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ORIGINAL ARTICLE

Safety of intra-operative blood salvage during liver transplantation in patients with hepatocellular carcinoma, a propensity score-matched survival analysis

Oana Anisa Nutu[1], Dimitri Sneiders[2], Darius Mirza[1], John Isaac[1], M. Thamara P. R. Perera[1] & Hermien Hartog[1]

1 The Liver Unit, Queen Elizabeth Hospital, Birmingham, UK
2 Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC Transplant Institute, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands

Correspondence
Hermien Hartog, MD PhD FEBS, The Liver Unit, Queen Elizabeth Hospital, Mindelsohn Way, Birmingham B15 2GW, UK.
Tel.: 0044 12137 14064;
fax: 0044 121141 1804;
e-mail: hermien.hartog@uhb.nhs.uk

*Both authors contributed equally and should be considered first author.

SUMMARY

Intra-operative blood salvage (IBS) reduces the use of allogeneic blood transfusion. However, safety of IBS during liver transplantation (LT) for hepatocellular carcinoma (HCC) is questioned due to fear for dissemination of circulating malignant cells. This study aims to assess safety of IBS. HCC patients who underwent LT from January 2006 through December 2019 were included. Patients in whom IBS was used were propensity score matched (1:1) to control patients. Disease-free survival and time to HCC recurrence were assessed with Cox regression models and competing risk models. IBS was used in 192/378 HCC LT recipients, and 127 patients were propensity score matched. Cumulative disease-free survival at 12 and 60 months was 85% and 63% for the IBS group versus 90% and 68% for the no-IBS group. Use of IBS was not associated with impaired disease-free survival (HR 1.07, 95%CI: 0.65–1.76, $P = 0.800$) nor with increased HCC recurrence (Cause-specific cox model: HR 0.79, 95%CI: 0.36–1.73, $P = 0.549$, Fine and Gray model: HR: 0.79, 95%CI 0.40–1.57, $P = 0.50$). In conclusion, IBS during LT did not increase the risk for HCC recurrence. IBS is a safe procedure in HCC LT recipients to reduce the need for allogenic blood transfusion.

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Key words
hepatocellular carcinoma, intraoperative blood salvage, liver transplantation, recurrence, survival

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Introduction

Intra-operative blood salvage (IBS) is a technique that uses autologous blood transfusion and is a widely used strategy during surgery with potential massive blood loss in order to decrease use of allogenic blood transfusion. The mechanism relies on retrieving autologous blood through suction in the operating field, followed by a process of filtration and finally reinfusion [1,2].

Despite extensive use of the IBS during major abdominal surgery and liver transplantation for non-malignant disease, use of IBS remains controversial during liver transplantation in hepatocellular carcinoma (HCC) patients [3]. A major objection to use IBS in this situation is the underlying assumption that this may contribute to the dissemination of malignant cells [4].

Allogenic blood transfusion for blood loss during major surgery is essential but is nonetheless associated

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with risks. Massive allogeneic transfusion may lead to a phenomenon called transfusion-related immune modulation (TRIM) leading to increased risks of perioperative infection or tumor recurrence [5]. In contrast, IBS may help in the prevention of such immunological reactions, addressing defense mechanism with the help of the natural killer cells. *In vitro* models showed increased production of cytokines with the use of IBS, which promote downregulation of the immune system, improve overall immunocompetence, and may reduce the risk of infection and recurrence following transfusions [5,6].

Several studies have proven the safety of IBS in different types of malignancies, but only a few of them have evaluated the use in liver transplantation for HCC [7,8]. The aim of this study is to evaluate the safety of IBS in a long-term survival basis using a large propensity score-matched cohort from a single center. The main objective of the study is to assess the HCC recurrence and the long-term survival comparing patients who received IBS and those who did not.

Methods

This study was conducted according to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) recommendations for observational studies [9].

Study design

The prospectively maintained liver transplantation database of the Queen Elizabeth hospital Birmingham was retrospectively reviewed. All adult (>18 years) patients diagnosed with HCC undergoing orthotopic liver transplantation between January 2006 and December 2019 with a minimum follow-up of 12 months were eligible for inclusion. All cases of whom survival data were unavailable were considered non-informative and were therefore excluded. Patients who had only incidental HCC findings on pathological examination and patients receiving living donor liver transplantation were excluded. Patients who received intra-operative blood salvage were compared with patients who did not receive intra-operative blood salvage. Propensity score matching (1:1) was performed to ensure balanced groups. The primary outcome was defined as disease-free survival, defined as survival time until either recurrence of HCC or patient mortality. Secondary outcomes comprised time to patient mortality and time to HCC recurrence.

Data collection

Relevant donor, recipient, and outcome data were extracted from the prospective database, and additional relevant data were extracted from the patient records retrospectively. Relevant recipient data included the following: age, BMI (kg/m^2), sex, number of allogenic blood transfusion units, intra-operative blood salvage (ml), primary liver disease (alcohol related, HCV, HBV, PBC, and other), pre-liver transplantation loco-regional therapies, number of viable tumors, cumulative viable tumor size, differentiation (complete necrosis, well differentiated, moderately differentiated, or poorly differentiated), presence of satellite nodules, microvascular invasion, and macrovascular invasion. Included donor variables comprised donation after cardiac death (DCD), donation after brain death (DBD), and donor risk index. Outcomes included time to HCC recurrence and time to patient mortality.

Statistical analysis

Statistical analysis was performed with R-studio (R-version 4.0, © 2009–2020 R-studio, Inc.). Discrete variables were presented as absolute numbers with percentages (%). Continuous variables were presented as mean and standard deviation (SD). Discrete variables were statistically compared with the chi-square test, and continuous variables were compared either with the Student's –t-test or Mann–Whitney U test as appropriate. In the matched sample, discrete variables were compared with the Mcnemar–Bowker test, and continuous variables were compared with the Wilcoxon signed rank test. Two groups were identified: patients who had received IBS during liver transplantation (IBS group) and those who had not (no-IBS group). First, the proportion of missing data for each variable was assessed (Table S1). The percentage of missing data was low and was considered missing at random, as missing data were unlikely to be related to either use of IBS or post-transplantation HCC recurrence or mortality. Therefore, multiple imputations were used to maximize use of available data for propensity score matching. All variables of interest were included in the imputation model, and outcome data were only included as predictor, but not imputed. Continuous variables were imputed according to the predictive mean matching method, discrete variables with use of logistic regression, or multinominal logistic regression. In total, 10 imputations for each missing observation were performed. Subsequently, propensity scores were calculated with use of logistic regression, and

Transplant International 2021; 34: 2887–2894

variables included in the model are summarized in Table 1. The propensity scores from the imputed datasets were pooled, and the mean propensity score was added to the original dataset. Patients in the IBS group were matched (1:1) to patients in the no-IBS group based on the propensity score (caliper 0.1). Three natural splines were fitted on the variables BMI and number of viable tumors. To assess the balance of the matched sample, baseline variables were compared after matching with standardized mean differences (SMD <0.1). Survival was assessed with the use of Kaplan–Meier plots and compared with a log-rank test. For the propensity score-matched sample, univariable (cause-specific) cox regression with strata for matched pairs was performed. Additionally, competing risk regression (Fine and Gray model) was performed. The proportional hazard assumption was assessed with use of Schonefeld residuals plots. To assess non-linear effect of continuous variables, splines were fitted and compared to models without splines. To assess potential dose–effect relation of IBS, the volume of IBS was fitted as continuous variable with natural cubic splines in separate models; additionally, categories of increasing IBS volume were fitted in separate models. Disease-free survival and time to HCC recurrence were additionally studied with use of multivariable cox regression on unmatched data. Additionally, multivariable competing risk regression (Fine and Gray model) was performed. Variables included in multivariable cox regression were defined in advance of the analysis and included: cumulative viable tumor size, macrovascular invasion, microvascular invasion, satellite nodules, and use of IBS. For illustrative purposes, cumulative survival proportions at 12, 36, and 60 months post-transplantation were extracted from life tables. A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

Data on 192 patients who had received IBS and 185 patients who had not were available, and mean follow-up was 78 ± 46 months and 65 ± 32 months for the no-

Table 1. Characteristics of the propensity score-matched and -unmatched samples.

	Unmatched				Propensity score matched			
	no IBS	IBS	SMD	*P*	no IBS	IBS	SMD	*P*
n	186	192			127	127		
Age	58.35 (7.74)	59.22 (7.31)	0.115	0.278	58.76 (6.78)	59.29 (7.89)	0.072	0.471
BMI (kg/m^2)	27.85 (4.79)	29.23 (4.95)	0.284	0.009	28.27 (4.71)	28.86 (5.29)	0.117	0.156
Primary liver disease								
Alcohol related liver disease	43 (23.1)	50 (26)	0.067	0.016	31 (24.4)	30 (23.6)	0.018	0.986
Other	24 (12.9)	13 (6.8)	0.244		13 (10.2)	11 (8.7)	0.063	
NASH	9 (4.8)	26 (13.5)	0.254		8 (6.3)	9 (7.1)	0.023	
HCV/HBV	101 (54.3)	95 (49.5)	0.096		71 (55.9)	72 (56.7)	0.016	
PBC	9 (4.8)	8 (4.2)	0.034		4 (3.1)	5 (3.9)	0.039	
Loco-regional therapy	105 (58)	88 (45.8)	0.246	0.019	64 (51.6)	66 (52)	0.007	1
Number of viable tumours	1.86 (2.11)	1.84 (1.68)	0.012	0.612	1.69 (1.46)	1.72 (1.59)	0.022	0.995
Cumulative viable tumour size	3.9 (3.28)	3.55 (3.2)	0.107	0.45	3.41 (2.66)	3.59 (3.42)	0.056	0.924
Microvascular invasion	93 (50)	103 (53.6)	0.073	0.478	66 (52)	66 (52)	<0.001	1
Macrovascular invasion	14 (7.5)	14 (7.3)	0.009	0.93	9 (7.1)	8 (6.3)	0.032	1
Satellite nodules	14 (7.5)	16 (8.3)	0.03	0.772	8 (6.3)	10 (7.9)	0.061	0.814
Tumour grade								
Complete necrosis	18 (9.7)	27 (14.1)	0.111	0.043	15 (11.9)	15 (11.8)	0.023	0.624
Well differentiated	40 (21.6)	45 (23.4)	0.046		28 (22.2)	29 (22.8)	0.019	
Moderately differentiated	117 (63.2)	98 (51)	0.237		73 (57.9)	75 (59.1)	0.032	
Poorly differentiated	10 (5.4)	22 (11.5)	0.191		10 (7.9)	8 (6.3)	0.019	
DCD	68 (37.4)	91 (47.4)	0.204	0.05	55 (44)	56 (44.1)	0.002	1
Donor risk index	1.88 (0.53)	2.02 (0.61)	0.243	0.054	1.93 (0.54)	1.95 (0.59)	0.032	0.956

Categorical variables are presented as absolute numbers and percentage, and continuous variables are presented as mean and standard deviation.

BMI, body mass index; DCD, donation after cardiac death; HCV/HBV, hepatitis C/B virus; IBS, intra-operative blood salvage; NASH, non-alcoholic steatohepatitis; PBC, primary, biliary cirrhosis.

IBS and IBS groups, respectively. Baseline characteristics of the unmatched and matched samples are presented in Table 1. After propensity score matching, no significant differences were present between the IBS and no-IBS groups, and the data appeared well balanced. Only BMI had a SMD slightly over the threshold (> 0.1). In total, 127 patients who had received IBS could be matched to control patients with a similar propensity score. 7 control cases and 10 IBS cases were discarded, since propensity scores were outside the region of common support. In another 52 control cases and 55 IBS cases, no additional match was available with a similar propensity score. The use of allogenic blood transfusion units was higher among patients who had simultaneously received IBS (mean number of units, no-IBS: 1.1 ± 1.7 vs. IBS: 2.7 ± 3.15, $P < 0.001$). Among the IBS group, mean volume of autologous blood transfused was 1075 ml (SD: 1014 ml, range 200–7260 ml).

Univariable survival analysis on the propensity score-matched sample

In univariable analysis, use of IBS was not associated with significantly impaired disease-free survival or higher incidences of either patient mortality or HCC recurrence (Fig. 1). At each point in time, the chance of surviving without HCC recurrence was equal for patients who had received IBS compared with patients who had not (HR 1.07, 95%CI: 0.65–1.76, $P = 0.800$). Similarly, the chance of HCC recurrence at each point in time was similar in both groups (HR: 0.79, 95%CI: 0.36–1.73, $P = 0.549$). When assessing time to HCC recurrence in a competing risk model, absence of any association remained similar (HR: 0.79, 95%CI 0.40–1.57, $P = 0.50$). The cumulative proportion of patients alive without HCC recurrence at 12, 36, and 60 months was 85%, 67%, and 63% for the IBS group versus 90%, 75%, and 68% for the no-IBS group (Fig. 2).

Dose–effect relation

When fitted as a continuous variable with a natural cubic spline with three degrees of freedom to account for non-linear effects, increasing volume of IBS was not associated with a significantly increased log hazard for both disease-free survival and HCC recurrence (Fig. 3). Additionally, IBS was divided into categories of increasing volume and fitted as ordinal variable in univariable cox regression. Again, increasing volume of IBS appeared not associated with impaired disease-free survival nor increased risk for HCC recurrence (Table 2).

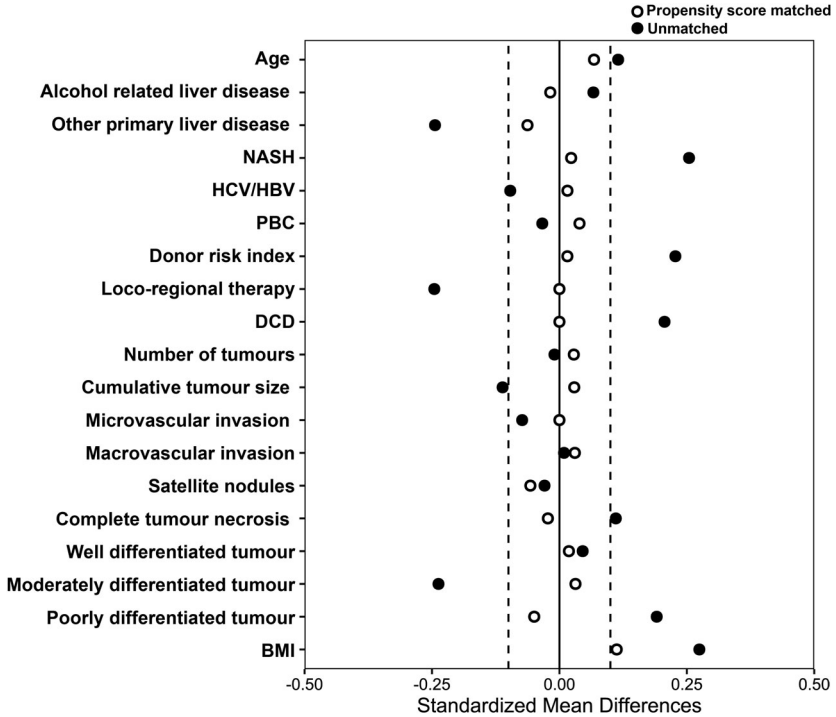

Figure 1 Balance of the propensity score-matched sample.
Standardized mean differences are given for the unmatched propensity score-matched sample. BMI: body mass index, NASH: non-alcoholic steatohepatitis, HCV/HBV: hepatitis C/B virus, PBC: primary, biliary cirrhosis, DCD: donation after cardiac death.

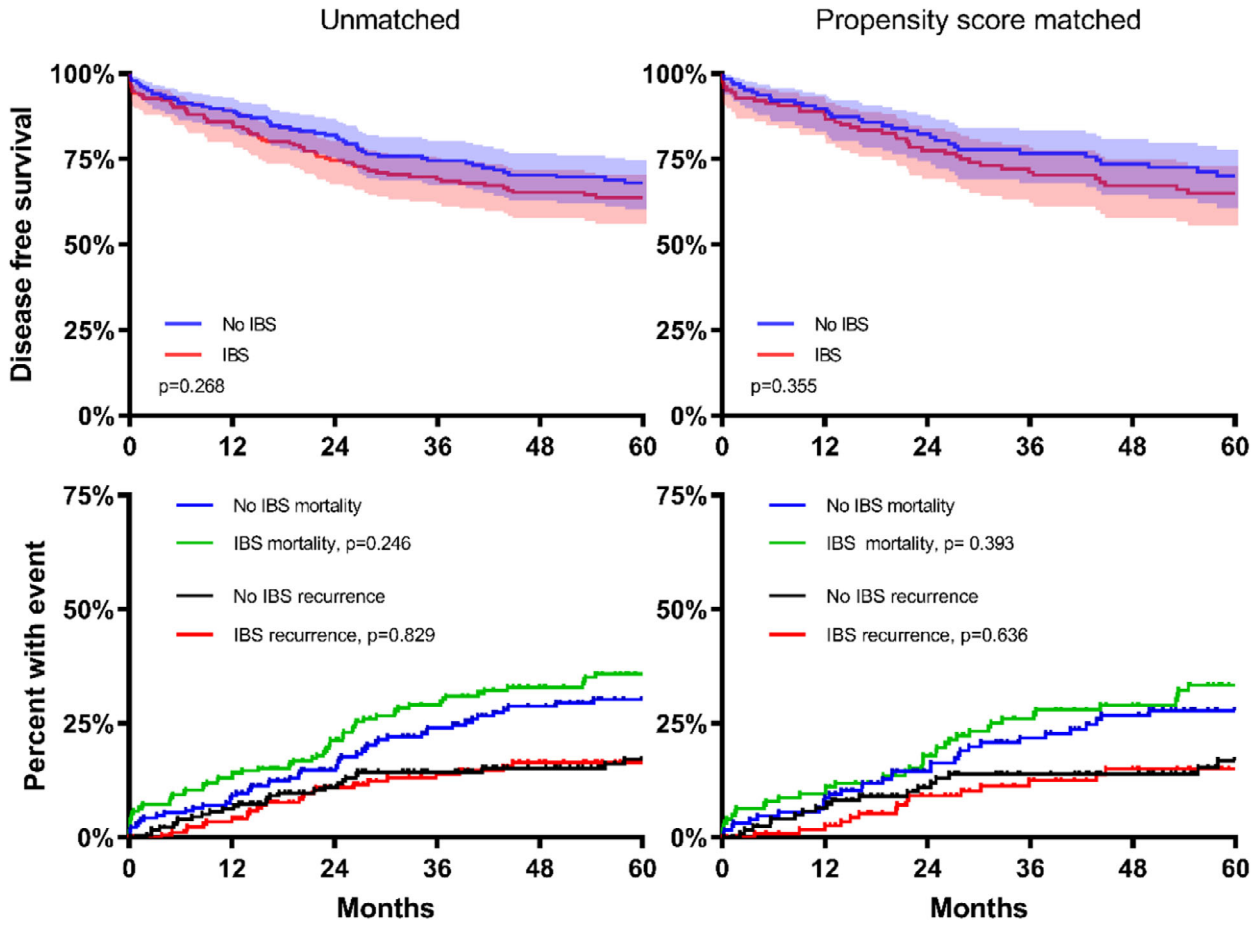

Figure 2 KM-curves of disease-free survival, recurrence, and mortality in the unmatched and propensity score-matched samples. Colored area represents 95% confidence interval, P for log-rank test.

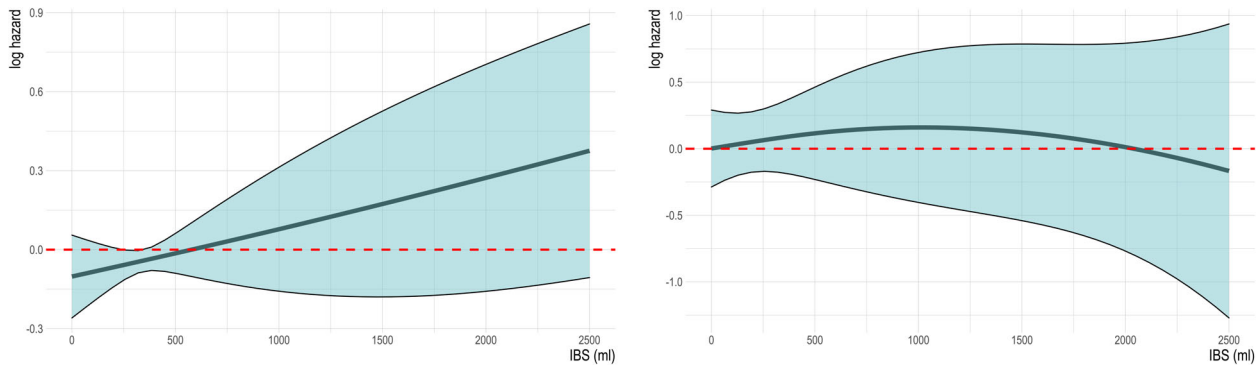

Figure 3 Log hazard ratio plotted against increasing volume of IBS for disease-free survival (left) and HCC recurrence (right). IBS (intra-operative blood salvage) was fitted as continuous value with a natural spline with three degrees of freedom, and dotted lines represent 95% confidence intervals.

Multivariable survival analysis

Results of multivariable analysis are presented in Table 3. IBS was not associated with impaired disease-free survival in multivariable analysis (HR: 1.19, 95%CI 0.85–1.67, $P = 0.305$). Similarly, the chance of HCC recurrence at each point in time was similar in both groups (HR: 0.97, 95%CI 0.56–1.69, $P = 0.917$). When assessing time to HCC recurrence in a multivariable competing risk model absence of any association

Table 2. Univariable cox regression, propensity score-matched data.

	Log-HR	HR (95%CI)	*P*
Univariable cox regression: disease-free survival			
IBS	0.06454	1.07 (0.65–1.76)	0.8
Cause-specific cox regression: HCC recurrence			
IBS	−0.2412	0.79 (0.36–1.73)	0.549
Competing risk regression (Fine and Gray): HCC recurrence			
IBS	−0.233	0.79 (0.40–1.57)	0.50
Dose–effect relation, cox regression: disease-free survival			
≤500 ml IBS	−0.20067	0.82 (0.34–1.97)	0.655
500–1000 ml IBS	0.09531	1.1 (0.47–2.59)	0.827
>1000 ml IBS	0.28768	1.33 (0.56–3.16)	0.514
Dose–effect relation, cause-specific cox regression: HCC recurrence			
≤500 ml IBS	$2.5 \cdot 10^{-16}$	1 (0.2–4.96)	1
500–1000 ml IBS	$9.46 \cdot 10^{-17}$	1 (0.32–3.1)	1
>1000 ml IBS	$2.5 \cdot 10^{-1}$	0.4 (0.08–2.06)	0.273

IBS, intra-operative blood salvage; HR, hazard ratio.

Table 3. Multivariable cox regression, unmatched data.

	Log-HR	HR (95%CI)	*P*
Cox regression disease-free survival			
IBS	0.17604	1.19 (0.85–1.67)	0.305
Cumulative viable tumor size	0.04759	1.05 (1–1.11)	0.075
Macrovascular invasion	0.73818	2.09 (1.27 to −3.45)	0.004
Microvascular invasion	0.45874	1.58 (1.08–2.32)	0.018
Satellite nodules	0.3231	1.38 (0.82–2.32)	0.221
Cause-specific cox regression: HCC recurrence			
IBS	–0.0296	0.97 (0.56–1.69)	0.917
Cumulative viable tumor size	0.10768	1.11 (1.03–1.2)	0.004
Macrovascular invasion	1.06593	2.9 (1.5–5.61)	0.001
Microvascular invasion	0.94473	2.57 (1.22–5.41)	0.013
Satellite nodules	0.89622	2.45 (1.26–4.77)	0.008
Competing risk regression (Fine and Gray): HCC recurrence			
IBS	–0.125	0.88 (0.50–1.55)	0.660
Cumulative viable tumor size	0.122	1.12 (1.03–1.22)	0.009
Macrovascular invasion	1.166	3.21 (1.68–6.13)	<0.001
Microvascular invasion	0.833	2.42 (1.18–1.78)	0.0160
Satellite nodules	0.917	2.50 (1.22–5.14)	0.0130

IBS, intra-operative blood salvage; HR, hazard ratio.

remained similar (HR: 0.88, 95%CI 0.50–1.55, $P = 0.660$).

Discussion

Use of IBS during oncological surgery, including liver transplantation for hepatocellular carcinoma, remains controversial. Based on present results, use of IBS during liver transplantation for HCC patients is not associated with impaired disease-free survival or increased risks for HCC recurrence. Moreover, no evidence of a dose–effect relation was found.

Concerns that IBS may reintroduce malignant cells in the bloodstream first appeared after publication of the guidelines from American Medical Council on autologous blood transfusion in 1986 based on a single case

Transplant International 2021; 34: 2887–2894

report [10]. Additionally, in 1995, Hansen *et al.* performed a study analyzing the blood shed from a surgical field during abdominal oncologic surgery, isolating tumor cells with capacity of proliferation, invasiveness, and tumorigenicity. However, subsequent studies during the following decades failed to effectively prove the potential of tumor cells to replicate and metastasize due to in vivo infusion of autologous blood [11].

With the development of the leukocyte depletion filter (LDF), the Consensus Conference on autologous transfusion in 1998 concluded based on *in vitro* data that the combination of IBS and LDF gives protection from infusion of malignant cells into the patient bloodstream [12]. Moving forward, in a cohort of patients with hepatic resections, Martin *et al.* found that there were no cytokeratin-positive cancer cells in the filtered salvaged blood [4,13,14]. These findings have encouraged the use of IBS during liver transplantation in HCC patients and, although often underpowered and predominantly of shorter follow-up, no previous clinical study shows a clear relation between extensive use of IBS and recurrence of HCC [4,14]. Controversially, Kumar *et al.* applied flow cytometry technique to 11 blood samples from patients with metastatic spinal disease and found tumor cells in 3/11 samples even after leukofiltration [15].

Assessing causality or absence of causality based on observational data is challenging, and effects of unknown confounding factors may always play a role. The strength of the current study is that it provides the longest follow-up to date to the existing literature, corrected for most important pathologic confounders, and carefully assessed a dose–effect relation. Disease-free survival and HCC recurrence rates found in present study are consistent with previous studies, and analyzing the recurrence trends, most recurrences in both groups occur during the first 3 years following the liver transplant. Factors related to recurrence in current data were conformed to those previously described, among them micro- or macrovascular invasion, the presence of satellite nodules in the explant specimen, and cumulative tumor burden [16,17]. No dose–effect relation was present, and effects remained similar in the propensity score-matched sample. This provides strong evidence to support safety of IBS during liver transplantation for HCC candidates. A more recent study excluded those with complete necrosis following loco-regional therapies prior to transplant and found no increased risk for HCC recurrence after IBS considering only patients with viable HCC in the explant [18]. In present study, patients with complete necrosis were equally distributed among both groups after matching.

There are several perioperative strategies to reduce the volume of blood transfused during liver transplantation isovolemic hemodilution, and use of thromboelastogram and the use of autotransfusion mechanisms are among the most frequently adopted [19]. It is well known that allogenic transfusion is not risk free [20]. Bacterial and viral infections, anaphylaxis, hemolytic reactions, and acute kidney injury were all previously reported. Tumor recurrence may be another potential side effect; however, underlying mechanisms to this relation are not well known. A recent study reported a dose-depended relation between tumor recurrence and units of allogeneic blood transfused [21].

In present study, the need for allogenic blood transfusion was higher in the IBS group and this was consistent with findings from previous studies. In the no-IBS group, the median requirement for allogenic transfusion was 1.1 unit of RBC while, in the IBS group, this was 2.6 ($P < 0.001$). Among the IBS group, the mean volume of autologous blood transfused was 1075 ml. The percentage hematocrit of processed blood after IBS is approximately 55%, while for allogeneic transfusion, this is approximately 75–80%. The total average requirement of blood transfusions in this study was estimated to be 1458 ml for the IBS vs. 253 ml for non-IBS.

Increased blood transfusion requirement in patients who received IBS is probably explained through confounding by intra-operative blood loss. Some studies suggested increased blood loss in patients receiving autologous blood transfusion may be attributable to dissemination of fibrinolytic compounds from the transplanted liver that are not being washed out by the cell saver [18,22]. However, when assessing IBS on a broader spectrum of abdominal surgery (not limited to liver transplantation), IBS has proven to be effective in reducing the need for allogeneic blood transfusion [23]. Moreover, IBS has proven to be cost-effective while used during liver transplantation in case of massive bleeding [24].

This study has some limitations inherent to its retrospective nature. We could not correct for the potential confounding effect of higher blood loss and transfusion requirements in IBS. Also, the effect of other blood products was not evaluated, which might theoretically alter the immune response and influence in the oncological outcome. The overall mortality rate after the use of IBS appeared slightly higher. The association between higher blood loss and use of IBS, due to intra-operative complications or problems, may be associated with

increased early mortality. Finally, data at hand may be limited by the quality of data extraction and clinical reporting. Nevertheless, missing data were unlikely to be related to endpoints or study groups and assumed to be missing at random. Multiple imputations allowed for the use of all available data, including data with incidental missing observations.

Present results encourage standard use of autologous blood transfusion as a secure strategy for the potential blood loss during a liver transplantation for HCC patients to diminish the use of autologous blood transfusion. Autologous blood transfusion does not lead to impaired disease-free survival or increased HCC recurrence rates.

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Conflict of interest

The authors declare no conflict of interest related to the submitted work.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Number of missing data entries.

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