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Should Cell Salvage Be Used in Liver Resection and Transplantation? A Systematic Review and Meta-analysis

Luckshi Rajendran, MD, MEd, Tori Lenet, MD,†‡ Risa Shorr, MLIS,§ Jad Abou Khalil, MDCM, MSc, FRCSC,† Kimberly A. Bertens, MD, MPH, FRCSC,† Fady K. Balaa, MD, MEd, FRCSC,† and Guillaume Martel, MD, MSc, FRCSC, FACS†‡✉*

Objective: To evaluate the effect of intraoperative blood cell salvage and autotransfusion (IBSA) use on red blood cell (RBC) transfusion and postoperative outcomes in liver surgery.

Background: Intraoperative RBC transfusions are common in liver surgery and associated with increased morbidity. IBSA can be utilized to minimize allogeneic transfusion. A theoretical risk of cancer dissemination has limited IBSA adoption in oncologic surgery.

Methods: Electronic databases were searched from inception until May 2021. All studies comparing IBSA use with control in liver surgery were included. Screening, data extraction, and risk of bias assessment were conducted independently, in duplicate. The primary outcome was intraoperative allogeneic RBC transfusion (proportion of patients and volume of blood transfused). Core secondary outcomes included: overall survival and disease-free survival, transfusion-related complications, length of hospital stay, and hospitalization costs. Data from transplant and resection studies were analyzed separately. Random effects models were used for meta-analysis.

Results: Twenty-one observational studies were included (16 transplant, 5 resection, n = 3433 patients). Seventeen studies incorporated oncologic indications. In transplant, IBSA was associated with decreased allogeneic RBC transfusion [mean difference –1.81, 95% confidence interval (−3.22, −0.40), $P = 0.01$, $I^2 = 86\%$, very-low certainty]. Few resection studies reported on transfusion for meta-analysis. No significant difference existed in overall survival or disease-free survival in liver transplant [hazard ratio (HR) = 1.12 (0.75, 1.68), $P = 0.59$, $I^2 = 0\%$; HR = 0.93 (0.57, 1.48), $P = 0.75$, $I^2 = 0\%$] and liver resection [HR = 0.69 (0.45, 1.05), $P = 0.08$, $I^2 = 0\%$; HR = 0.93 (0.59, 1.45), $P = 0.74$, $I^2 = 0\%$].

Conclusion: IBSA may reduce intraoperative allogeneic RBC transfusion without compromising oncologic outcomes. The current evidence base is limited in size and quality, and high-quality randomized controlled trials are needed.

Keywords: autotransfusion, blood conservation, cancer, cell salvage, hepatectomy, liver resection, transfusion

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From the *Division of General Surgery, University of Toronto, Toronto, ON, Canada; †Department of Surgery, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; ‡Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; and §Library Services, The Ottawa Hospital, Ottawa, ON, Canada.

✉gumartel@toh.ca.

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Liver surgery, including liver transplantation and resection, is technically challenging due to the complex and variable regional anatomy and rich hepatic blood supply.[1] There have been increasing use of restrictive blood transfusion strategies and improvements in surgical techniques over time. Despite this, intraoperative blood loss requiring allogeneic red blood cell (RBC) transfusion remain an important clinical consideration. Rates of perioperative allogeneic RBC transfusion are variable, but remain elevated in patients undergoing liver transplantation (50.5%–62.6%)[2,3] or resection (17%–23%).[4]

Although at times lifesaving, allogeneic RBC transfusions are associated with significant short- and long-term morbidity. Short-term complications are well described and include inadequate dosing, wrong product, and volume overload,[5] as well as a small risk of viral or bacterial transmission, and allergic or immune transfusion reactions.[6] Long-term complications include higher postoperative infection rates, prolonged hospital stay, higher rates of graft failure, and possibly more rapid cancer recurrence.[7–9] RBCs are also limited, altruistically donated, and expensive resources, costing on average USD$761 per unit.[10] Consequently, minimizing intraoperative blood loss and reducing allogeneic RBC transfusions are important considerations for hepatobiliary surgeons, and a priority recently highlighted by the World Health Organization (WHO) patient blood management strategy.[11]

Intraoperative blood cell salvage and autotransfusion (IBSA) has emerged as a cost-effective blood loss management strategy.[12] It is increasingly utilized in surgery, and has been shown to decrease allogeneic RBC transfusions by up to 40% in adult elective cardiac and orthopedic surgery.[13] IBSA systems collect blood from the operative field; this salvaged blood is then anticoagulated with heparinized saline or citrate, processed, and reinfused, salvaging ~60% to 80% of lost blood from surgery.[14,15]

IBSA adoption in oncologic surgery has been limited by concerns of reinfusion and dissemination of malignant cells, and potential implications on cancer-specific survival and recurrence.[13,16,17] More recently, observational studies have demonstrated that IBSA can be used in oncologic surgery to decrease transfusion requirements without worsening oncologic outcomes.[18–21] Furthermore, additional technologies including leukocyte depletion filters (LDF) can be incorporated with IBSA, potentially filtering out tumor cells from the salvaged blood during oncologic operations.[22]

Currently there is no consensus on the efficacy and safety of IBSA in liver surgery, and concerns about oncologic safety remain. Therefore, the objective of this work was to perform a systematic review and meta-analysis to define the impact of IBSA on intraoperative allogeneic RBC transfusion and postoperative outcomes in patients undergoing either liver resection or transplantation.

METHODS

A protocol was written and registered prospectively with the Prospective Register of Systematic Reviews (PROSPERO) (CRD42021231600). This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Table, Supplemental Digital Content 1, http://links.lww.com/SLA/E79).[23]

Search Strategy and Data Sources

A search strategy was designed in collaboration with a dedicated information specialist with experience developing search strategies for systematic reviews. The following databases were searched from inception until May 2021: EMBASE Classic +, Ovid MEDLINE, The Cochrane Central Register of Controlled Trials, and Transfusion Evidence Library.[24] References identified in relevant systematic reviews were screened for additional studies missed in the initial search. There were no language, date, or publication status restrictions. The search strategy is available in Document, Supplemental Digital Content 2, http://links.lww.com/SLA/E80.

Study Eligibility Criteria

The study population of interest included all patients undergoing liver surgery (either resection or transplantation) for any indication, including oncologic and nononcologic operations. Within this population, the implementation of any IBSA device, regardless of the addition of irradiation or LDF, and a corresponding comparator control arm (no IBSA use) was necessary for inclusion. The primary outcome was the proportion of patients receiving intraoperative allogeneic RBC transfusion, and the volume of intraoperative allogeneic RBC transfused. Secondary outcomes were prioritized into "core" secondary outcomes considered relevant to clinicians and patients in perioperative decision-making, emphasizing survival outcomes, perioperative complications, and resource utilization.[25,26] These core secondary outcomes included overall survival (OS), disease-free survival (DFS), transfusion-related complications, length of hospital stay, and hospitalization costs. Other secondary outcomes included transfusion of other blood products [fresh frozen plasma (FFP) and platelets], and postoperative hemoglobin. Randomized controlled trials (RCTs) and observational cohort studies reporting at least 1 outcome of interest were eligible for inclusion. Case reports, case series with fewer than ten patients, and studies with no control group were excluded.

Study Selection and Data Extraction

Titles and abstracts were screened, and the full text of eligible publications were examined both independently and in duplicate by 2 reviewers. Reasons for full-text exclusion were documented. Disagreements were resolved by consensus or in discussion with a senior reviewer (G.M.). Conference abstracts were included as part of the gray literature, in the absence of related full text, to avoid publication bias.[27] The snowballing technique was performed with manual review of the reference lists of included papers and relevant systematic reviews.[28]

Relevant data were extracted from included papers using a data extraction form (Table, Supplemental Digital Content 3, http://links.lww.com/SLA/E81). Data extraction was conducted independently and in duplicate. The data extraction form was piloted on five studies by the 2 reviewers, with modifications made to ensure complete and accurate data extraction and consensus in methodology.

The following study details and population demographic characteristics were extracted: study design, timeline, location, sample size, number in each intervention arm, use of adjustment techniques for baseline patient characteristics, age, presence of cirrhosis, Child-Pugh score, duration of follow-up, and average preoperative hemoglobin. Data on surgical indications, blood loss, cancer-specific variables (including number of lesions, size, tumor grade, differentiation, and vascular invasion), liver resection–specific variables (including number of major and minor resections and operative time), and liver transplant specific variables (including type of transplant, model of end stage liver disease score, and proportion transplanted within Milan criteria) were also extracted. Extracted outcome data included: proportion of patients receiving intraoperative autologous RBC transfusion, volume of autologous RBC transfusion (mL), proportion of patients exposed to allogeneic RBC transfusion, volume of allogeneic RBC transfusion (units or mL), postoperative hemoglobin (g/L), transfusion of other blood products (platelets, FFPin units or mL), postoperative complications, length of stay, hospital cost, OS, DFS, and disease recurrence.

Risk of Bias and Quality Assessment

Risk of bias was performed independently and in duplicate by 2 reviewers using the methodological index for non-randomized studies (MINORS) criteria.[29] on the basis of this instrument, each included study was assessed based on 12 items, and scored as 0 (if not reported), 1 (if reported but inadequate), or 2 (reported and adequate), with a maximum score of 24. Studies with a MINORS score of at least 17 were considered of high quality.[29] Disagreements were resolved by consensus or by the senior author (G.M.). No study was excluded based on risk of bias. The Grading of Recommendations Assessment Development and Evaluation (GRADE) tool was used to assess the certainty of the evidence based on the study design, risk of bias, inconsistency of evidence, precision, directness, and overall effect.[30]

Data Synthesis and Statistical Analysis

The unit of analysis was the individual study participant. Primary and secondary outcomes were pooled for the meta-analysis when appropriate. Both unadjusted and adjusted outcome data were extracted. When both unadjusted and adjusted data were available for a given outcome, adjusted data were preferentially used for meta-analysis. Sensitivity analyses of adjusted data were also performed when possible. Dichotomous variables were summarized using proportions or odds ratios with 95% confidence intervals (95% CI). Continuous variables were represented by the mean, standard deviation, median, range, and interquartile range, as well as mean differences (MDs) with 95% CI. Time-to-event variables were summarized by hazard ratios (HR) and 95% CI. Liver transplants and liver resections were analyzed separately. Only studies with malignant surgical indication were included in analysis for oncologic outcomes (OS and DFS). For all other outcomes, subgroup analysis of benign versus malignant surgical indication was planned a priori. Preplanned sensitivity analyses included analysis of adjusted data and studies at low risk of bias (MINORS score ≥ 17).

RBC and platelet transfusions reported as a volume (mL) were converted to units by dividing by 300.[31,32] FFP units reported as a volume were converted to units by dividing by 250.[33] Where appropriate, means and SD were estimated from medians and ranges or interquartile ranges using the method of Wan et al.[34] Where HRs were not reported, they were derived from Kaplan-Meier curves using the methods described by Tierney et al.[35] All meta-analyses were performed using Review Manager 5 (The Cochrane Collaboration, Oxford, United

Kingdom).[36] Random effects models were used to account for expected between-study differences in populations, study designs, and transfusion strategies. The I^2 statistic was used to estimate statistical heterogeneity. Categories of low (0%–25%), moderate (25%–50%), and substantial (50%–100%) were used to interpret the I^2 statistic. The threshold for interpretation was defined according to the Cochrane Handbook for Systematic Reviews of Interventions.[37] A P value of <0.05 was considered statistically significant.

RESULTS

A total of 2365 citations were screened. One study by Kwon et al[24] shared an overlapping patient population with Han et al,[38] and included only patients with advanced hepatocellular carcinoma (HCC) beyond transplant criteria. The former was excluded, whereas the latter was included. After full-text screening, 22 studies met eligibility criteria and were included in the review for data extraction (Fig. 1). Two studies, Fujimoto et al[39] and Hirano et al[40] included the same patient population, with the former reporting intraoperative blood loss, allogeneic and autologous transfusion, whereas the latter reported long-term survival outcomes. These results were collated and considered as a single study (Fujimoto/Hirano). This led to 21 unique patient populations for analysis.

Study Characteristics

A total of 3433 patients were included, with 8 studies having fewer than 100 patients.[41–48] Table 1 provides the characteristics of the included studies. All included studies were observational cohorts, with all except one being retrospective in nature.[45] Studies were conducted in heterogeneous patient populations. Eleven studies adjusted for confounding using multivariate analysis (n = 6)[16,44,49,53,54,56] propensity score matching (n = 3)[17,38,48] or simple matching (n = 2).[39,45] Sixteen studies included patients who underwent liver transplantation (2667 patients, 77.7%),[16,17,38,41–47,49–54] whereas 5 studies included patients undergoing hepatic resection (766 patients, 22.3%).[39,48,55–57]

All studies reported using IBSA technology for blood salvage. Twelve studies reported some return of the salvaged blood back to patients (Table 1).[16,17,38,42,45–47,50–54] Of these, 5 studies reported blood was returned back in only a proportion of the patients (32%–65%).[17,52–54,56] Four studies implied that all patients in the IBSA group were transfused with the salvaged blood, by receiving the continuous autotransfusion system or autotransfusion with LDF.[41,43,48,49] There was some variability in the intervention and control groups between studies; 1 study combined preoperative phlebotomy with IBSA in the intervention group.[39] In another study, the Pringle maneuver was utilized as an alternative blood conservation strategy in the control group.[55] Another study excluded all patients who received perioperative allogeneic RBC transfusion.[56]

The indication for IBSA use was recorded in fourteen studies (Table 1).[16,17,38,39,46–52,54–56] Two studies specifically excluded transplant patients with malignancy or sepsis from IBSA use.[46,50] Another 2 studies included patients with incidentally found HCC on explant pathology[16,17] or those who had known HCC, but excessive intraoperative blood loss.[16] One study included 5/39 (12.8%) patients in the IBSA group that were presumed to be tumor-free or who had treated HCC.[47] Four studies had center or contemporary time period differences between intervention groups.[39,48,51,52] In addition, 5 studies utilized LDF before autotransfusion.[38,43,48,49,51] One study also had 2 subgroups of patients with or without utilization of irradiation for salvaged blood, which were combined into the intervention cell salvage group for data extraction and analysis purposes.[47]

Given the limited availability of studies reporting primary and secondary outcomes, subgroup analysis was only possible

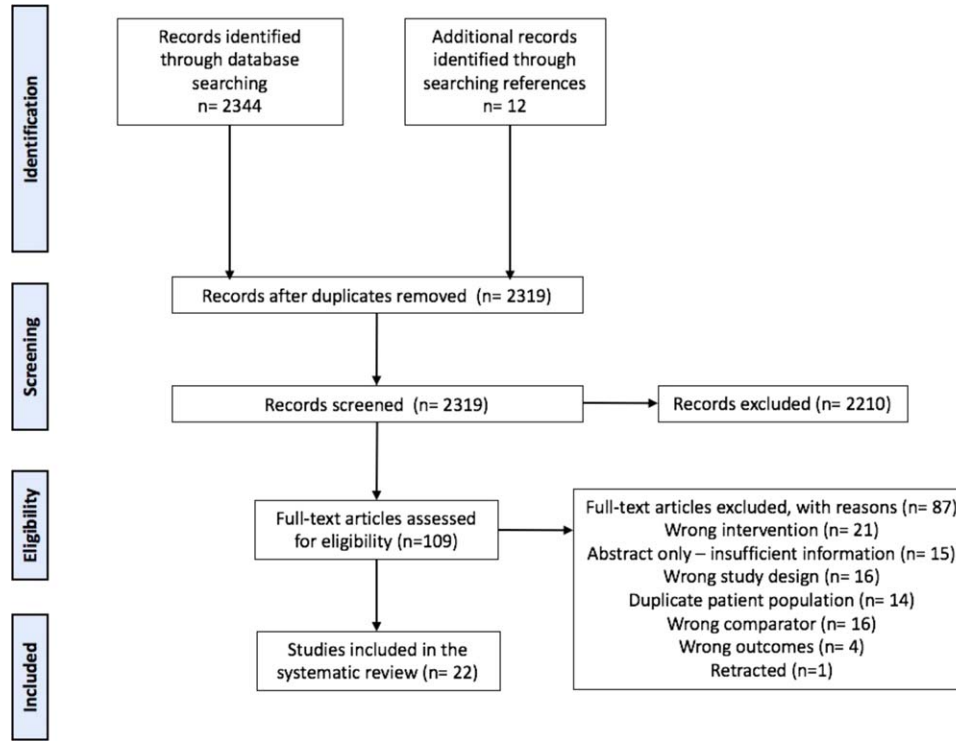

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA flow diagram of screened, included, and excluded studies.

TABLE 1. Study Characteristics of Liver Transplant and Liver Resection Populations

	References	Design	Adjustment	Surgical Indication	Intervention (% Autologous)	Control (% Autologous)	Cell Salvage Technology	IBSA Indications
Transplant	Akbulut et al[41]	Retrospective	None	HCC	Implied 100	0	Fresenius CATS	NS
	Araujo et al[49]	Retrospective	MV	1 degree hepatic malignancy	Implied 100	0	Fresenius CATS+LDF	Surgery/ anesthesia decision
	Brajtbord et al[42]	Retrospective	None	All	100	0	Haemonetics Cell Saver 3	NS
	Dos Reis et al[50]	Retrospective	None	All	100	0	Cell Saver	All, excluding malignancy, sepsis
	Foltys et al[16]	Retrospective	MV	HCC	100	0	Haemonetics Cell Saver 5	All, excluding malignancy, unless major blood loss/ incidental
	Gupta et al[43]	Retrospective	None	HCC	Implied 100	0	Autotransfusion + LDF	NS
	Han et al[38]	Retrospective	PSM	HCC	100	0	Haemonetics Cell Saver 5 +LDF	All, autologous transfusion based on hemoglobin
	Ivanics et al[17]	Retrospective	PSM	Cirrhosis	Proportion NS	0	Haemonetics Cell Saver 5	All, excluding malignancy; incl. incidental HCC
	Kim et al[51]	Retrospective	None	HCC	100	0	Haemonetics Cell Saver 5 +LDF	One center all IBSA (vs Control other center no IBSA)
	Lai et al[44]	Retrospective	MV	HCC	NS	0	NS	NS
	Massicotte et al[52]	Retrospective	None	All	Proportion NS	0	Fresenius CATS	All in period 2 (vs historic controls)
	Muscari et al[45]	Retrospective	Matched	HCC	100	0	Haemonetics Cell Saver 5	NS
	Pereira et al[53]	Retrospective	MV	All	Proportion NS	0	NS	NS
	Pinto et al[54]	Retrospective	MV	HCC	Proportion NS	0	Haemonetics Cell Saver Elite Autotransfusion	Blood loss > 1000 mL or hemodynamic instability
	Sankarankutty et al[46]	Retrospective	None	All	100	0	Haemonetics Cell Saver 5	All, excluding HCC and sepsis
	Weller et al[47]	Retrospective	None	HCC	100	0	Haemonetics Cell Saver 5, CATS ± irradiation	Anesthesiology decision, tumor-free /treated HCC (5 cases)
Resection	Fujimoto/ Hirano et al[39,40]	Retrospective cohort	Matched	HCC	100*	0	Haemonetics Cell Saver	All between 1988–1989 (vs Control 1986–1987)
	Jia et al[55]	Retrospective cohort	None	Benign disease	100	0; all pringle	Haemonetics blood apheresis system	< 1 L blood loss, tumor > 1 cm from large vessel; no malignancy
	Kang et al[56]	Retrospective cohort	MV	CRC metastases	Proportion NS autologous only	0*	Cell Saver	≥ 200 mL salvaged blood
	Perlmutter et al[57]	Retrospective cohort	None	CRC metastases	100	0	NS	NS
	Zacharias et al[48]	Retrospective cohort	PSM	All	Implied 100	0	Dideco Electa Essential Concept Cell Saver+LDF	All after January 2013 (vs Control 2007–2012)

*Preoperative phlebotomy and intraoperative cell salvage blood transfused.
**Excluded all autologous and allogeneic blood transfusion.
CATS indicates continuous autologous transfusion system; CRC, colorectal cancer; MV, multivariate; NS, not specified; PSM, propensity score matching.

TABLE 2. Transplant Patient Demographics

References	Intervention	N	Cirrhosis (%)	Child Score A/B/C (%)	MELD	Within Milan (%)	Oncologic (%)	Operative Time (min)	Preoperative Hgb	Blood Loss (L)
Akbulut et al[41]	IBSA	24	100	25/46/29	14.5 ± 0.9	33	100			
	Control	59	100	31/49/20	13.6 ± 0.8	37	100			
	Overall	83	100	29/48/23		36	100			
Araujo et al[49]	IBSA	122	85		10.5 [9–17]	100	100			
	Control	36	97		9 [8–13.5]	100	100			
	Overall	158	88		10 [8–15]	100	100			
Brajtbord et al[42]	IBSA	22								
	Control	22								
	Overall	44								
Dos Reis et al[50]	IBSA	345			31.3					
	Control	325			27.9					
	Overall	670			29.6 ± 9.4		31.6			
Foltys et al[16]	IBSA	40	93	30/18/52		60	100			
	Control	96	86	61/25/14		60	100			
	Overall	136	88	43/25/32*		60	100			
Gupta et al[43]	IBSA	43					100			
	Control	51					100			
	Overall	94					100			
Han et al[38]	IBSA	283			13 ± 6	60	100			
	Control	114			12 ± 7	62	100			
	Overall	397				61	100			
Ivanics et al[17]	IBSA	76	71	1/33/66	21 [17–25]		100	483 [420–570]	99.5 [87–112]	3.2 [2.0–5.5]
	Control	34	73	3/32/65	22.5 [20–27]		100	493 [411–546]	95.5 [82–109]	2.0 [0–4.0]
	Overall	110	72	2/33/66	22 [18–26]		100		99 [86–111]	2.0 [1.5–5.0]
Kim et al[51]	IBSA	121		4/38/58	18.4 ± 8.8	66	100		107 ± 20	1.4 ± 1.2
	Control	109		28/36/37	16.9 ± 6.8	77	100		112 ± 25	1.4 ± 2.7
	Overall	230		15/37/48*		71	100			*
Lai et al[44]	IBSA	10		50"/50			100			**
	Control	72		72"/28			100			
	Overall	82		69"/31			100			
Massicotte et al[52]	IBSA	75	68		17 ± 9		17	266 ± 68	108.5 ± 24.3	1.4 ± 0.6
	Control	75	64		17 ± 8		7	225 ± 57	105.7 ± 22.5	0.8 ± 0.3
	Overall	150	66		17 ± 9		12	*	107.0 ± 23.4	1.1 ± 0.6*
Muscari et al[45]	IBSA	31	100	58/22/18		58	100			
	Control	16	100	80/20/0		68	100			
	Overall	47	100	64/21/13		62	100			
Pereira et al[53]	IBSA	70								
	Control	148								
	Overall	218								
Pinto et al[54]	IBSA	122			13 ± 5		100			2.7 ± 2.0
	Control	34			12 ± 5		100			2.4 ± 2.0
	Overall	156			12 ± 5		100			2.6 ± 2.0
Sankarankutty et al[46]	IBSA	22		9/59/23	15.1 ± 5			603 ± 94		8.4 ± 4.0
	Control	19		16/53/16	14.9 ± 4.3			671 ± 117		10.8 ± 7.0
	Overall	41	85	12/56/20						
Weller et al[47]	IBSA	39					100	333 ± 110		
	Control	12					100	328 ± 93		
	Overall	51			16.4 ± 9.4		100		118 ± 24	

"Child score A & B (combined).
*Significant difference, $P < 0.05$.
**Significant difference for unadjusted data, $P < 0.05$.
Hgb indicates hemoglobin; MELD, Model of End Stage Liver Disease; N, number of patients.

for surgical indication (malignant vs benign) and risk of bias (high vs low) for certain outcomes. Other prespecified subgroup analyses were not possible.

Liver Transplant Population Characteristics

Of the sixteen studies of patients undergoing liver transplantation, 7 reported the proportion of patients with cirrhosis (68%–100% IBSA vs 64%–100% control)[16,17,41,45,46,49,52] (Table 2). Only 1 study reported a significant difference between the intervention groups, with a greater proportion of cirrhotic patients in the control group.[49] Two studies reported a significant difference in Child-Pugh scores, with greater proportion of Child-Pugh class C patients in the IBSA group.[16,51] Of the 6 studies that reported the proportion of patients within Milan criteria for transplantation, there was no significant differences between the intervention and control groups.[16,38,41,45,49,51] Similarly, there was no significant

differences between the 2 groups in model of end stage liver disease scores.[17,38,41,49–52,54]

Thirteen studies included patients who underwent transplantation for a known oncologic indication, or were found to have incidental malignancy on explant pathology (1774/2667 patients, 66.5%).[16,17,38,41,43–45,47,49–52,54] Of these studies, 924 patients were in the IBSA group, 638 patients in control group, and the grouping was not specified for the remaining 212 patients. Twelve of these studies included patients with HCC.[16,17,38,41,43,45,47,49–52,54] Five studies included only patients with a preoperative diagnosis of HCC within the IBSA and control groups.[38,45,47,49,54] One study included only patients with an incidental diagnosis of HCC on explant pathology.[17] Two studies included a mix of patients with either preoperative or incidentally diagnosed HCC.[16,41] The remainder of the 4 HCC-related liver transplant studies did not specify the timing of HCC diagnosis.[43,50–52]

Three studies reported a statistically significant difference in intraoperative blood loss between the IBSA and control groups.[44,51,52] One study reported significantly greater blood loss in the control group.[51] Two studies reported greater intraoperative blood loss in the IBSA group,[44,52] with 1 reporting a significantly longer operative time in the IBSA group.[52]

Liver Resection Population Characteristics

Of the 5 studies including patients undergoing liver resection (Table 3),[39,48,55–57] 1 study reported a significantly greater proportion of patients undergoing major liver resection (3 or more segments) and longer operative time in the IBSA group.[56] Two studies reported greater blood loss in the IBSA group compared with the control group.[55,56] Four of the 5 studies included patients who underwent liver resection and had an oncologic diagnosis (622/766 patients, 81.2%).[39,48,56,57] Of these studies, 155 patients were in the IBSA group, 169 were in the control group, and the grouping was not specified for the remaining 294 patients. One included patients with preoperatively diagnosed HCC in both cohorts,[39] and 2 included patients undergoing liver resection for colorectal liver metastases.[56,57] One study combined both benign and malignant indications within each population,[48] and another study included only patients who had resection for benign disease.[55]

Risk of Bias and Certainty Assessment

Risk of bias assessment for the included studies is presented in Figure 2. Overall, 5 studies were considered at high risk of bias (MINORS score <17),[44,46,51,53,55] with the remainder being at low risk of bias. Of the 21 studies, 1 had a reported but inadequately stated aim,[53] and 1 had an inadequate control group (use of Pringle manoeuvre).[55] Three studies compared intervention and control groups from different time periods.[40,48,52] All studies had appropriate endpoints; however, 2 studies did not have appropriate follow-up for their measured outcome of interest.[41,55] Fourteen studies either did not report or had >5% loss to follow-up.[16,17,38,39,43,44,46,47,49,51,54–57] Six studies had some degree of prospective data collection,[16,39,42,43,45,49] with the remainder having only retrospective data collection. Eleven studies reported equivalent baseline characteristics,[17,38,39,41–43,47,52,54,55,57] whereas eight studies had clinically significant differences in baseline characteristics between the intervention and control groups.[16,44,45,48–51,56] Two studies did not report baseline characteristics.[46,53] In addition, 2 studies did not report statistical analyses,[41,46] and 3 studies were considered to have inadequate statistical methods,[42,43,53] due to insufficient information and reporting only *P* values without associated effect sizes. The results of the GRADE assessment are presented in Supplemental Digital Content 4, http://links.lww.com/SLA/E82.

Primary Outcome—Intraoperative Allogeneic RBC Transfusion

Liver Transplantation

Of the 16 studies of patients undergoing liver transplantation, only 3 studies (867 patients) recorded the proportion of patients who underwent intraoperative allogeneic RBC transfusion,[45,50,52] ranging from 10% to 80% in the IBSA group compared with 21% to 98% in the control group. A statistically significant difference was reported in the matched population cohort of Muscari et al, with 3/31 (10%) patients in the IBSA group and 9/16 (56%) in the control receiving allogeneic RBC transfusion ($P = 0.0009$).[45] Massicotte et al[52] demonstrated no statistically significant difference in the number of patients receiving intraoperative allogeneic RBC transfusion between IBSA 14/75 (18.7%) and control 16/75 (21.3%) groups. Dos Reis et al[50] showed a greater proportion transfused in the IBSA group 248/345 (71.8%) versus 152/325 (46.7%) control, although no statistical test of significance was reported in either studies. Significant heterogeneity and the limited number of studies reporting this outcome precluded meta-analysis.

Eleven studies (1853 patients) reported the number of units of allogeneic packed RBCs transfused intraoperatively in the IBSA and control groups (Table 4).[16,17,42,45–47,50–54] Volumes of transfused allogeneic RBC varied widely between studies, from 0.4 to 12.3 units in the IBSA group versus 0.4 to 22.3 units in the control group. Five studies (1275 patients) demonstrated a significantly greater number of units of allogeneic RBCs transfused in the control group.[17,45,50,51,53] On meta-analysis of 10 studies (1125 patients; 568 IBSA, 557 control), patients in the IBSA group received significantly fewer allogeneic RBC units than those in the control (MD –1.81, 95% CI −3.22 to −0.40, $P = 0.01$, $I^2 = 86\%$, very-low certainty; Fig. 3a].[16,17,42,45–47,51–54] Subgroup analysis of 6 transplant studies all with an oncologic diagnosis (672 patients; 379 IBSA, 293 control) demonstrated no significant difference in allogeneic RBC transfusion volume between IBSA and control groups (MD −1.28, 95% CI −3.26 to 0.70, $P = 0.20$, $I^2 = 85\%$).[16,17,45,47,51,54] A sensitivity analysis of seven transplant studies at low risk of bias (636 patients) also showed no significant difference between groups (MD −0.54, 95% CI −1.65 to 0.58, $P = 0.34$, $I^2 = 77\%$).[16,17,42,45,47,52,54]

Liver Resection

Of the 5 studies that included patients who underwent liver resection, 2 studies (168 patients) reported the proportion of patients transfused with allogeneic blood.[39,48] Zacharias et al[48] performed a matched cohort study of 64 patients and demonstrated a significantly lower proportion of patients in the IBSA group receiving allogeneic blood (28% IBSA vs 72% control; $P < 0.001$). Fujimoto et al[39] (104 patients) showed a greater proportion of patients transfused with allogeneic RBC in control group (79.6% IBSA vs 98% control, $P < 0.05$). This was also the only study that recorded the average quantity of allogeneic RBC units transfused intraoperatively (Table 4), demonstrating a significantly lower allogeneic RBC transfusion volume in the IBSA group (2.71 ± 1.32 IBSA vs 11.55 ± 6 control; $P < 0.05$).[39]

Core Secondary Outcomes

Meta-analysis of 5 studies (601 patients with oncologic diagnosis; 387 IBSA, 214 control) conducted in the liver transplant population demonstrated no significant difference in OS

TABLE 3. Resection Patient Demographics

References	Intervention	N	Cirrhosis (%)	Child Score A/B/C (%)	Major Resection (>3 segments)	Oncologic (%)	Operative Time (min)	Preoperative Hgb	Blood Loss (L)
Fujimoto/ Hirano et al[39,40]	IBSA	54	69			100			1.7 ± 0.7
	Control	50	70			100			1.8 ± 0.8
	Overall	104	69			100			
Jia et al[55]	IBSA	68		90/10/0		0	102 ± 18	126 ± 12	0.8 ± 0.1
	Control	57		91/9/0		0	90 ± 24	129 ± 11	0.2 ± 0.07
	Overall	125		90/10/0		0			*
Kang et al[56]	IBSA	74			21 (28.4)	100	284.7 ± 77.8		0.9 ± 0.5
	Control	73			5 (6.9)	100	219.2 ± 80.8		0.3 ± 0.3
	Overall	147			*	100	*		*
Perlmutter et al[57]	IBSA								
	Control								
	Overall	294				100			
Zacharias et al[48]	IBSA	41			21/32 (66)**	66	238 ± 65**	132 ± 22**	1.1 ± 0.8**
	Control	55			21/32 (66)**	84	284 ± 75**	131 ± 22**	.08 ± 0.5**
	Overall	96			42/64 (66)**	80	*		0.99 ± 0.7**

*Significant difference, $P < 0.05$
**After propensity score matching
Hgb indicates hemoglobin; N, number of patients.

(HR 1.12, 95% CI 0.75–1.68, $P = 0.59$, $I^2 = 0\%$, low certainty) (Fig. 3b).[17,41,43,49,54] All of these studies had low risk of bias. Meta-analysis of 5 studies (763 patients with oncologic diagnosis; 429 IBSA, 334 control) also showed no significant difference in DFS (HR 0.93, 95% CI 0.57–1.48, $P = 0.75$, $I^2 = 0\%$, low certainty) (Fig. 3c).[16,41,49,51,54]

Meta-analysis of 2 studies (251 patients with oncologic diagnosis; 128 IBSA, 123 control) conducted in the liver resection population showed no significant difference in OS (HR 0.69, 95% CI 0.45–1.05, $P = 0.08$, $I^2 = 0\%$, low certainty) (Fig. 4a).[39,56] Meta-analysis of 2 studies (441 patients with oncologic diagnosis; 74 IBSA, 73 control, 294 not specified) also showed no significant difference in DFS (HR 0.93, 95% CI 0.59–1.45, $P = 0.74$, $I^2 = 0\%$, low certainty) (Fig. 4b).[56,57]

One study (230 patients) showed significantly fewer infectious complications in the IBSA group (57.9% vs 74.3%,

		Clearly stated aim	Consecutive patients	Prospective data collection	Appropriate endpoints	Unbiased outcome assessment	Appropriate follow-up	<5% loss to follow-up	Adquate control group	Contemporary groups	Baseline equivalence of groups	Sample size calculation	Adequate statistical analysis	MINORS score
Transplant	Akbulut 2013	2	2	1	2	0	1	2	2	2	2	2	0	18
	Araujo 2016	2	2	2	2	0	2	0	2	2	1	0	2	17
	Brajtbord 1989	2	2	2	2	0	2	2	2	2	2	0	1	19
	DosReis 2017	2	2	1	2	0	2	2	2	2	1	0	2	18
	Foltys 2011	2	2	2	2	0	2	0	2	2	1	0	2	17
	Gupta 2016	2	2	2	2	0	2	0	2	2	2	0	1	17
	Han 2016	2	2	1	2	0	2	0	2	2	2	1	2	18
	Ivanics 2021	2	2	1	2	0	2	0	2	2	2	0	2	17
	Kim 2013	2	2	1	2	0	2	0	2	2	1	0	2	16
	Lai 2019	2	2	1	2	0	2	0	2	2	1	0	2	16
	Massicotte 2007	2	2	1	2	0	2	2	2	1	2	1	2	19
	Muscari 2005	2	2	2	2	0	2	2	2	2	1	0	2	19
	Pereira 2012	1	2	1	2	0	2	2	2	2	0	0	1	15
	Pinto 2021	2	2	1	2	0	2	1	2	2	2	2	2	20
	Sankarankutty 2006	2	2	1	2	0	2	1	2	2	0	0	0	14
	Weller 2021	2	2	1	2	0	2	0	2	2	2	0	2	17
Resection	Fujimoto/Hirano 1993/2005	2	2	2	2	0	2	1	2	1	2	0	2	18
	Jia 2019	2	2	1	2	0	1	0	1	2	2	0	2	15
	Kang 2019	2	2	1	2	0	2	0	2	2	1	1	2	17
	Perlmutter 2020	2	2	1	2	0	2	0	2	2	2	0	2	17
	Zacharias 2018	2	2	1	2	0	2	2	2	1	1	0	2	17

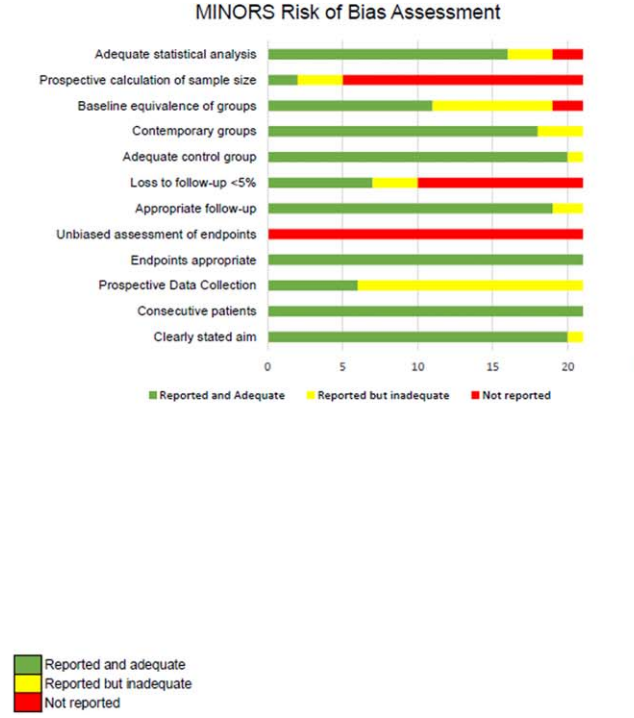

FIGURE 2. Methodological Index for Nonrandomized Studies (MINORS) risk of bias assessment scores compiled from each included study.

TABLE 4. Outcomes

		Intraoperative Allogeneic RBC Units Transfused (Mean ± SD)			Overall Survival [HR (95% CI)]		Disease-free Survival [HR (95% CI)]		
	Study	IBSA	Control	*P*	IBSA Versus Control	*P*	IBSA Versuss Control	*P*	Follow-up (IBSA/Control) (mo)
Transplant	Akbulut et al[41]				1.3 [0.51–3.27]	0.6	1.24 [0.37–4.19]	0.9	25.8 ± 15.1/17.9 ± 12.8
	Araujo et al[49]				1.56 [0.74–3.28]**	0.24	0.59 [0.09–3.72]	0.953	Median 25/32
	Brajtbord et al[42]	9.7 ± 9.6	13.4 ± 16.9	> 0.05					
	Dos Reis et al[50]	2.4	3.39	< 0.001					
	Foltys et al[16]	10.5 ± 4.6	14 ± 7.64	0.043			2.65 [0.58–12.15]	0.286	Median 37.7/28.8
	Gupta et al[43]				0.5 [0.02–14.46]	0.75		0.546	1-yr survival*
	Han et al*[38]								
	Ivanics et al*[17]	3.67 ± 3.14	6.67 ± 4.71	0.007	1.26 [0.52–3.05]	0.61			Median 68.4/70.8
	Kim et al[51]	3.7 ± 3.6	9.9 ± 17.9	< 0.001			0.75 [0.32–1.72]	0.314	Median 53/33
	Lai et al[44]								
	Massicotte et al[52]	0.4 ± 1.2	0.4 ± 0.9						
	Muscari et al*[45]	12.25 ± 8.25	7.75 ± 3.67	0.005					
	Pereira et al[53]	3.3 ± 6.1	9.4 ± 14.1	< 0.001					
	Pinto et al[54]	1.8 ± 2.8	2 ± 2.2		0.7 [0.33–1.47]**	0.203	0.8 [0.36–1.79]	0.74	45 ± 33/55 ± 51
	Sankarankutty et al[46]	9.6 ± 8	22.3 ± 21						
	Weller et al[47]	2.47 ± 2.48	2 ± 2						
Resection	Fujimoto/ Hirano* et al[39,40]	2.71 ± 1.32	11.55 ± 6.04	0.05	0.79 [0.45–1.39]	< 0.05			Up to 10-yr postoperative*
	Jia et al[55]								
	Kang et al[56]				0.58 [0.31–1.11]**		0.95 [0.54–1.65]**		Median 59/54
	Perlmutter et al[57]						0.89 [0.43–1.86]	0.76	
	Zacharias et al*[48]								

*Matched data presented preferentially where available.
**Adjusted data presented preferentially where available.

$P = 0.012$),[51] whereas 2 studies (281 patients) showed no significant difference.[54,55] The average length of hospital stay ranged widely from 5.8 to 35 days IBSA versus 7.7 to 33 days control. One study (125 patients) demonstrated significantly shorter length of stay in the IBSA group (5.8 ± 1.6 d IBSA vs 7.7 ± 2.1 d control, $P < 0.05$) and lower average costs (55,400 ± 15,400 CAD IBSA vs 66,700 ± 21,600 CAD control, $P < 0.05$).[55] Three other studies (303 patients) showed no difference in length of stay.[41,48,54]

Other Secondary Outcomes

On meta-analysis of seven studies (767 patients; 318 IBSA, 449 control), there was no significant difference in the average FFP units transfused (MD −1.88, 95% CI −6.33 to 2.56, $P = 0.41$, $I^2 = 85\%$, very-low certainty) (Figure, Supplemental Digital Content 5a, http://links.lww.com/SLA/E83).[16,42,45–47,51,53] Meta-analysis of 6 studies (669 patients; 424 IBSA, 245 control) showed no significant difference in the average platelet units transfused (MD 0.02, 95% CI −0.25 to 0.30, $P = 0.87$, $I^2 = 0\%$, very-low certainty) (Figure, Supplemental Digital Content 5b, http://links.lww.com/SLA/E83).[17,38,42,46,47,53] One study (150 patients) demonstrated significantly higher postoperative hemoglobin in the IBSA group (93.8 ± 19.3 g/L IBSA vs 85.2 ± 17.8 g/L control, $P < 0.0001$),[52] whereas 2 other studies (176 patients) showed no significant difference.[47,55]

DISCUSSION

This review identified 21 unique studies (3433 patients) comparing IBSA use with control (no IBSA use) during liver surgery. Despite significant heterogeneity, most studies reported lower rates and volumes of intraoperative allogeneic RBC transfusion in patients undergoing IBSA. In addition, there was no significant difference in OS or DFS between the groups among patients undergoing surgery for an oncologic indication.

The efficacy and safety of cell salvage use has been well established in other surgical domains. One previous Cochrane review of 75 RCTs similarly showed that use of IBSA minimized need for allogeneic RBC transfusion by 38% in elective cardiac and orthopedic surgery, without negatively impacting patient outcomes.[13] Meybohm et al[58] recently performed a Cochrane review of prospective RCTs that specifically used washed cell salvage within all fields of surgery, though predominantly consisting of orthopedic, cardiac, and vascular surgeries. Their study also showed that IBSA use reduces exposure to allogenic RBC transfusion up to 39% (relative risk [RR] = 0.61, 95% CI 0.57–0.65, $P < 0.001$, $I^2 = 87\%$), saving 0.20 units on average per patient.[58] Furthermore, they showed significantly lower infection rates and length of stay in the IBSA group, and no differences in mortality. Although we are unable to draw strong conclusions from the currently available observational studies in liver surgery, our systematic review and meta-analysis suggests that IBSA use decreases exposure to allogeneic RBC transfusion, without compromising postoperative and oncologic outcomes in patients undergoing liver transplantation or resection for any indication.

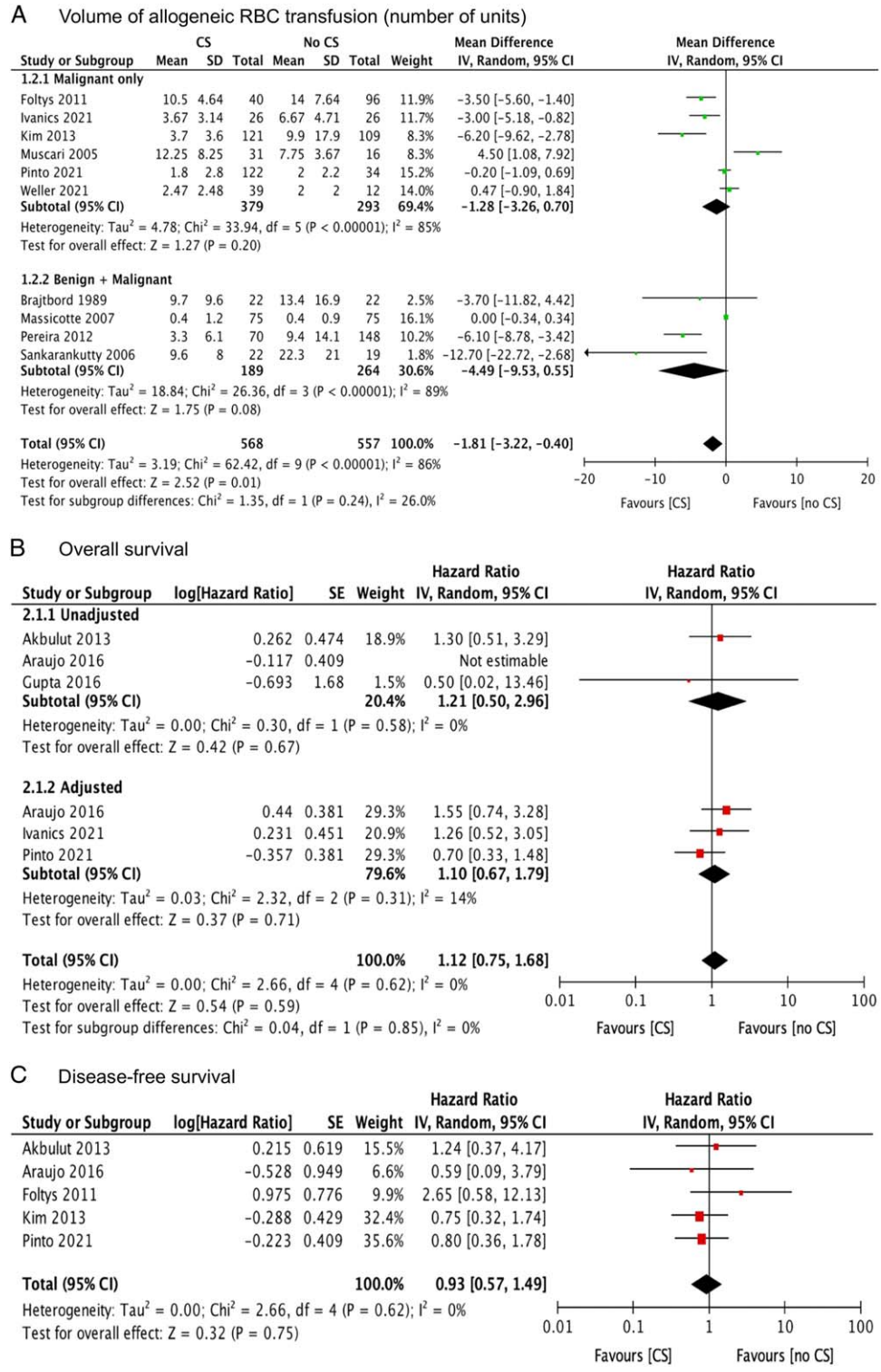

FIGURE 3. A series of forest plot generated from included liver transplant studies for various reported outcomes comparing cell saver (CS) or IBSA use and control (no CS), presented as hazard ratios, with weighted mean difference (IV) and 95% confidence interval (CI). A, Forest plot for all studies that reported volume of intraoperative allogeneic RBC transfused (number of units), with further subgroup analysis of studies including malignancy only indications for transplant (1.2.1) and studies including a mix of benign and malignant indications for transplant (1.2.2). B, Forest plot for all studies that reported overall survival with further subgroup analysis of studies with unadjusted data (2.1.1) and data adjusted with either multivariate analysis or propensity score matching (2.1.2). C, Forest plot for all studies that reported disease-free survival.

IBSA use was highlighted as a key component in the World Health Organization 2010 Patient Blood Management initiative to optimize and reduce use of blood transfusions towards improving patient morbidity and mortality.[11] Although IBSA technology is an important research priority, its clinical adoption has been limited secondary to concerns of dissemination of malignant cells in oncologic surgeries and worse cancer-specific survival and recurrence,[13,16,17] as well as the associated notable costs of using IBSA technology.

Various IBSA technology exists, many which were incorporated within our study. LDFs are commonly used adjuncts, applied to collected autologous blood.[59] LDFs minimize the

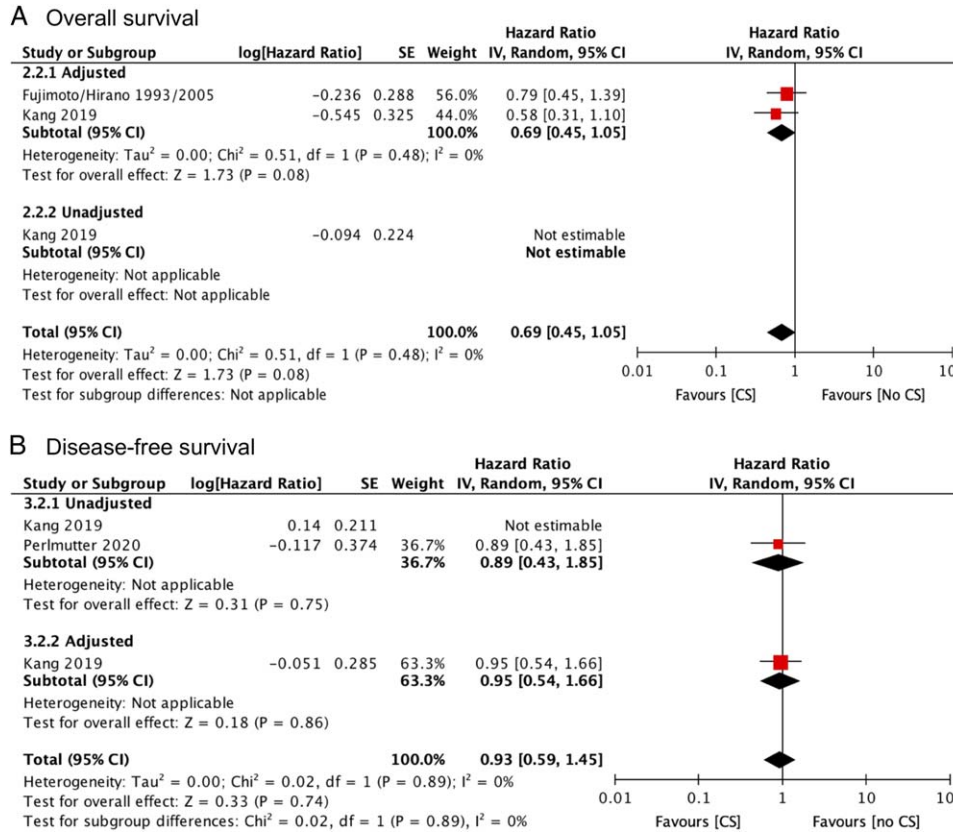

FIGURE 4. A series of forest plot generated from included liver transplant studies for various reported outcomes comparing cell saver (CS) or IBSA use and control (no CS), presented as hazard ratios, with weighted mean difference (IV) and 95% confidence interval (CI). A, Forest plot for all studies that reported overall survival with further subgroup analysis of 2 studies with data adjusted with either multivariate analysis or matching (2.2.1) and 1 study with unadjusted data. B, Forest plot for all studies that reported disease-free survival with subgroup analysis of 2 studies with unadjusted data (3.2.1) and 1 study with multivariate adjusted data.

reinfusion of activated leukocytes and inflammatory mediators,[60] and potentially removes some tumor cells from the salvaged blood.[22,61] Consequently, this theoretically decreases the risk of tumor recurrence.[51] However, some studies propose that not all nucleated cells are removed, and a potential for tumor cell reinfusion may persist.[62,63] Five studies in this review used cell salvage technology combined with LDF, and all included patients underwent either transplantation or resection in patients with an oncologic diagnosis.[38,43,48,49,51] The other sixteen studies either did not incorporate LDF or did not report its use. Similarly, irradiation of autologous blood is another potential adjunctive methodology that can remove viable tumor cells.[47] It also can lead to delayed reinfusion of the autologous blood, which can consequently influence allogeneic transfusion requirements and survival outcomes. The inclusion of various technologies within these studies increased clinical heterogeneity between-study interventions, thus limiting the ability of meta-analysis to accurately analyze the overall effects of IBSA use in liver surgery.

From a health economics perspective, allogeneic blood transfusion is limited by availability of altruistically donated blood, and the financial burden of high processing, storage, and administration costs.[10,64,65] Although usage and setup of IBSA devices have notable associated costs, multiple studies have demonstrated considerable cost benefits from IBSA given the associated reduction of allogeneic RBC transfusions in the setting of high blood loss and transfusion risk.[12,66–68] Lemke et al[12] performed a cost decision-analysis model at a tertiary high-volume hepatobiliary center, which demonstrated that routine use of IBSA for hepatic resections was cost minimizing. They recommended that for optimal cost benefit and resource utilization, a preoperative risk assessment should be performed to predict blood transfusion risk, with implementation of IBSA when expected risk exceeds 25%.[12] Similarly, Klein et al recommended IBSA use in all operations with potential for over 500 mL of intraoperative blood loss.[66] As both liver resection and transplantation continue to carry a high but variable risk of intraoperative blood loss and transfusion, the implementation of IBSA, informed by individual preoperative patient bleeding and transfusion risks, should be considered.

This review had several limitations. Firstly, there was significant heterogeneity in study designs, which limits the conclusions that can be drawn from data meta-analysis. Variability existed in patient eligibility for the intervention and control groups, and most studies provided limited information regarding factors for patient selection. For instance, all patients in the intervention cohort utilized an intraoperative blood salvage device, but not all patients subsequently receive autotransfusion (ie, return of this salvaged blood). In addition, there is variation between studies in reporting the proportion of patients and volume of autologous blood transfused in the IBSA group, as well as variations in reporting of adjuvant cell salvage technology such as LDF and irradiation. This difference in classification methodology likely biased the results of the meta-analysis. Specifically, for the outcome of intraoperative allogeneic RBC transfusion, studies that included only patients who received autotransfusion of salvaged blood in the intervention group may have selected for patients with either higher intraoperative blood loss or bleeding risk. These patients would also be more likely to require allogeneic blood transfusions, which may have biased the effect towards the null. Furthermore, 1 study excluded patients who received allogeneic transfusion from their study cohort.[56] This likely selected for patients in the control group that had better prognosis (ie, less

advanced disease or less complicated operations), as patients requiring transfusion in the intervention group would have received autologous RBC transfusion. This biases the survival outcomes away from the null. Future trials using the intention to treat principle would produce a more realistic representation of the clinical value of IBSA.

The indications for surgery (either resection or transplantation) and indications for IBSA use were also variable between studies. One study included only patients with incidentally found HCC on liver explants,[17] whereas another study included some patients who were assumed to be tumor-free/treated HCC in the IBSA group.[47] Patients in these cohorts likely had smaller, less advanced cancers that were less likely to recur or affect OS. Furthermore, despite pooling all available existing studies, the number of total patients included in the group with an oncologic diagnosis was small. Statistical power depends on the survival and recurrence rates of the respective cancers. The 5-year survival after resection of colorectal liver metastases is dependent on multiple factors including the primary tumor stage and surgical technique, ranging from 16% to 74%.[69] The 5-year post-transplant survival for HCC ranges from 70% to 87%.[70] It is likely that any meta-analyses including multiple malignancies and tumor stages are likely to be underpowered to detect significant differences in oncologic outcomes.

Selection likely biased individual study results, particularly among studies that did not use adjustment techniques. Surgeons may have been more likely to use IBSA in patients at higher risk of bleeding.[67] This phenomenon is evident when assessing the baseline imbalances between study groups. For example, IBSA studies often reported greater surgical blood loss, longer operative time, or a greater proportion of patients with advanced liver cirrhosis. Although some studies attempted to account for these baseline indifferences using multivariable adjustment or matched cohort, the potential for residual confounding remains high. However, this emphasizes the benefit of IBSA use, as a significant reduction in allogeneic blood transfusion was demonstrated despite IBSA being preferentially used in operations involving greater blood loss.

Furthermore, statistical heterogeneity for the primary outcome (allogeneic intraoperative RBC transfusion) was high, and could not be explained by subgroup analysis. Mean allogeneic RBC transfusion requirements varied greatly between the 2 groups (0.4–12.25 units/person IBSA vs 0.4–13.4 units/person control). The observed statistical heterogeneity likely reflects differences in international and temporal transfusion practices, incorporation of additional blood conservation strategies into some study designs, and methodological differences between studies. There are also significant differences between liver resection and liver transplantation in terms of potential for blood loss, complexity of the operation, and risk of postoperative morbidity and mortality. Previous studies have also demonstrated that rates of blood loss and blood product transfusion, particularly in liver transplantation, can be quite variable, ranging from a median of 2 to 13 RBC units/person.[71,72]

Finally, all included studies were observational, with all but one being of retrospective design. One driver for the lack of clinical trials is related to safety concerns of IBSA use in oncologic surgery, due to the theoretical risk of disseminating malignant cells, resulting in metastasis, recurrence, and poor cancer-specific survival.[13,16,17] Our review and other publications have not found any significant difference in cancer-related outcomes between patients who did and did not receive IBSA in oncologic liver surgery.[73–75] However, majority of the existing literature and oncologic studies included within our review examines HCC. Data are limited on the oncologic safety of IBSA use in liver surgery for malignancies beyond HCC, such as colorectal liver metastasis or cholangiocarcinoma, which may have significantly greater circulating tumor burden compared with early-stage HCC. This limits our ability to draw conclusions for IBSA use in all liver-related oncologic surgery, and consequently more studies in this populations are needed. These findings highlight the lack of existing high-quality evidence, and the need for adequately powered clinical trials to assess the efficacy and safety of IBSA use in liver surgery, particularly given the significant cost benefit associated with the use of IBSA in routine practice.

CONCLUSION

This systematic review suggests that IBSA use may reduce intraoperative allogeneic RBC transfusion requirements in liver resection and transplantation, without evidence of worse OS or DFS in oncology patients. Adequately powered RCTs are needed, given the low degree of certainty of these conclusions, and the high risk for residual confounding among included observational studies.

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