 7–10 g/dl) could decrease the OS significantly compared with non-transfusion. However, until now, there have been no direct comparisons between different transfusion triggers on prognosis, and very few articles report the trigger of transfusion. Since it is relatively rare in clinical circumstances that bleeding over 1000 ml as a transfusion trigger, we performed a sensitivity analysis, and the results showed that the effect of transfusion on OS was not changed when the article was omitted. Anaemia itself could negatively affect the prognosis of malignancy and could increase the risk for overall mortality, and the presence of anaemia was an independent risk factor for postoperative complications and a longer hospital stay after colon surgery.
surgery [49]; therefore, preoperative therapy for anaemia was recommended to reduce the need for blood transfusions, and iron supplements have no influence on tumour progression [50].

It is known that allogeneic transfusion can aggravate perioperative immunosuppression in cancer patients, and autogenous transfusion seems to be superior to allogeneic transfusion [51, 52], but Harlaar et al. did not find any benefit from autologous transfusion compared with allogeneic transfusion after long-term follow-up in colorectal cancer patients [53]. The clinical data for autogenous transfusion in cancer patients are sparse, and the safety of autogenous transfusion is still a big concern in the clinic, as autogenous transfusion has the potential risk to induce iatrogenic metastasis.

There are some limitations of our meta-analysis. All of the included articles were observational studies, published from 1990 to 2018. The methods and drugs for anaesthesia and analgesia were not mentioned in these trials and may be different to some extent. Some other risk factors such as preoperative Hb level, different kinds and storage durations of blood products, operation duration, and the staging of cancer might affect the prognosis of colorectal cancer surgery. According to the subgroup analysis, different types of surgical procedure had different outcomes. However, most of the included articles did not describe colonic and rectal cancers surgery separately, so that the articles including colon cancer or rectal cancer are taken together in our meta-analysis. Therefore, prospective controlled clinical
trials with large sample sizes need to be conducted to verify the results of our meta-analysis.

Conclusion

The results of our meta-analysis suggest that perioperative transfusion causes a dramatically negative effect on long-term prognosis and increases the short-term complications after colorectal cancer surgery.

Abbreviations

CSS: Cancer-specific survival; DFS: Disease-free survival; OS: Overall survival

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Availability of data and materials

The datasets supporting the conclusion are included in the article.

Authors’ contributions

H-LL participated in the design of the study, revised the manuscript, and edited the language. Q-YP collected the data, performed the statistical analysis, and drafted the manuscript. RA collected the data and revised and proofread the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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