Systematic Review and Meta-Analysis

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# The impact of perioperative allogeneic blood transfusion on prognosis of hepatocellular carcinoma after radical hepatectomy

## A systematic review and meta-analysis of cohort studies

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**Abstract**

This meta-analysis aims to clarify the clinical impacts of allogeneic blood transfusion (ABT) on hepatectomy outcome in hepatocellular carcinoma (HCC) patients. A systematic literature search was performed for relevant articles in international and Chinese databases up to May 2018. Random- or fixed-effect meta-analysis was used to pool the effect estimates. Publication bias was assessed by Egger's and Peters's test. Heterogeneity was assessed using the $I^2$ statistic. The strength of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation system. A total of 29 studies met the eligibility criteria. Meta-analysis showed HCC patients in ABT group had lower survival rate at 1, 3, 5, and 10 years after radical hepatectomy than those in no blood transfusion (NBT) group (RR = 0.9, 95%CI: 0.87–0.93, $P < .05$; RR = 0.83, 95%CI: 0.77–0.89, $P < .05$; RR = 0.7, 95%CI: 0.65–0.74, $P < .05$; RR = 0.64, 95%CI: 0.54–0.75, $P < .05$). Similar results were observed in disease-free survival (DFS) (respectively: RR = 0.86, 95%CI: 0.82–0.91, $P < .05$; RR = 0.77, 95%CI: 0.67–0.79, $P < .05$; RR = 0.71, 95%CI: 0.64–0.79, $P < .05$; RR = 0.62, 95%CI: 0.48-0.8, $P < .05$). Cancer recurrence rate was higher for the patients in ABT group at 1 and 3 years (RR = 1.5, 95%CI: 1–2.24, $P < .05$; RR = 1.27, 95%CI: 1.09–1.49, $P < .05$, respectively), but not statistically significant at 5years (RR = 1.08, 95%CI: 0.98–1.19, $P = .512$). The HCC patients in ABT group increased postoperative complications occurrence compared with those in NBT group (RR = 1.87, 95%CI: 1.42–2.45, $P < .05$). This meta-analysis demonstrated that ABT was associated with adverse clinical outcomes for HCC patients undergoing radical hepatectomy, including poor survival, DFS, and complications. Surgeons should reduce blood loss during hepatectomy and avoid perioperative allogenic blood transfusion.

**Abbreviations:** ABT = allogeneic blood transfusion, DFS = disease-free survival, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HCC = hepatocellular carcinoma, NBT = no blood transfusion, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RR = Relative risk.

**Keywords:** allogeneic blood transfusion, hepatocellular carcinoma, meta-analysis, prognosis

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the fifth most common cause of cancer-related death worldwide.[1] Liver transplantation is an alternative treatment for the early stage HCC patients with chronic liver dysfunction, while hepatectomy is still the primary treatment option for HCC patients due to the limited number of available donors.[2] Improving understanding of the best surgical and perioperative management continues to decrease the perioperative morbidity and mortality of hepatectomy for HCC patients. Especially improved surgical techniques have decreased bleeding during hepatectomy and the transfusion rate has decreased from 62% to 22% over the past 2 decades;[3,4] Nevertheless, blood transfusion remains necessary when excessive intraoperative bleeding occurs.

Meanwhile, transfusion could cause knownside effects, such as infectious disease, hemolytic transfusion reaction, hepatic ischemia-reperfusion injury, and transfusion-related acute lung injury. Some studies demonstrated that perioperative blood transfusion not only caused such problems, but it could affect long-term survival of HCC patients after radical hepatectomy.[5] But others reported no significant association between perioperative blood transfusion and prognosis of HCC after radical hepatectomy.[6] Therefore, the impact of allogeneic blood

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transfusion (ABT) on postoperative outcomes are still controversial.

In order to clarify the inconsistent issue, a meta-analysis is necessary to be performed. Our study aims to inspect the correlation between ABT and survival rate, disease-free survival (DFS), cancer recurrence, and complications of HCC patients undergoing radical hepatectomy.

## 2. Material and methods

### 2.1. Search strategy for eligible studies

We conducted this meta-analysis with adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[7] A systematic literature search was conducted in PubMed, Web of Science, Embase, and CBM for relevant articles up to May 2018, using various combinations of the keywords:

hepatocellular carcinoma, HCC, liver cancer, and blood transfusion. References cited in the relevant articles were investigated for any potential and eligible studies.

### 2.2. Eligibility criteria

Eligibility criteria for all included studies were as follows: evaluation of the correlation between ABT and clinical prognosis (survival rate, DFS, cancer recurrence, and postoperative complications) of HCC patients undergoing radical hepatectomy; it must be clinical studies, and the original data could be obtained; studies focused on autogenic blood transfusion or non-primary HCC were excluded.

### 2.3. Data extraction and quality assessment

In this meta-analysis, all patients were divided into ABT group and NBT group. ABT was defined as perioperative transfusion of allogeneic blood products, while NBT was defined as patients who did not receive any transfusion. Two authors independently extracted participants' information including first author's name, publication year, patients' age and sex, number of patients included in ABT and NBT group, cancer differentiation, survival rate, DFS, cancer recurrence, and postoperative complications. Discrepancies were resolved through discussion.

The methodological quality of the included studies was assessed independently by 2 authors using the Newcastle–Ottawa scale,[8] which allocates a maximum of 9 stars each to case selection, comparability of cohorts (ABT and NBT), and outcomes assessment. A study awarded 6 or more stars was considered as a high-quality study. In addition, the strength of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE system).[9]

### 2.4. Statistical analysis

Statistical analysis was performed using statistical software R (version 3.2.3). For studies that did not show the corresponding

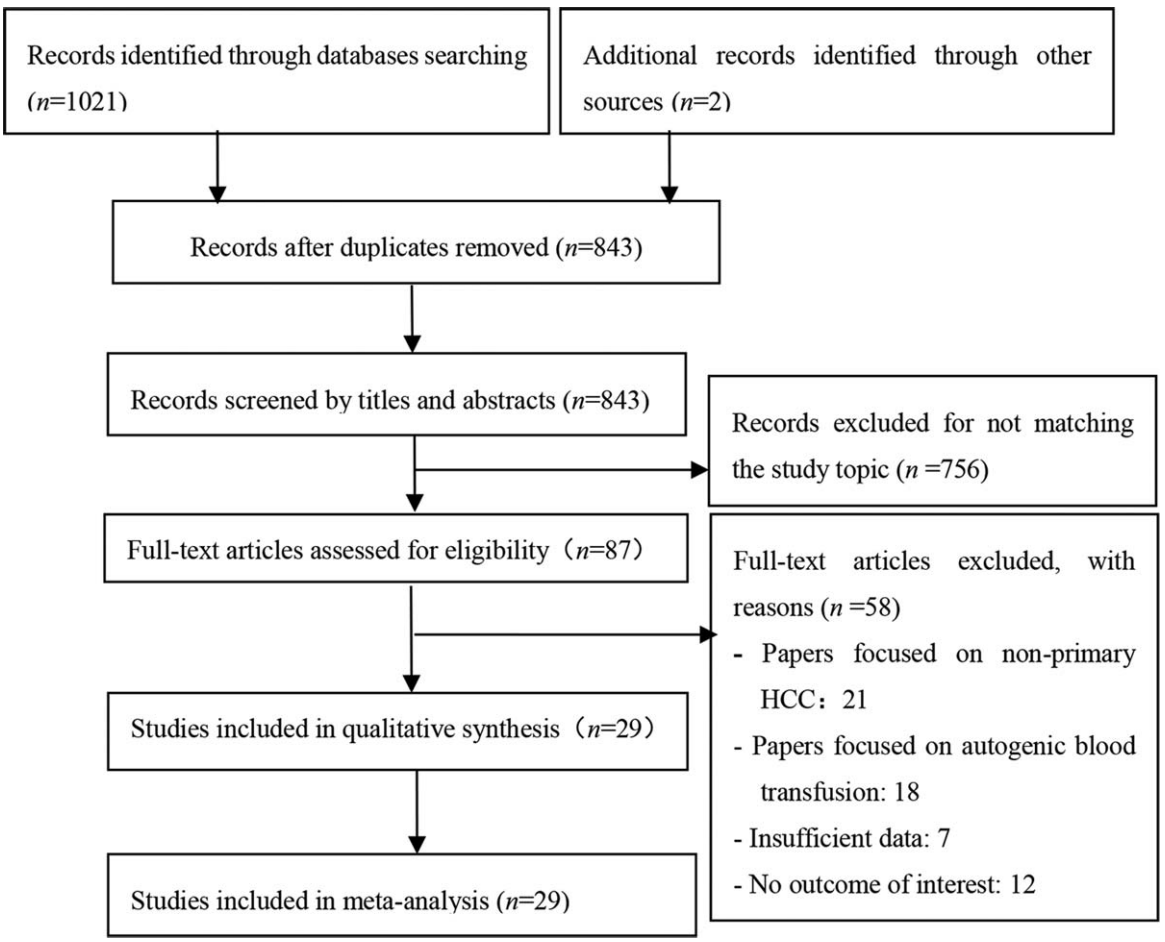


**Figure 1.** Flowchart of literatures selection.

results, the Engauge Digitizer was applied to extract survival data from the Kaplan–Meier curves (http://sourceforge.net). The relative risk (RR) of survival rate, DFS, cancer recurrence rate, and postoperative complications were considered 4 main outcomes in our study. For each outcome, RR was calculated and reported with 95% confidence interval (CI). In this meta-analysis, $\chi^2$, and $I^2$ statistics were used to test possible heterogeneity among studies. If the heterogeneity of any outcome was >50% or $P < .05$, the random-effect model was used to calculate summary estimate; if not, the fixed-effect model was applied. Meanwhile, the potential impact of transfusion amount and rates, age, cancer size, and participants on the outcomes were assessed by stratified analysis. Besides, sensitivity analysis was conducted to test whether the results of the meta-analysis were sensitive to restrictions on any of the included studies. Egger's and Peters's tests were applied to assess publication bias.

## 3. Results

### 3.1. Literature search and study characteristics

The selection of studies for inclusion in the meta-analysis was shown in flow diagram (Fig. 1). Of the initial 1021 citations retrieved, 29 studies met our inclusion criteria and were included in the final meta-analysis.[5,6,10–36] 5 studies[12,28–30,35] were prospective cohort studies and 24 studies[5,6,10,11,13–27,31–34,36] were retrospective cohort studies. Detailed study characteristics were shown in Table 1. Of the 29 studies with a total of 7241 participants, 2908 cases (40.2%) received ABT and 4333 cases (59.8%) were grouped as NBT. Outcomes reported in each study including survival rate (n = 19), DFS (n = 19), cancer recurrence (n = 3), and postoperative complications (n = 10). According to the Newcastle–Ottawa scale, all included studies were of high quality. Characteristics of the included studies and quality scores were listed in Table 1.

### 3.2. Survival rate

In this meta-analysis, there were ten studies providing 1-year survival rate,[5,6,10–13,17,29,33,36] 13 studies providing 3-year survival rate,[5,6,10–13,17,22,24,29,30,33,36] 19 studies providing 5-year survival rate,[5,6,10–15,17–19,22,24,25,29,30,32,33,36] and 6 studies providing 10-year survival rate.[5,6,11,12,15,24] As displayed in (Fig. 2A–D), meta-analyses demonstrated that there was a lower 1-, 3-, 5-, and 10-year survival rate for patients with ABT than those with NBT (respectively: RR = 0.9, 95%CI: 0.87–0.93, $P < .001$; RR = 0.83, 95%CI: 0.77–0.89, $P < .0001$; RR = 0.7, 95%CI: 0.65–0.74, $P < .001$; RR = 0.64, 95%CI: 0.54–0.75, $P < .001$). The heterogeneity of 1-, 5-, and 10-year survival rate was >50%, the random-effect model was used to calculate summary estimate; the heterogeneity of 3-year DFS was < 50%, the fixed-effect model was applied.

Results of the stratified meta-analyses for postoperative 5-year survival rate were shown in Table 2. When stratified by transfusion amount, we found that the impact of transfusion amount on 5-year survival rate was significant (subgroup

**Table 1**

**Characteristics of studies included in the meta-analysis.**

| | | | Participants | | Sex (M/F) | | Age (mean) | | Liver cirrhosis | | Child A/B | | Cancer size, cm | | TNM stage+ | | Differentiation# | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Country | Design | ABT | NBT | ABT | NBT | ABT | NBT | ABT | NBT | ABT | NBT | ABT | NBT | ABT | NBT | ABT | NBT | Study quality |
| Wada, 2017[5] | Japan | RCS | 198 | 444 | 156/42 | 353/91 | 66.2 | 65 | 49.5% | 39.0% | 175/23 | 411/33 | 5.9 | 3.6 | — | — | 143/40 | 302/111 | 9 |
| Yang, 2016[10] | China | RCS | 234 | 234 | 202/32 | 204/30 | 49.7 | 50.1 | 73.5% | 76.5% | 200/34 | 200/34 | — | — | — | — | 33/201 | 26/208 | 7 |
| Xu, 2016[11] | China | RCS | 68 | 154 | – | | 51.8 | | – | | 216/6 | | — | — | — | — | — | | 8 |
| Harada, 2015[12] | Japan | PCS | 91 | 388 | 58/33 | 261/127 | 64.4 | 68 | 79.1% | 55.7% | 91/0 | 388/0 | 4.1 | 3 | — | — | 16/75 | 51/337 | 8 |
| Ye, 2013[13] | China | RCS | 93 | 37 | 69/24 | 33/4 | 47.1 | 50.7 | — | | 90/3 | 36/1 | — | — | 36/57 | 18/19 | — | | 6 |
| Kuroda, 2012[6] | Japan | RCS | 60 | 60 | 50/10 | 48/12 | 59.4 | 60.7 | 50.0% | 58.3% | 43/17 | 46/14 | 6.2 | 6.1 | — | — | 1/59 | 3/57 | 9 |
| Okamura, 2011[14] | Japan | RCS | 87 | 289 | 303/73 | | 61.4 | | — | | 354/22 | | 3.4 | | — | — | — | | 7 |
| Nanashima, 2011[15] | Japan | RCS | 100 | 83 | 148/35 | | 65 | | — | | — | | — | — | — | — | — | | 7 |
| Yang, 2011[16] | China | RCS | 164 | 141 | 279/26 | | 49 | 49.2 | 76.7% | 76.7% | 270/35 | | 10.3 | | — | — | — | | 7 |
| Chen, 2010[17] | China | RCS | 87 | 79 | 74/13 | 65/14 | 47.5 | 47.4 | 77.1% | 77.1% | — | | 9.6 | 8.9 | 59/17 | 56/17 | — | | 7 |
| Abdel—Wahab, 2010[18] | Egypt | RCS | 87 | 72 | 119/40 | | 55 | | — | | 138/21 | | — | — | — | — | — | | 7 |
| Choi, 2009[19] | Korea | RCS | 94 | 96 | 143/47 | | 51 | | 56.7% | 56.7% | — | | — | — | — | — | — | | 6 |
| Wang, 2009[20] | China | RCS | 62 | 411 | 379/94 | | 53.1 | | 44.4% | 44.4% | 394/79 | | 5.5 | | — | — | — | | 8 |
| Sugita, 2008[21] | Japan | RCS | 101 | 123 | 80/21 | 92/31 | 61.7 | 64.4 | 62.4% | 48.0% | — | | 5.9 | 4 | — | — | 13/88* | 27/96* | 9 |
| Kaibori, 2008[22] | Japan | RCS | 269 | 141 | 210/59 | 117/24 | 64 | 64.7 | 41.3% | 36.2% | — | | 4.5 | 2 | 162/107 | 102/39 | 251/18 | 135/6 | 9 |
| Sasaki, 2006[23] | Japan | RCS | 184 | 233 | 309/108 | | — | | 67.9% | 67.9% | 309/108 | | — | — | — | — | — | | 8 |
| Hanazaki, 2005[24] | Japan | RCS | 210 | 158 | 156/54 | 122/36 | 62 | 63 | 62.3% | 36.1% | 146/64 | 142/16 | 5.1 | 3.5 | 154/56 | 146/12 | — | | 9 |
| Laurent, 2005[25] | France | RCS | 36 | 72 | 89/19 | | 64 | | 63.0% | 63.0% | — | | 9.3 | | — | — | — | | 6 |
| Wei, 2003[26] | China | RCS | 45 | 110 | 122/33 | | 52 | | 34.9% | 34.9% | — | | 11 | | — | — | — | | 6 |
| Ercolani, 2003[27] | Italy | RCS | 71 | 153 | 182/42 | | 62.5 | | 78.6% | 78.6% | 185/39 | | — | — | — | — | — | | 6 |
| Sasaki, 2002[28] | Japan | PCS | 23 | 52 | 59/16 | | 61.7 | | — | | 46/29 | | — | — | — | — | — | | 7 |
| Kwon, 2001[29] | Japan | PCS | 53 | 55 | 41/12 | 42/13 | 62.1 | 61.6 | 50.9% | 45.5% | 40/13 | 46/9 | 3.7 | 3.3 | 43/10 | 43/12 | 51/2 | 52/3 | 9 |
| Kitagawa, 2001[30] | Japan | PCS | 23 | 52 | — | | 60.2 | 60.9 | 55.5% | 55.5% | — | | — | — | — | — | — | | 7 |
| Makino, 2000[31] | Japan | RCS | 117 | 78 | 85/32 | 71/7 | 60.8 | 60.7 | 77.8% | 61.5% | 74/30 | 58/17 | 5 | 3.5 | — | — | — | | 9 |
| Asahara, 1999[32] | Japan | RCS | 23 | 152 | 19/4 | 114/38 | 60.1 | | 78.3% | 69.1% | — | | — | — | — | — | 2/18* | 10/122* | 8 |
| Wu, 1999[33] | China | RCS | 151 | 60 | 131/20 | 48/12 | 53 | 53.5 | — | | — | | — | — | — | — | — | | 7 |
| Yamamoto, 1996[34] | Japan | RCS | 85 | 301 | 311/75 | | 59.7 | | 59.3% | 59.3% | 265/121 | | — | — | — | — | — | | 6 |
| Itasaka, 1995[35] | Japan | PCS | 38 | 33 | 33/5 | 28/5 | 58.2 | 57.9 | 94.7% | 84.8% | 34/4 | 33/0 | — | — | — | — | — | | 9 |
| Matsumata, 1993[36] | Japan | RCS | 54 | 72 | 43/11 | 62/10 | 58.4 | 57.1 | 62.3% | 52.1% | — | | 4.1 | 3.4 | — | — | — | | 9 |

ABT = allogeneic blood transfusion, NBT = no blood transfusion, PCS = prospective cohort study, RCS = retrospective cohort study.

+ I+II/III+IV.

# Cancer differentiation (well + moderate/poor)

* well/moderate + poor.

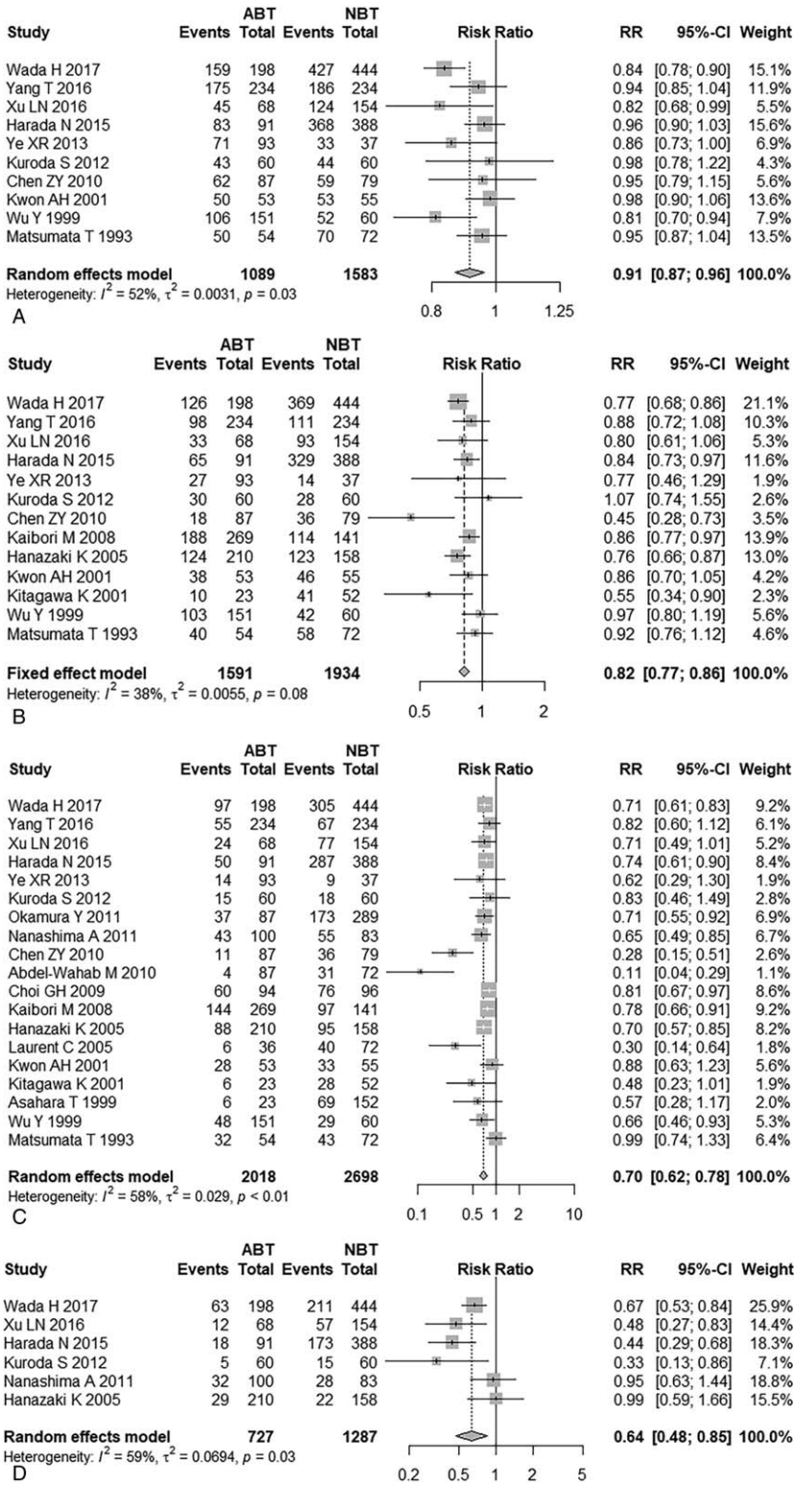


**Figure 2.** Forest plot of postoperative survival rate associated with ABT for HCC. (A) for 1-year survival rate, (B) for 3-year survival rate, (C) for 5-year survival rate, and (D) for 10-year survival rate. ABT = allogeneic blood transfusion, HCC = hepatocellular carcinoma.

differences $P < .05$), even low transfusion amount might decrease the 5-year survival rate (compared to high transfusion amount group, 5-year survival rate of low transfusion amount group decreased by about 55%). When examining differences over cancer size, we also found that cancer size had a significant impact on 5-year survival rate (subgroup differences $P < .05$). Compared to studies with small cancer size, 5-year survival rate of studies with large cancer size decreased by about 45%. In the stratified analysis, we did not find that there was the association between transfusion rate and 5-year survival rate.

**Table 2**

**Stratified analysis for 5-year survival rate, 5-year DFS and complication.**

| Subgroup | No. of studies | 5-year OS RR (95%CI) | $I^2$ | $P^*$ |
|---|---|---|---|---|
| Transfusion amount | | | | |
| >788 ml | 4 | 0.78 (0.70, 0.87) | 0.0% | <.0001 |
| ⩽788 ml | 4 | 0.30 (0.14, 0.65) | 84.0% | |
| NA | 11 | 0.73 (0.67, 0.79) | 0.0% | |
| Transfusion rate | | | | |
| >42.8% | 12 | 0.70 (0.65, 0.77) | 69.1% | .6495 |
| ⩽42.8% | 7 | 0.68 (0.62, 0.76) | 10.7% | |
| Age | | | | |
| >60.96 year | 8 | 0.70 (0.66, 0.77) | 16.5% | .3064 |
| ⩽60.96 year | 11 | 0.66 (0.59, 0.75) | 72.4% | |
| Cancer size | | | | |
| >4.42 cm | 3 | 0.42 (0.20, 0.88) | 74.9% | .0010 |
| ⩽4.42 cm | 7 | 0.75 (0.69, 0.81) | 0.0% | |
| NA | 9 | 0.64 (0.57, 0.72) | 75.0% | |
| Participants | | | | |
| >248 | 6 | 0.74 (0.68, 0.80) | 0.0% | .0259 |
| ⩽248 | 13 | 0.63 (0.57, 0.70) | 73.3% | |
| Study design | | | | |
| PCS | 3 | 0.74 (0.63, 0.88) | 13% | .3776 |
| RCS | 16 | 0.68 (0.60, 0.78) | 63% | |

| Subgroup | No. of studies | 5-year DFS RR (95%CI) | $I^2$ | $P^*$ |
|---|---|---|---|---|
| Transfusion amount | | | | |
| >876 mL | 3 | 0.69 (0.52, 0.92) | 0.0% | .8305 |
| ⩽876 mL | 4 | 0.62 (0.32, 1.20) | 69.7% | |
| NA | 12 | 0.73 (0.65, 0.82) | 34.0% | |
| Transfusion rate | | | | |
| >37.8% | 11 | 0.75 (0.65, 0.86) | 40.7% | .2782 |
| ⩽37.8% | 8 | 0.66 (0.56, 0.79) | 30.3% | |
| Age | | | | |
| >61.62 years | 9 | 0.74 (0.57, 0.96) | 57.0% | .9279 |
| ⩽61.62 years | 9 | 0.70 (0.59, 0.83) | 0.0% | |
| NA | 1 | 0.69 (0.50, 0.95) | 0.0% | |
| Cancer size | | | | |
| >4.87 cm | 4 | 0.59 (0.32, 1.09) | 67.0% | .7808 |
| ⩽4.87 cm | 7 | 0.72 (0.62, 0.85) | 0.0% | |
| NA | 8 | 0.75 (0.57, 0.98) | 51.0% | |
| Participants | | | | |
| >252 | 6 | 0.70 (0.61, 0.81) | 0.0% | .7345 |
| ⩽252 | 13 | 0.73 (0.62, 0.86) | 51.1% | |
| Study design | | | | |
| PCS | 4 | 0.59 (0.43, 0.80) | 0.0% | .2980 |
| RCS | 15 | 0.73 (0.65, 0.82) | 39% | |

| Subgroup | No. studies | Complications RR (95%CI) | $I^2$ | $P^*$ |
|---|---|---|---|---|
| Transfusion amount | | | | |
| >788 mL | 3 | 1.23 (0.98, 1.55) | 0.0% | .0039 |
| ⩽788 mL | 5 | 2.15 (1.69, 2.74) | 17.0% | |
| NA | 2 | 2.66 (1.18, 6.00) | 64.0% | |
| Transfusion rate | | | | |
| >38.56% | 6 | 1.61 (1.32, 1.98) | 68.1% | .0089 |
| ⩽38.56% | 4 | 2.26 (1.94, 2.62) | 83.1% | |
| Age | | | | |
| >63.47 year | 3 | 1.93 (1.71, 2.19) | 39.3% | <.0001 |
| ⩽63.47 year | 7 | 1.58 (1.39, 1.8) | 55.7% | |
| Cancer size | | | | |
| >5.28 cm | 4 | 1.59 (1.31, 1.94) | 34.0% | .0086 |
| ⩽5.28 cm | 5 | 2.31 (1.50, 3.54) | 78.0% | |
| NA | 1 | 0.99 (0.70, 1.41) | 0.0& | |
| Participants | | | | |
| >283 | 5 | 2.12 (1.82, 2.46) | 84.0% | .0259 |
| ⩽283 | 5 | 1.58 (1.29, 1.94) | 58.4% | |
| Study design | | | | |
| PCS | 3 | 1.24 (0.90, 1.70) | 14.0% | .0812 |
| RCS | 7 | 2.12 (1.57, 2.86) | 78.0% | |

DFS = disease-free survival, NA = not available, NO. = number, OS = overall survival, RR = relative risk.

* Test for subgroup differences (fixed-effect model), between subgroups *P* value.

### 3.3. Disease-free survival

In this meta-analysis, there were 13 studies providing 1-year DFS,[5,6,10,12,17,20,21,24,25,29–31,36] 16 studies providing 3-year DFS,[5,6,10,12,15,17,20,21,24,25,27–31,36] 19 studies providing 5-year DFS,[5,6,10,12,15,17,19–21,23–25,27–32,36] and 4 studies providing 10-year DFS.[5,12,23,24] As displayed in (Fig. 3A–D), perioperative ABT was associated with a significant increased risk in reducing 1-, 3-, 5-, and 10-year DFS (respectively: RR = 0.86, 95%CI: 0.82–0.91, $P < .05$; RR = 0.77, 95%CI: 0.67–0.79, $P < .05$; RR = 0.71, 95%CI: 0.64–0.79, $P < .05$; RR = 0.62, 95%CI: 0.48–0.8, $P < .05$). The heterogeneity of 3-year DFS was >50%, the random-effect model was applied to calculate summary estimate; the heterogeneity of 1-, 5-, and 10-year DFS was < 50%, the fixed-effect model was used.

Results of the stratified meta-analyses for postoperative 5-year DFS were shown in Table 2. When stratified by transfusion amount, transfusion rate, age, cancer size, and sample size, we did not find that they had a significant impact on 5-year DFS (subgroup differences $P > .05$).

### 3.4. Cancer recurrence rate

The cancer recurrence data were available in 3 studies.[15,27,34] As shown in Figure 4A–C, meta-analysis demonstrated cancer recurrence rates at 1 and 3 years after radical hepatectomy for HCC patients were higher in the ABT group than in NBT group (respectively: RR = 1.5, 95%CI: 1–2.24, $P < .05$; RR = 1.27, 95% CI: 1.09–1.49, $P < .05$), but not statistically significant at 5years (RR = 1.08, 95%CI: 0.98–1.19, $P = .512$).

### 3.5. Postoperative complication rate

Ten studies reported the relationship between ABT and postoperative complication rate.[5,6,12,14,16,17,22,26,29,35] Meta-analysis demonstrated that postoperative complication rate was higher in ABT group than in NBT group (RR = 1.87, 95%CI: 1.42–2.45, $P < .05$) (Fig. 5). Significant heterogeneity among studies was present ($I^2 = 78\%$), and the random-effect model was applied.

Results of the stratified meta-analyses for postoperative complication rate were shown in Table 2. When stratified by transfusion amount, we found that the impact of transfusion amount on postoperative complication rate was significant (subgroup differences $P < .05$), even low transfusion amount might increase postoperative complication rate (compared to

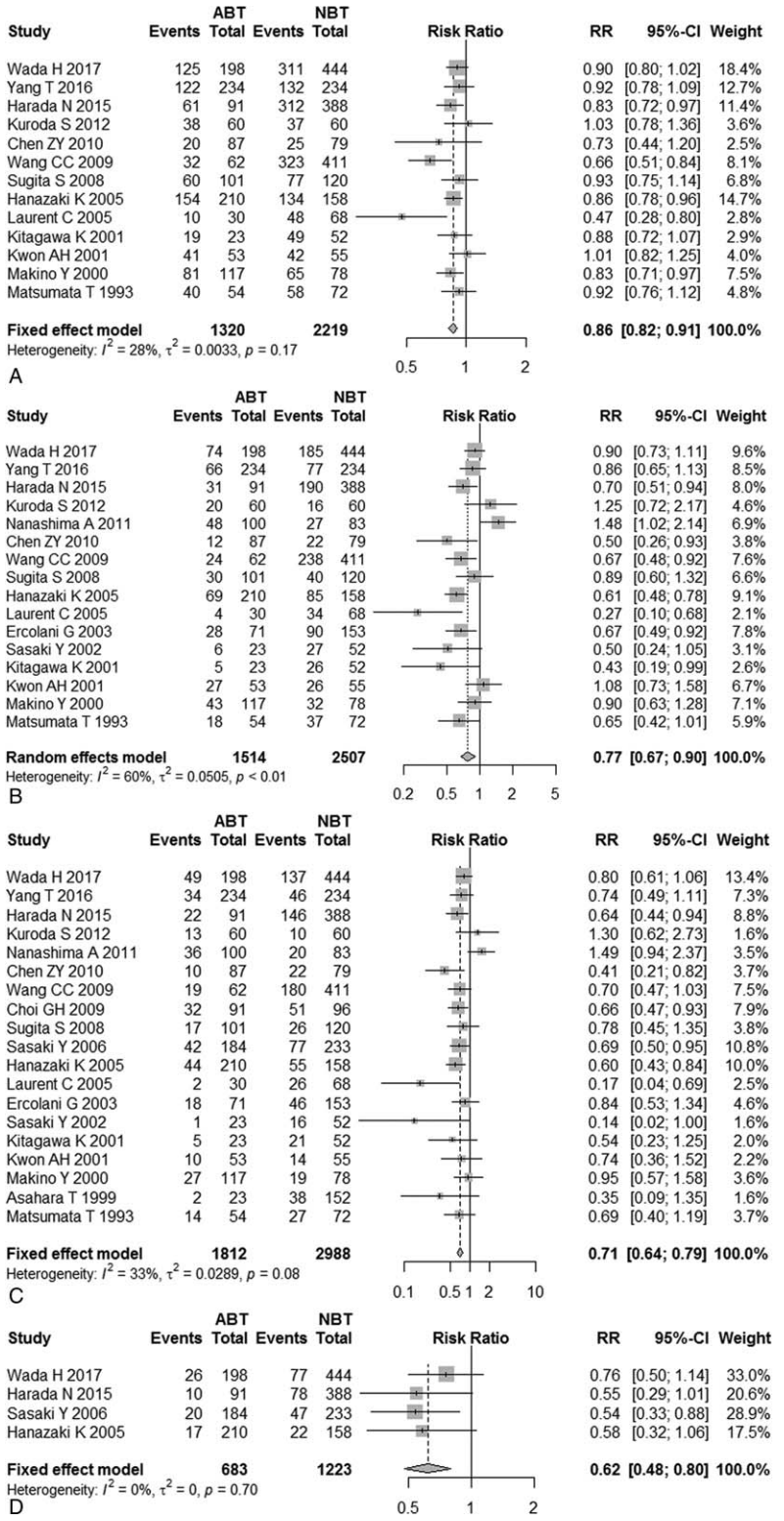


**Figure 3.** Forest plot of postoperative DFS associated with ABT for HCC. (A) For 1-year DFS, (B) for 3-year DFS, (C) for 5-year DFS, and (D) for 10-year DFS. ABT = allogeneic blood transfusion, DFS = disease-free survival, HCC = hepatocellular carcinoma.

high transfusion amount group, postoperative complication rate of low transfusion amount group increased by about 75%). Meanwhile, we also found that postoperative complication rate was associated with the transfusion rate (subgroup differences $P < .05$). Compared to studies with high-transfusion rate, postoperative complication rate of studies with low transfusion rate increased by about 40%. When examining differences over age, cancer size, and sample size, we also found that they had a significant impact on postoperative complication rate (subgroup differences $P < .05$).

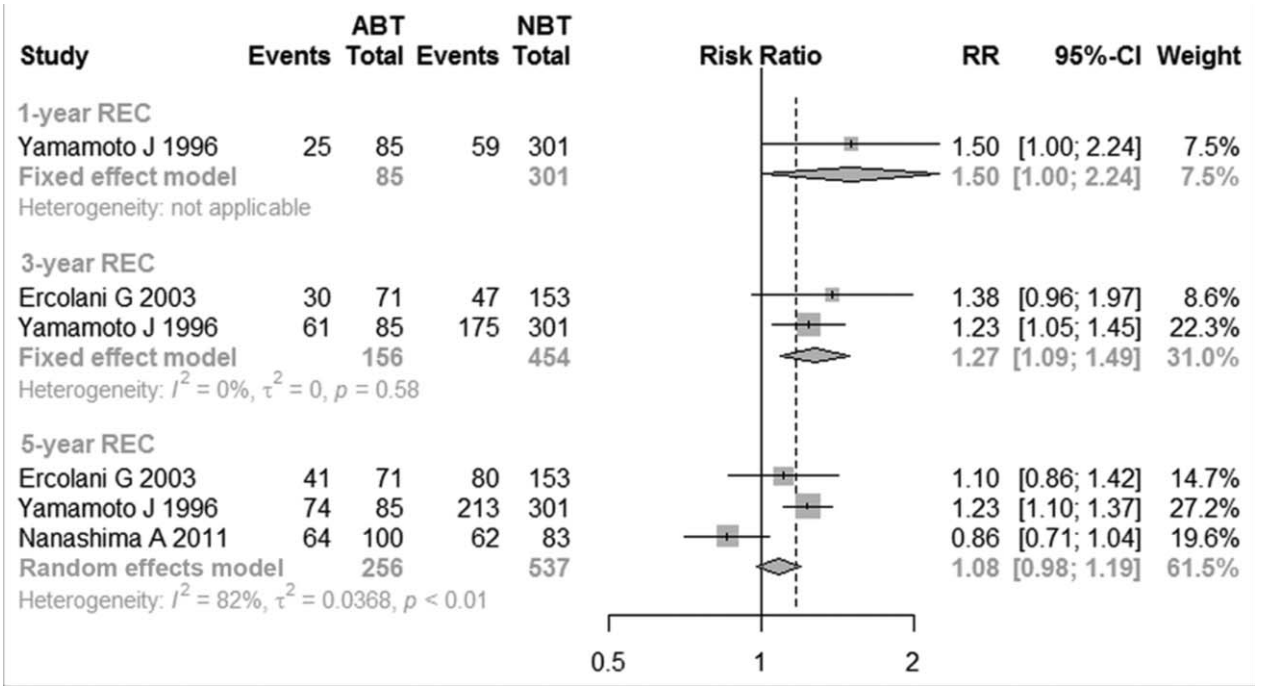


**Figure 4.** Forest plot of postoperative recurrence associated with ABT for HCC. (A) For 1-year recurrence, (B) for 3-year recurrence, and (C) for 5-year recurrence. ABT = allogeneic blood transfusion, HCC = hepatocellular carcinoma.

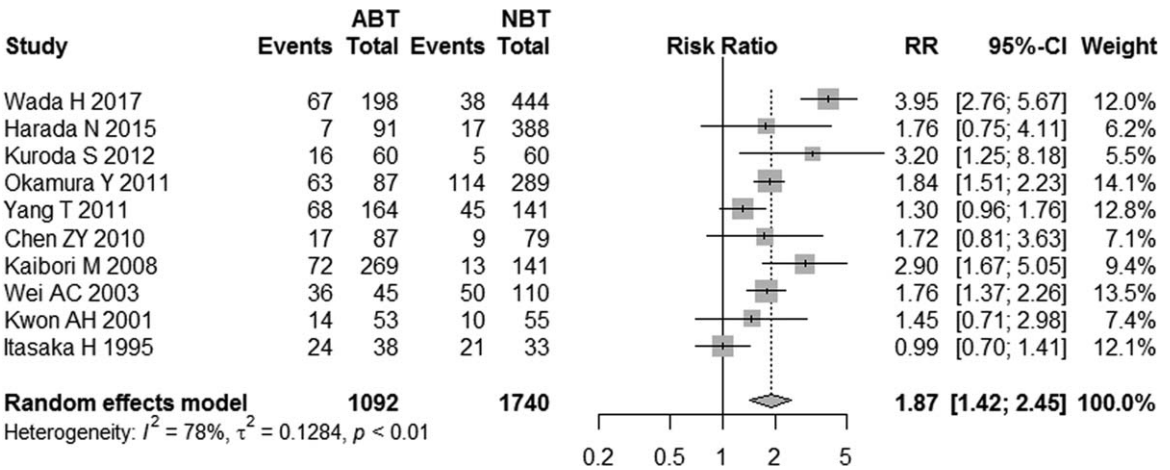


**Figure 5.** Forest plot of postoperative complications rate associated with ABT for HCC. ABT = allogeneic blood transfusion, HCC = hepatocellular carcinoma.

### 3.6. Quality of evidence of the primary outcomes

The GRADE system was applied to assess the evidence for the outcomes, and the quality of evidence was summarized in Table 3. As a result, the overall quality of evidence for the outcomes was low. Thus, further prospective studies are likely to have an important impact on the confidence in the effect estimate and may change the current estimate.

### 3.7. Sensitivity analysis

Sensitivity analysis was performed for 5-year survival rate and postoperative complication rate by excluding one study at a time and calculating the pooled RRs for the remaining studies (Supplementary Information, http://links.lww.com/MD/C569). The results demonstrated that no individual study had excessive impact on the stability of the pooled effect and that the result of this analysis was robust.

### 3.8. Publication bias

Publication bias was measured by the Egger's and Peters's test. Egger's test for 5-year survival rate, 5-year DFS, and postoperative complication rate did not show the asymmetry typically associated with publication bias (*P* value: .0937, .1629, and .6988, respectively). Evidence of publication bias was also not seen with the Peters's test of 5-year survival rate (*P* = .1527),

**Table 3**

**Strength of evidence for outcomes of HCC patients with ABT compared with NBT.**

| Outcomes | Illustrative comparative risk* (95%CI) Assumed risk NBT (per 1000) | Corresponding risk ABT (per 1000) | Relative effect RR (95%CI) | No. of participants (studies) | Quality of evidence (GRADE) |
|---|---|---|---|---|---|
| Survival rate | | | | | |
| 1-year survival rate | 895 | 805 (778 to 832) | 0.9 (0.87 to 0.93) | 2672 (10 studies) | ⊕⊕◯◯†,‡ low |
| 3-year survival rate | 726 | 603 (559 to 646) | 0.83 (0.77 to 0.89) | 3525 (13 studies) | ⊕⊕⊕◯† moderate |
| 5-year survival rate | 581 | 407 (378 to 430) | 0.7 (0.65 to 0.74) | 4716 (19 studies) | ⊕⊕◯◯†,‡ low |
| 10-year survival rate | 393 | 252 (212 to 295) | 0.64 (0.54 to 0.75) | 2014 (6 studies) | ⊕◯◯◯†,‡,§ very low |
| Disease-free survival | | | | | |
| 1-year DFS | 727 | 661 (632 to 698) | 0.91 (0.87 to 0.96) | 3539 (13 studies) | ⊕⊕◯◯†,§ low |
| 3-year DFS | 460 | 354 (308 to 414) | 0.77 (0.67 to 0.9) | 4021 (16 studies) | ⊕⊕◯◯†,‡ low |
| 5-year DFS | 327 | 232 (209 to 258) | 0.71 (0.64 to 0.79) | 4800 (19 studies) | ⊕⊕⊕◯† moderate |
| 10-year DFS | 183 | 114 (88 to 147) | 0.62 (0.48 to 0.8) | 1906 (4 studies) | ⊕⊕◯◯†,§ low |
| Cancer recurrence | 661 | 714 (648 to 787) | 1.08 (0.98 to 1.19) | 793 (3 studies) | ⊕◯◯◯†,‡,§ very low |
| Complication | 185 | 346 (263 to 453) | 1.87 (1.42 to 2.45) | 2832 (10 studies) | ⊕◯◯◯†,‡,¶ very 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.

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

† Risk of bias was unclear or high in the study/studies.

‡ Serious unexplained inconsistency (large heterogeneity, $P < .05$, point estimates, and confidence intervals vary considerably).

§ Imprecision due to few events and confidence intervals include appreciable benefit or harm.

¶ Definition of postoperative complication varied or was unclear.

ABT = allogeneic blood transfusion, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HCC = hepatocellular carcinoma, NBT = no blood transfusion, RR = relative risk.

5-year DFS ($P = .1019$), and postoperative complication rate ($P = .1373$).

## 4. Discussion

Although perioperative ABT is very common in hepatectomy, the clinical impact of ABT on HCC patients undergoing radical hepatectomy remains controversial, especially in connection to recurrence. In this meta-analysis, perioperative blood transfusion adversely affected long-term prognosis of HCC patients undergoing radical hepatectomy. Our study showed that perioperative blood transfusion of any amount correlates with poorer survival rate and disease-free survival, but not with recurrence. The pooled RR values for 5-year survival rate and 5-year DFS after radical hepatectomy all were 0.7 in this meta-analysis, which meant that 5- survival rate and 5-DFS of ABT group were reduced by about 30% compared to NBT group. In stratified analyses, we found that the impact of transfusion amount on 5-year survival rate was significant (subgroup differences $P < .05$), even low transfusion amount might decrease the 5-year survival rate of HCC patients. However, we did not find that there was the association between transfusion amount and 5-year DFS (subgroup differences $P > .05$). In our analysis, there was no statistical significance between high and low transfusion rate for the survival rate and disease-free survival (subgroup differences $P > .05$); therefore, it was believed that transfusion itself mediated its effects on the survival rate and disease-free survival rather than the transfusion rate, which was consistent with Wada et al.[5] Similar adverse effect of ABT on clinical prognosis was also observed in other malignancies. For example, a recent meta-analysis performed by Cata and his team on bladder cancer demonstrated that ABT was significantly associated with poor survival rate (HR = 1.27).[37]

Regarding cancer recurrence, Wada et al[5] and Nanashima et al[15] reported that ABT did not promote recurrence; however, Ercolani et al,[27] Asahara et al,[32] and Yamamoto et al[34] reported ABT could increase the recurrence rate of HCC after radical hepatectomy. Meanwhile, the meta-RR for 5 years was 1.08 in this meta-analysis ($P = .512$). That is to say, patients in ABT and NBT group had a similar chance of cancer recurrence. In our analysis, postoperative complication rate was significantly higher in ABT group than in NBT group, which was speculated that immunosuppression modulated by blood transfusion induced postoperative complication rate.[38] The absolute peripheral blood lymphocyte count is significantly reduced in patients who receive ABT [21] and one study reported that the natural killer cell activity of transfused patients was reduced on postoperative day 7.[29] Our results supported the consensus that ABT induced postoperative complication rate and adversely affected the survival of HCC after radical hepatectomy.

Further, we reviewed clinical practice guidelines for liver cancer from China,[39] the United States,[40] Europe,[41] Singapore,[42] and South Korea,[43] and found that only Korea's guideline referred to intraoperative transfusion, and stated one reason why hepatic resection had recently become safer was the reduction in the case of intraoperative hemorrhage and transfusion. Korea's guideline stated blood transfusion compromised anticancer immunologic mechanisms and increased postoperative recurrence.[43] The most commonly reported mechanisms of transfusion-related immunomodulation included decreased function of killer cells, decreased ratio of helper-to-suppressor T lymphocytes, decreased efficacy of antigen presentation, induced tolerance for specific antigens, and suppression of hematopoiesis.[44] Different from others, Procter and colleagues[45] reported that depletion of extracellular arginine in serum, an amino acid essential for normal immunity, might be the mechanism of the immunosuppressive effect of packed red blood cells. However, it also had been speculated that the infusion of growth factors (vascular endothelial growth factor and transforming growth factor-b) and an enhanced inflammatory response as a result of the exposure of the recipient immune system to donor microparticles could also stimulate spread and

proliferation of cancer cells.[46] Our meta-analysis was not designed to investigate these possibilities; however, our results supported the hypothesis that the perioperative administration of ABT was an independent risk factor for reduced survival rate and DFS after radical hepatectomy for HCC similar to what has been reported for other cancers such as bladder and colon.[37,47]

The quality of the evidence varied for different outcomes (Table 3). The quality of the evidence of most outcomes was low and very low. The chief reason was that most of the included studies were retrospective cohort studies, although all studies were of high quality evaluated by the Ottawa–Newcastle score to grade; consequently, the risk of confounding factors was not clear. The included studies collected patients with widely varied stages of disease, including TNM I, II, III, and IV. Stage of the disease was the most important prognostic factor of recurrence and survival in HCC patients. Besides, the disease stage was a significant confounder that was hard to control in retrospective cohort studies. Moreover, the patients with advanced disease were more likely to receive adjuvant therapy, which might be another confounder. Small sample sizes resulted in wide confidence intervals for 10-year survival rate, 10-year DFS, and cancer recurrence, while other factors decreased the quality of the evidence. Future studies should measure differences in clinically important outcomes.

There were several limitations that must be taken into account in this meta-analysis. Most included studies were retrospective cohort studies, and many confounding factors cannot be eliminated, which may contribute significantly to the heterogeneity, such as staging systems, surgical techniques, surgical approach, adjuvant therapies, transfusion criteria, and supportive care, etc. Thus, the results should be explained with caution. Theoretically, a large-scale randomized clinical trial could avoid many of these limitations but would be very difficult to implement. In this situation, a randomized clinical trial would be unethical because it would be unacceptable to administer a transfusion without a clinical indication or to withhold transfusion from a patient who needed blood.

## 5. Conclusion

In conclusion, despite the quality of the evidence varied for different outcomes, our findings suggested that perioperative blood transfusion had an adverse effect on prognosis of HCC patients after radical hepatectomy, which might reduce the survival rate and disease-free survival, and increase postoperative complication rate. To promote long-term outcomes, surgeons should reduce bleeding during liver resection and avoid perioperative allogenic blood transfusion. Besides, the overall quality of the evidences was poor due to imprecision and risk of bias, which might weaken our confidence in these results. A prospective large-scale study, in which the confounding factors were strictly balanced, was needed.

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