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Blood Cell Salvage and Autotransfusion Does Not Worsen Oncologic Outcomes Following Liver Transplantation with Incidental Hepatocellular Carcinoma: A Propensity Score-Matched Analysis

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ABSTRACT

Background. Intraoperative blood cell salvage and autotransfusion (IBSA) during liver transplantation (LT) for hepatocellular carcinoma (HCC) is controversial for concern regarding adversely impacting oncologic outcomes.

Objective. We aimed to evaluate the long-term oncologic outcomes of patients who underwent LT with incidentally discovered HCC who received IBSA compared with those who did not receive IBSA.

Methods. Patients undergoing LT (January 2001–October 2018) with incidental HCC on explant pathology were retrospectively identified. A 1:1 propensity score matching (PSM) was performed. HCC recurrence and patient survival were compared. Kaplan–Meier survival analyses were performed, and univariable Cox proportional hazard analyses were performed for risks of recurrence and death.

Results. Overall, 110 patients were identified (IBSA, $n = 76$ [69.1%]; non-IBSA, $n = 34$ [30.9%]). Before matching, the groups were similar in terms of demographics, transplant, and tumor characteristics. Overall survival was similar for IBSA and non-IBSA at 1, 3, and 5 years (96.0%, 88.4%, 83.0% vs. 97.1%, 91.1%, 87.8%, respectively; $p = 0.79$). Similarly, the recurrence rate at 1, 3, and 5 years was not statistically different (IBSA 0%, 1.8%, 1.8% vs. non-IBSA 0%, 3.2%, 3.2%, respectively; $p = 0.55$). After 1:1 matching (26 IBSA, 26 non-IBSA), Cox proportional hazard analysis demonstrated similar risk of death and recurrence between the groups (IBSA hazard ratio [HR] of death 1.26, 95% confidence interval [CI] 0.52–3.05, $p = 0.61$; and HR of recurrence 2.64, 95% CI 0.28–25.30, $p = 0.40$).

Conclusions. IBSA does not appear to adversely impact oncologic outcomes in patients undergoing LT with incidental HCC. This evidence further supports the need for randomized trials evaluating the impact of IBSA use in LT for HCC.

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Blood loss during liver transplantation (LT) often necessitates transfusion. Intraoperative blood cell salvage and autotransfusion (IBSA) is frequently deployed in LT to avoid or decrease allogeneic transfusion use. Allogeneic blood products have many drawbacks, including the

association with increased morbidity and mortality,[1,2] increased cost, infectious exposure, and antibody formation.[3] IBSA mitigates many of these risks and has several advantages over traditional allogeneic blood transfusions in terms of avoidance of immunomodulation and antibody formation, cost effectiveness, and also a decrease in a recipient's exposure to transfusion-related infections.[3]

LT offers curative-intent potential for patients with hepatocellular carcinoma (HCC) who meet the strict selection criteria, such as the Milan criteria.[4] In addition, LT also corrects any underlying cirrhosis. HCC is the leading indication for LT at many centers.[5,6] Despite the near routine need for transfusion during LT, IBSA is rarely used in LT for HCC due to the potential risk of disseminating cancer cells to the patient when blood loss is salvaged and autotransfused. Therefore, HCC patients undergoing LT at many centers receive allogeneic blood products exclusively.

Several studies, primarily in Asia, have demonstrated no adverse outcomes in overall survival or recurrence for patients receiving IBSA during LT for HCC compared with those who do not receive IBSA.[7–11] Several studies in urologic and gynecologic oncology surgery also have shown no adverse oncologic outcomes with the use of IBSA.[12–14] Furthermore, IBSA use in hepatic surgery has been evaluated and found to be safe, reduces the allogeneic blood transfusion rate, and may even promote survival compared with allogeneic transfusion.[15,16] Currently, there is a paucity of data from North American LT centers regarding oncologic outcomes with IBSA use during LT for HCC. Therefore, in many North American LT centers, the use of IBSA during LT for HCC continues to be controversial for concerns of adversely impacting oncologic outcomes.

Despite the lack of IBSA use in LT for HCC, incidental HCC on explant pathology following LT is common, especially in patients with viral hepatitis-related cirrhosis. Therefore, in centers that utilize IBSA during LT, patients with incidental HCC may receive IBSA inadvertently. Therefore, we sought to evaluate the long-term oncologic outcomes of patients who underwent LT with incidentally discovered HCC on final explant pathology who received IBSA, compared with a similar group of patients with incidental HCC who did not receive IBSA, to assess the overall oncologic risks.

METHODS

This study was approved by our institutional Research Ethics Board (REB; REB#15-9989) and a waiver of informed consent was obtained.

Study Population

We assessed adults (≥18 years) who underwent LT between January 2001 and October 2018 at our institution. Patients were followed until March 2020. All patients were listed and underwent LT for indications other than HCC but had HCC diagnosed incidentally on the liver explant specimen. At our institution, IBSA is available and used in every non-cancer LT; however, not all patients from whom blood is salvaged have blood autotransfused (e.g. volume overload or low blood volume salvaged). Patients were grouped into IBSA and non-IBSA groups depending on whether they received salvage blood autotransfusion during the LT.

We recorded patients' age, sex, etiology of liver disease, Model for End-Stage Liver Disease (MELD) score at LT, Child–Pugh score at LT, serum α-fetoprotein (AFP) at LT, time on the waitlist, amount and type of blood products transfused (intra- and postoperatively [up to 48 h]), type of allograft (deceased vs. living donor), preoperative hemoglobin (g/L), platelets (*1000) and international normalized ratio (INR), intraoperative estimated blood loss (L), warm ischemic time (WIT; minutes), cold ischemia time (CIT; minutes), and previous abdominal surgery. AFP was categorized to reflect clinically relevant categories (ng/mL, <20, 20–99, 100–999, >1000). Explant pathology characteristics included the number of tumors, size of the largest tumor, microvascular invasion, and tumor differentiation. Tumor differentiation was defined according to the modified Edmondson criteria.[17] This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for retrospective studies.[18]

Process of Intraoperative Blood Cell Salvage and Autotransfusion and Institutional Policy

Blood salvage was performed using Cell Saver 5 (Haemonetics, Braintree, MA, USA). Shed blood from the operative field was suctioned to the reservoir of the device containing anticoagulant. If sufficient blood was collected, it underwent centrifugation and washing and was processed to a red blood cell (RBC) concentrate (approximately 50–80% hematocrit). Once the re-infusion bag reached 500 mL, the salvaged blood was autotransfused for a target intraoperative blood hemoglobin of 80 g/L. No leukocyte depletion filter was used in the process of cell salvage. Per our institutional policy, IBSA is contraindicated in any surgical procedure involving HCC.

Outcome Measures

The study's primary endpoints were the impact of intraoperative IBSA on post-LT survival and HCC tumor recurrence.

Propensity Score Matching

A propensity score was constructed based on the predicted probability of IBSA receipt using logistic regression. This was performed to control for the effect of confounding and represents a method for addressing selection bias. Covariates selected were variables that are associated with degree of liver dysfunction and blood loss during LT.[19–24] Given that the variables are associated with blood loss, by extension we posited that they would also be associated with IBSA receipt (blood cell salvage autotransfusion). These included preoperative hemoglobin,[20,22] MELD,[19,20] preoperative platelet count,[24] preoperative INR,[24] Child–Pugh score,[21,25] allograft type, WIT,[19] previous abdominal surgery,[21] CIT,[25] and recipient age.[19] Matching was then performed using these covariates in a 1:1 ratio between IBSA and non-IBSA receipt using a greedy, nearest-neighbor matching algorithm with no replacement.[26] Matching quality was evaluated with standardized mean differences between the treated and control groups. A difference <10% was used as indicative of a negligible imbalance between groups.[27]

Statistical Analysis

Descriptive data were expressed using medians and interquartile range (IQR) and compared using Student's *t*-tests and Mann–Whitney U tests. Categorical variables were expressed using number percentages and compared using Chi-square and Fisher's exact tests. Disease-free survival was defined as patients being alive without recurrence at last follow-up. Disease-free and overall survival were estimated using the Kaplan–Meier method, and groups were compared using log-rank tests. Univariable Cox proportional hazard regression models were constructed after matching to evaluate the impact of IBSA on mortality and recurrence. A multivariable model was not performed as propensity score matching (PSM) was selected as the method for confounding adjustment. All two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Population and Pathology

Between January 2001 and October 2018, 110 LT patients with incidental HCC on explant pathology were identified. Of these, 76 (69.1%) received IBSA and 34 (30.9%) did not. The median blood volume autotransfused in the IBSA group was 750 mL (IQR 500–1480). The two groups were similar in age, sex, etiology of liver disease, serum AFP at LT, Child–Pugh score, and MELD score at LT. The most common etiology of liver disease was hepatitis C virus (HCV) cirrhosis in both groups (IBSA 42.1% vs. non-IBSA 52.9%; $p = 0.86$). The time on the LT waitlist was similar between the groups (median number of months [IQR] IBSA 4.7 [1.9–14.5] vs. non-IBSA 3.4 [1.4–9.3]; $p = 0.35$). The units of allogeneic pRBC and platelets transfused were similar between groups. The majority of patients received a deceased donor liver graft (71.8%), and the proportions of deceased donor liver transplant (DDLT) and living donor liver transplant (LDLT) patients were similar between the IBSA and non-IBSA groups. The amount and types of blood products used intra- and postoperatively were similar between the groups (Table 1)

Explant Pathology

Both groups were similar in terms of tumor number (median [IQR] IBSA $1^{1,2}$ vs. non-IBSA $1^{1,2}$; $p = 0.50$), size of the largest tumor (median, cm [IQR] IBSA 1.2 [0.8–1.6] vs. non-IBSA 1.5 [1.0–1.8]; $p = 0.11$), rates of microvascular invasion (IBSA 7.9% vs. non-IBSA 8.8%), and tumor differentiation (moderate differentiation IBSA 69.3% vs. non-IBSA 83.3%; $p = 0.40$) (Table 1)

Survival Analysis in the Unmatched Cohort

The post-LT follow-up was similar between groups (median months [IQR] IBSA 68.4 [36.3–92.9] vs. non-IBSA 70.8 [17.3–105.1]; $p = 0.94$). Overall survival was similar at 1, 3, and 5 years (IBSA 96.0%, 88.4%, 83.0% vs. non-IBSA 97.1%, 91.1%, 87.8%, respectively; $p = 0.79$). Similarly, recurrence rate was not statistically different at 1, 3, and 5 years (IBSA 0%, 1.8%, 1.8% vs. non-IBSA 0%, 3.2%, 3.2%, respectively; $p = 0.55$) (Figs. 1 and 2). Of the four patients who recurred, two had intrahepatic recurrence (both in the IBSA group) and two had extrahepatic recurrence (both in the non-IBSA group).

TABLE 1 Descriptive statistics in the IBSA and no IBSA transfusion groups before matching

	Overall ($n = 110$)	IBSA ($n = 76$ (69.1%))	No IBSA ($n = 34$ (30.9%))	p-value[a]	SMD
Demographics and tumor characteristics					
Age, years [median (IQR)]	55.5 (50.9–60.9)	56.0 (51.6–60.9)	54.6 (49.5–60.2)	0.63	0.016
Sex, male [*n* (%)]	91 (82.7)	61 (80.3)	30 (88.2)	0.31	0.23
Etiology of cirrhosis [*n* (%)]				0.86	
Hepatitis C infection	50 (45.5)	32 (42.1)	18 (52.9)		0.28
Hepatitis B infection	11 (10.0)	8 (10.5)	3 (8.8)		0.06
NASH	18 (16.4)	14 (18.4)	4 (11.8)		0.16
Acute liver disease	22 (20.0)	16 (21.1)	6 (17.7)		0.11
Others	9 (8.2)	6 (7.9)	3 (8.8)		0.08
Serum AFP at transplant, ng/mL [*n* (%)]				0.85	0.002
< 20	99 (90.8)	69 (92.0)	30 (88.2)		
20–99	7 (6.4)	4 (5.3)	3 (8.8)		
100–999	3 (2.8)	2 (2.7)	1 (3.0)		
> 1000	0 (0.0)	0 (0.0)	0 (0.0)		
Child–Pugh score [*n* (%)]				0.84	
A	2 (1.8)	1 (1.3)	1 (3.0)		0.11
B	36 (32.7)	25 (32.9)	11 (32.4)		0.02
C	72 (65.5)	50 (65.8)	22 (64.7)		0.02
MELD score at transplant [median (IQR)]	22 (18–26)	21 (17–25)	22.5 (20–27)	0.28	0.20
Previous abdominal surgery [*n* (%)]	27 (24.5)	21 (27.6)	6 (17.7)	0.26	0.22
Liver transplant characteristics					
Hemoglobin pretransplant, g/L [median (IQR)][b]	99 (86–111)	99.5 (87–112)	95.5 (82–109)	0.24	0.19
Platelets pretransplant, times 1000 [median (IQR)][b]	68 (47–92)	70.5 (48–93.5)	67 (42–88)	0.73	0.06
INR pretransplant [median (IQR)][b]	1.8 (1.5–2.3)	1.8 (1.5–2.3)	1.9 (1.6–2.5)	0.20	0.22
Estimated blood loss, ml [median (IQR)][b]	2.6 (1.5–5)	3.2 (2–5.5)	2 (0–4)	0.002	0.57
Postoperative transfusion (up to 48 h post-transplant) [*n* (%)]	68 (61.8)	49 (64.5)	19 (55.9)	0.39	0.26
RBC	36 (32.7)	23 (30.3)	13 (38.2)	0.41	0.14
FFP	23 (20.9)	14 (18.4)	9 (26.5)	0.34	0.27
Platelets	24 (21.8)	15 (19.7)	9 (26.5)	0.43	0.23
Cryoprecipitate	2 (1.8)	1 (1.3)	1 (2.9)	0.52	0.12
Albumin	52 (47.3)	39 (51.3)	13 (38.2)	0.20	0.32
Number of postoperative RBC transfusions	0 (0–1)	0 (0–1)	0 (0–1.5)	0.23	0.61
Number of postoperative FFP transfusions	0 (0–0)	0 (0–0)	0 (0–1.5)	0.19	0.56
Number of postoperative platelet transfusions	0 (0–0)	0 (0–0)	0 (0–1.5)	0.33	0.31
Number of postoperative cryoprecipitate transfusions	0 (0–0)	0 (0–0)	0 (0–0)	0.53	0.26
Number of postoperative albumin transfusions	0 (0–2)	1 (0–2)	0 (0–2)	0.36	0.26
WIT, min [median (IQR)][b]	50 (41.5–59.0)	47.5 (40.5–59)	53 (47–58)	0.34	0.25
CIT, min [median (IQR)][b]	358 (166–502)	358 (184–502)	339 (158–520)	0.92	0.03
Operation duration, min [median (IQR)][b]	488 (420–570)	483 (420–570)	493 (411–546)	0.70	0.02
Time on the waiting list, months [median (IQR)]	3.8 (1.7–13.9)	4.7 (1.9–14.5)	3.4 (1.4–9.3)	0.35	0.10
Units of intraoperative pRBC transfusions [median (IQR)]	5 (3–8)	5 (3–7)	6 (4–10)	0.05	0.38
Units of intraoperative platelet transfusions [median (IQR)]	2 (1–5)	2 (1–5)	2 (1–5)	0.83	0.17
Blood given through cell saver, mL [median (IQR)]	750 (500–1480)	750 (500–1480)	–	–	–

TABLE 1 contiuned

	Overall ($n = 110$)	IBSA ($n = 76$ (69.1%))	No IBSA ($n = 34$ (30.9%))	p-value[a]	SMD
Type of graft [n (%)]				0.12	
Deceased donor liver graft	79 (71.8)	58 (76.3)	21 (61.8)		0.26
Living donor liver graft	31 (28.2)	18 (23.7)	13 (38.2)		0.26
Explant pathology characteristics					
Number of viable tumors at explant [median (IQR)]	1 (1–2)	1 (1–2)	1 (1–2)	0.77	0.16
Size of the largest viable tumor at explant, cm [median (IQR)]	1.2 (1.0–1.7)	1.2 (0.8–1.6)	1.5 (1.0–1.8)	0.11	0.29
Microvascular invasion [n (%)]	9 (8.18)	6 (7.9)	3 (8.8)	1.0	0.03
Tumor differentiation [n (%)]				0.40	
Well differentiated	25 (23.8)	20 (26.7)	5 (16.7)		0.46
Moderately differentiated	77 (73.3)	52 (69.3)	25 (83.3)		0.21
Poorly differentiated	3 (2.7)	3 (4.0)	0 (0)		–
Outcomes					
Tumor recurrence [n (%)]	4 (3.6)	2 (5.9)	2 (2.6)	0.59	
Time to recurrence, months [median (IQR)]	46.7 (29.1–101.7)	84.2 (27.1–141.2)	46.7 (31.2–62.2)	1.0	
Death [n (%)]	30 (27.3)	18 (23.7)	12 (35.3)	0.25	
Time to death, months [median (IQR)]	70.8 (36.3–92.9)	68.4 (36.3–92.9)	70.8 (17.3–105.1)	0.94	

AFP α-fetoprotein, *CIT* cold ischemia time, *FFP* fresh frozen plasma, *IBSA* intraoperative blood salvage autotransfusion, *INR* international normalized ratio, *IQR* interquartile range, *MELD* Model for End-stage Liver Disease, *NASH* non-alcoholic steatohepatitis, *pRBC* packed red blood cells, *RBC* red blood cells, *SMD* standardized mean difference, *WIT* warm ischemia time

[a]*P* value corresponds to a two-sided Student *t*-test comparison between patients who received cell saver transfusion and patients who did not

[b]Missing <6

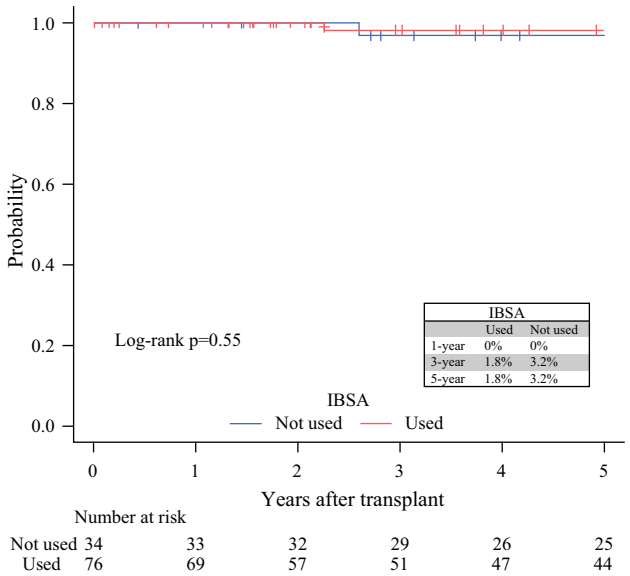

FIG. 1 Recurrence based on IBSA use in the unmatched cohort. *IBSA* intraoperative blood cell salvage and autotransfusion

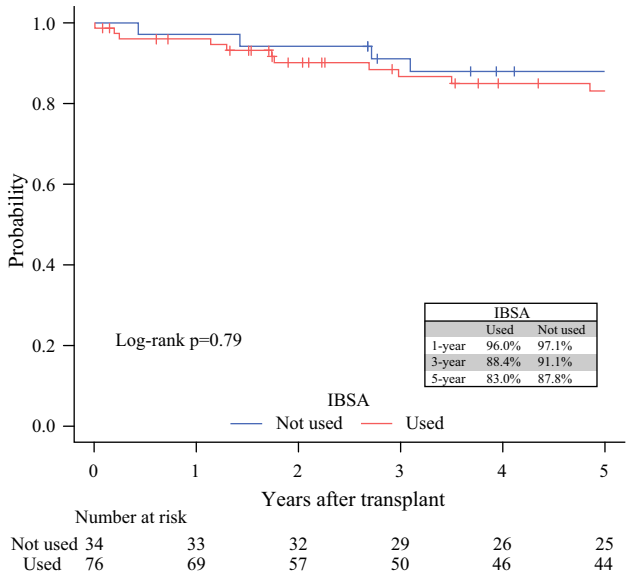

FIG. 2 Overall survival based on IBSA use in the unmatched cohort. *IBSA* intraoperative blood cell salvage and autotransfusion

Matched Cohort

Following PSM, 26 IBSA patients were matched with 26 non-IBSA patients. The standardized mean difference was <10% between groups (Table 2). Univariable Cox proportional hazard regression for risk of death demonstrated an equivalent risk between groups in the matched cohort (IBSA [ref. non-IBSA] HR 1.26, 95% CI 0.52–3.05; $p = 0.61$). The recurrence risk was also similar between groups (IBSA [ref. non-IBSA] HR 2.64, 95% CI 0.28–25.30; $p = 0.40$).

DISCUSSION

These findings demonstrate that IBSA use does not significantly impact oncologic outcomes of overall survival or recurrence in patients undergoing LT with incidentally discovered HCC. Moreover, the observed recurrence rates in IBSA do not exceed what has been traditionally accepted for post-LT HCC recurrence.

In the 1990s, Hansen et al. detected circulating tumor cells in a majority (93.4%) of 61 cancer patients during various oncologic surgeries. These cells demonstrated proliferative capacity, invasiveness, and tumorigenicity. As a consequence, caution was expressed towards autotransfusion of blood during oncologic surgery.[28] The process of IBSA was subsequently refined with leukocyte depletion filters, which could remove tumor cells and reduce the risk of tumor re-introduction during the cell-salvage process, although the efficacy of leukocyte depletion filters remains unproven by high-level prospective clinical data.[29] Gwak et al. evaluated the ability of one leukocyte depletion filter to remove HCC tumor cells.[29] Six groups of progressively increasing amounts of tumor cells were passed through the filter and subsequently evaluated using polymerase chain reaction on the resuspended pellet that remained after the filtration process.[29] The authors noted that the filter could remove tumor cells, although its effectiveness diminished with increasing HCC cell counts.[29] Nonetheless, several subsequent retrospective studies, mostly from Asia, have further demonstrated no increase in the risk of cancer recurrence with a leukocyte depletion filter in the process of IBSA use during LT for HCC, suggesting that either the number of tumor cells that enter the filtration process are few, the tumor cells that may re-enter the circulation do not harbor the potential for seeding and metastasis development, or that the process of autotransfusion does not alter the natural biological course of the disease.[8–11,30] The largest of these was by Han et al. from Korea, who performed a PSM analysis of LDLT recipients in whom the indication for LT was HCC.[7] Of 397 matched LDLT HCC patients, there were 222 IBSA patients and 97 non-IBSA patients.[7] There were no differences in the cumulative HCC recurrence rate at 1, 2, and 5 years (IBSA 10.8%, 14.9%, 20.3% vs. 10.4%, 19.1%, and 24.1%, respectively).[7] Similarly, the groups were equivalent in risk for overall, intrahepatic, or extrahepatic recurrence.[7] In contrast to many of the previously reported studies, our series did not use leukocyte depletion filters for any of the cases.

The studies that show equivalent oncologic outcomes between the IBSA and non-IBSA groups offer further evidence of oncologic safety of IBSA use during LT for HCC and suggest the urgent need for a prospective trial. From these studies, contraindication of IBSA during surgical procedures for HCC is unwarranted. The adverse oncologic effects of IBSA are mostly theoretical, and many of the abovementioned retrospective studies have failed to corroborate this association. Nonetheless, due to the low-level evidence afforded by their study designs, the development of safe clinical guidelines has been precluded. A clinical randomized control trial would address these limitations; however, it is further hindered by ethical constraints that oncologic safety cannot be guaranteed, again based on low-level evidence.

Moreover, likely reflective of the long study period and high center LT volume, our study presents the largest cohort of incidental HCCs after LT to date.[31–33] In a previous report by Pérez et al., oncologic outcomes of 27 incidental HCC patients after LT were compared with 141 patients with known HCC.[32] Both groups had similar rates of multinodular disease, vascular invasion, and tumor differentiation.[32] Although there was no difference between the risk of tumor recurrence on adjusted analysis, incidental HCC represented an independent risk for post-LT mortality. In that study, the 5-year recurrence-free survival was 79.7%, which was lower than the 5-year recurrence-free survival rates reported in our study of 98.2% and 96.8% in the IBSA and non-IBSA groups, respectively. Our results are also comparable with reported post-LT recurrence in the current literature, ranging from 9.8 to 17.3%.[34,35] Our study did not specifically aim to compare the outcomes of incidental HCC after LT with patients known to have HCC before LT; however, it does highlight that the oncologic risk, despite overall favorable tumor characteristics, is not negligible. As incidental HCCs carry a low risk of recurrence, conclusions cannot be directly extrapolated to patients with known HCC at the time of LT, who have a more significant tumor burden. Moreover, the presence and role of circulating tumor cells in patients with early HCC remains to be elucidated. Nonetheless, the results presented herein offer evidence for oncologic safety of cell-saver use, at least for the incidental HCCs, and further reinforce the need for a randomized clinical trial for higher-level evidence to drive potential practice change.

TABLE 2 Descriptive statistics in the IBSA and no IBSA transfusion groups after matching

	IBSA [$n = 26$]	No IBSA [$n = 26$]	p-value[a]	SMD
Demographics and tumor characteristics				
Age, years [median (IQR)]	54.9 (52.6–61.6)	54.6 (50.0–59.5)	0.58	0.1
Sex, male [n (%)]	18 (69.2)	22 (84.6)	0.19	0.44
Etiology of cirrhosis [n (%)]			0.96	
Hepatitis C infection	12 (46.2)	13 (50)		0.08
Hepatitis B infection	3 (11.5)	3 (11.5)		0.00
NASH	5 (15.4)	4 (15.4)		0.10
Acute liver disease	4 (15.4)	5 (19.2)		0.10
Others	2 (4.7)	1 (3.9)		0.14
Serum AFP at transplant, ng/mL [n (%)]			0.36	0.30
< 20	24 (92.3)	23 (88.5)		
0–99	1 (3.8)	3 (11.5)		
100–999	1 (3.8)	0 (0)		
> 1000	–	–		
Child–Pugh score [n (%)]			0.95	
A	1 (3.85)	1 (3.85)		0.00
B	10 (38.5)	9 (34.6)		0.08
C	15 (57.7)	16 (61.5)		0.08
MELD score at transplant [median (IQR)]	21 (18–23)	22 (18–28)	0.32	0.10
Previous abdominal surgery [n (%)]	8 (30.8)	5 (19.2)	0.34	0.10
Liver transplant characteristics				
Hemoglobin pretransplant, g/L [median (IQR)][b]	101 (89–121)	99 (91–113)	0.28	0.11
Platelets pretransplant, times 1000 [median (IQR)][b]	66.5 (52–98)	67.5 (46–88)	0.46	0.10
INR pretransplant [median (IQR)][b]	1.8 (1.5–2.3)	1.8 (1.6–2.3)	0.64	0.02
Estimated blood loss, mL [median (IQR)][b]	2 (1.5–3)	2 (0.8–4)	0.58	0.05
Postoperative transfusion [n (%)]	13 (50)	16 (61.5)	0.40	0.23
RBC	7 (26.9)	11 (42.3)	0.24	0.32
FFP	3 (11.5)	8 (30.8)	0.09	0.46
Platelets	5 (19.2)	9 (34.6)	0.21	0.37
Cryoprecipitate	0 (0)	1 (3.8)	0.31	0.26
Albumin	10 (38.5)	12 (46.2)	0.57	0.16
Number of postoperative RBC transfusions	0 (0–1)	0 (0–2)	0.12	0.34
Number of postoperative FFP transfusions	0 (0–0)	0 (0–2)	0.06	0.37
Number of postoperative platelet transfusions	0 (0–0)	0 (0–2)	0.24	0.29
Number of postoperative cryoprecipitate transfusions	0 (0–0)	0 (0–0)	0.32	0.11
Number of postoperative albumin transfusions	0 (0–2)	0 (0–2)	0.74	0.07
WIT, mins [median (IQR)][b]	46 (40–56)	53 (47–57)	0.07	0.06
CIT, mins [median (IQR)][b]	372 (120–497)	408 (191–540)	0.64	0.07
Operation duration, mins [median (IQR)][b]	470 (410–570)	465 (400–510)	0.52	0.23
Time on the waiting list, months [median (IQR)]	4.9 (2.3–13.3)	3.8 (1.5–9.3)	0.53	0.14
Units of pRBC transfusion [median (IQR)]	3 (2–6)	6 (4–10)	0.007	0.41
Units of platelets transfusion [median (IQR)]	1 (0–3)	2 (1–5)	0.19	0.01
Blood given through cell saver, mL [median (IQR)]	550 (400–830)	–	–	–
Type of graft [n (%)]			1.0	
Deceased donor liver graft	19 (73.1)	19 (73.1)		0.00
Living donor liver graft	7 (26.9)	7 (26.9)		0.00
Explant pathology characteristics				
Number of viable tumors at explant [median (IQR)]	1 (1–2)	1 (1–2)	0.76	0.29

TABLE 2 continued

	IBSA [$n = 26$]	No IBSA [$n = 26$]	p-value[a]	SMD
Size of the largest viable tumor at explant, cm [median (IQR)]	1.15 (0.7–1.6)	1.5 (1.2–2.0)	0.03	0.37
Microvascular invasion [n (%)]	1 (3.8)	3 (11.5)	0.29	0.27
Tumor differentiation [n (%)]			0.10	
Well differentiated	8 (30.8)	2 (9.1)		0.62
Moderately differentiated	17 (65.4)	20 (90.9)		0.26
Poorly differentiated	1 (3.8)	0 (0)		–

AFP α-fetoprotein, *CIT* cold ischemia time, *FFP* fresh frozen plasma, *IBSA* intraoperative blood salvage autotransfusion, *INR* international normalized ratio, *IQR* interquartile range, *MELD* Model for End-stage Liver Disease, *NASH* non-alcoholic steatohepatitis, *pRBC* packed red blood cells, *RBC* red blood cells, *SMD* standardized mean difference, *WIT* warm ischemia time

[a]*P*-value corresponds to a two-sided Student *t*-test comparison between patients who received cell saver transfusion and patients who did not

[b]Missing <6

Despite accumulating retrospective evidence, IBSA remains contraindicated in many North American LT centers (including our institution). Hence, the only possible study population available to address our clinical question was limited to LT patients with incidental HCCs on explant. These patients predictably had favorable tumor characteristics; they were generally small, solitary, and had low rates of microvascular invasion. In our analysis, no statistical difference in tumor characteristics was observed between patients who received IBSA and those who did not. Nonetheless, to the best of our knowledge, this is the first report of IBSA use in North America.

Generally, IBSA is used during LT to reduce the exposure to the recipient of allogeneic blood products, which represent a scarce resource and carry the potential of increasing morbidity and mortality.[36,37] At University Health Network, approximately 40–50% of LTs performed every year are for patients with HCC. During LT for HCC, significant blood loss is common and frequently requires blood transfusion.[23,38,39] At our institution, 72.9% of patients receive an allogenic blood transfusion, either intraoperatively or within the first 48 h after the LT for HCC (unpublished data). This number can potentially be reduced with the more widespread use of IBSA. Allogeneic blood transfusions may lead to transfusion-associated immunomodulation and, in some studies, are associated with an increased risk of HCC recurrence following liver resection; however, this remains controversial.[1,2,40,41] IBSA affords advantages over traditional allogeneic blood transfusions by not only potentially mitigating these factors and limiting the immunomodulatory effect, which can be detrimental, but possibly also by improving cost effectiveness.[3] IBSA can also decrease a recipient's exposure to viruses, protozoa, and prions.[3] Taken into combination, increased use of IBSA for HCC, particularly in centers where this indication represents the largest proportion of patients undergoing LT, may decrease the amount of allogeneic blood transfusions, and possibly morbidity and mortality, without adversely impacting oncologic outcomes.

Limitations

This study is limited by its retrospective and non-randomized design, with the potential for selection and misclassification bias. Given the study's single-institutional nature, the results may not be generalizable to other centers. Despite this being the largest study in North America to date, the number of patients is still small, limiting the study's statistical power to detect differences between groups examined. Moreover, although adjustments have been made for known covariates that may have confounded the results, there is potential for residual confounding and type 1 error.

CONCLUSION

IBSA does not appear to adversely impact oncologic outcomes in patients undergoing LT with incidental HCC compared with those not receiving IBSA. While the recurrence risk in both the IBSA and non-IBSA groups is not negligible, the rates are low and similar. This evidence supports the further need for randomized trials evaluating the impact of IBSA use in LT for HCC.

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REFERENCES

1. Makino Y, Yamanoi A, Kimoto T, El-Assal ON, Kohno H, Nagasue N. The influence of perioperative blood transfusion on intrahepatic recurrence after curative resection of hepatocellular carcinoma. *Am J Gastroenterol*. 2000;95(5):1294–300. https://doi.org/10.1016/S0002-9270(00)00820-0.
2. Harada N, Shirabe K, Maeda T, Kayashima H, Ishida T, Maehara Y. Blood transfusion is associated with recurrence of hepatocellular carcinoma after hepatectomy in Child-Pugh class a patients. *World J Surg*. 2015;39(4):1044–51. https://doi.org/10.1007/s00268-014-2891-6.
3. Phillips SD, Maguire D, Deshpande R, et al. A prospective study investigating the cost effectiveness of intraoperative blood salvage during liver transplantation. *Transplantation*. 2006;81(4):536–40. https://doi.org/10.1097/01.tp.0000199318.17013.c5.
4. Mazzaferro V, Regalia E, Doci R, et al. Carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693–9. https://doi.org/10.1056/NEJM199603143341104.
5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693–9. https://doi.org/10.1056/nejm199603143341104.
6. Sposito C, Cucchetti A, Mazzaferro V. Assessing competing risks for death following liver transplantation for hepatocellular carcinoma. *Dig Dis Sci*. 2019;64(4):1001–7. https://doi.org/10.1007/s10620-019-05538-1.
7. Han S, Kim G, Ko JS, et al. Safety of the use of blood salvage and autotransfusion during liver transplantation for hepatocellular carcinoma. *Ann Surg*. 2016;264(2):339–43. https://doi.org/10.1097/SLA.0000000000001486.
8. Akbulut S, Kayaalp C, Yilmaz M, et al. Effect of autotransfusion system on tumor recurrence and survival in hepatocellular carcinoma patients. *World J Gastroenterol*. 2013;19(10):1625–31. https://doi.org/10.3748/wjg.v19.i10.1625.
9. Kim JM, Kim GS, Joh JW, et al. Long-term results for living donor liver transplant recipients with hepatocellular carcinoma using intraoperative blood salvage with leukocyte depletion filter. *Transpl Int*. 2013;26(1):84–9. https://doi.org/10.1111/tri.12001.
10. Muscari F, Suc B, Vigouroux D, et al. Blood salvage autotransfusion during transplantation for hepatocarcinoma: Does it increase the risk of neoplastic recurrence? *Transpl Int*. 2005;18(11):1236–9. https://doi.org/10.1111/j.1432-2277.2005.00207.x.
11. Araujo RL, Pantanali CA, Haddad L, Filho JAR, D'Albuquerque LAC, Andraus W. Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence? *World J Gastrointest Surg*. 2016;8(2):161. https://doi.org/10.4240/wjgs.v8.i2.161.
12. Lyon TD, Ferroni MC, Turner RM 2nd, Jones C, Jacobs BL, Davies BJ. Short-term outcomes of intraoperative cell saver transfusion during open partial nephrectomy. *Urology*. 2015;86(6):1153–8. https://doi.org/10.1016/j.urology.2015.09.008.
13. Davis M, Sofer M, Gomez-Marin O, Bruck D, Soloway MS. The use of cell salvage during radical retropubic prostatectomy: does it influence cancer recurrence? *BJU Int*. 2003;91(6):474–6. https://doi.org/10.1046/j.1464-410x.2003.04129.x.
14. Connor JP, Morris PC, Alagoz T, Anderson B, Bottles K, Buller RE. Intraoperative autologous blood collection and autotransfusion in the surgical management of early cancers of the uterine cervix. *Obstet Gynecol*. 1995;86(3):373–8. https://doi.org/10.1016/0029-7844(95)00183-R.
15. Zacharias T, Ahlschwede E, Dufour N, Romain F, Theissen-Laval O. Intraoperative cell salvage with autologous transfusion in elective right or repeat hepatectomy: a propensity-score-matched case-control analysis. *Can J Surg*. 2018;61(2):105–13. https://doi.org/10.1503/cjs.010017.
16. Kitagawa K, Taniguchi H, Mugitani T, et al. Safety and advantage of perioperative autologous blood transfusion in hepatic resection for hepatocellular carcinoma. *Anticancer Res*. 2001;21(5):3663–7.
17. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7(3):462–503. https://doi.org/10.1002/1097-0142(195405)7:3%3c462::aid-cncr2820070308%3e3.0.co;2-e.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008.
19. Eghbal MH, Samadi K, Khosravi MB, et al. The impact of preoperative variables on intraoperative blood loss and transfusion requirements during orthotopic liver transplant. *Exp Clin Transpl*. 2019;17(4):507–12. https://doi.org/10.6002/ect.2016.0325.
20. Sobreira Fernandes D, Pereira Real CC, Sá Couto Romão PA, et al. Pre-operative predictors of red blood cell transfusion in liver transplantation. *Blood Transfus*. 2017;15(1):53–6. https://doi.org/10.2450/2016.0203-15.
21. Steib A, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. *Can J Anaesth*. 2001;48(11):1075–9. https://doi.org/10.1007/BF03020372.
22. Mangus RS, Kinsella SB, Nobari MM, et al. Predictors of blood product use in orthotopic liver transplantation using the piggyback hepatectomy technique. *Transplant Proc*. 2007;39(10):3207–13. https://doi.org/10.1016/j.transproceed.2007.09.029.
23. Triulzi DJ. Transfusion support in liver transplantation. *Curr Hematol Rep*. 2004;3(6):444–9.
24. Massicotte L, Sassine M-P, Lenis S, Roy A. Transfusion predictors in liver transplant. *Anesth Analg*. 2004;98(5):1245–51. https://doi.org/10.1213/01.ane.0000111184.21278.07.
25. De Santis GC, Brunetta DM, Nardo M, et al. Preoperative variables associated with transfusion requirements in orthotopic liver transplantation. *Transfus Apher Sci*. 2014;50(1):99–105. https://doi.org/10.1016/j.transci.2013.10.006.
26. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies.

Multivar Behav Res. 2011;46(3):399–424. https://doi.org/10.1080/00273171.2011.568786.
27. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228–34. https://doi.org/10.1080/03610910902859574.
28. Hansen E, Wolff N, Knuechel R, Ruschoff J, Hofstaedter F, Taeger K. Tumor cells in blood shed from the surgical field. *Arch Surg*. 1995;130(4):387–93. https://doi.org/10.1001/archsurg.1995.01430040049007.
29. Gwak MS, Lee KW, Kim SY, et al. Can a leukocyte depletion filter (LDF) reduce the risk of reintroduction of hepatocellular carcinoma cells? *Liver Transplant*. 2005;11(3):331–5. https://doi.org/10.1002/lt.20346.
30. Foltys D, Zimmermann T, Heise M, et al. Liver transplantation for hepatocellular carcinoma–is there a risk of recurrence caused by intraoperative blood salvage autotransfusion? *Eur Surg Res*. 2011;47(3):182–7. https://doi.org/10.1159/000330746.
31. Abdelfattah MR, Abaalkhail F, Al-Manea H. Misdiagnosed or incidentally detected hepatocellular carcinoma in explanted livers: Lessons learned. *Ann Transplant*. 2015;20:366–72. https://doi.org/10.12659/AOT.893782.
32. Pérez P, Rodriguez-Peralvarez M, Guerrero L, et al. Incidental hepatocellular carcinoma after liver transplantation: Prevalence, histopathological features and prognostic impact. *PLoS ONE*. 2017;12(4):e0175010. https://doi.org/10.1371/journal.pone.0175010.
33. Sotiropoulos GC, Malago M, Molmenti EP, et al. Liver transplantation and incidentally found hepatocellular carcinoma in liver explants: need for a new definition? *Transplantation*. 2006;81(4):531–5. https://doi.org/10.1097/01.tp.0000198739.42548.3e.
34. Goldaracena N, Mehta N, Scalera I, et al. Multicenter validation of a score to predict prognosis after the development of HCC recurrence following liver transplantation. *HPB*. 2019;21(6):731–8. https://doi.org/10.1016/j.hpb.2018.10.005.
35. Hong SK, Lee K-W, Yoon KC, et al. Different prognostic factors and strategies for early and late recurrence after adult living donor liver transplantation for hepatocellular carcinoma. *Clin Transplant*. 2019;33(10):e13703. https://doi.org/10.1111/ctr.13703.
36. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. *Br J Anaesth*. 2013;110(5):690–701. https://doi.org/10.1093/bja/aet068.
37. Vamvakas EC. Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt. *Transfusion*. 2006;46(3):492–5. https://doi.org/10.1111/j.1537-2995.2006.00748.x.
38. Kindscher J. Blood usage in a newly organized liver transplant program. *Transplant Proc*. 1993;25(2):1823.
39. Massicotte L, Denault AY, Beaulieu D, et al. Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. *Transplantation*. 2012;93(12):1276–81. https://doi.org/10.1097/TP.0b013e318250fc25.
40. Kuroda S, Tashiro H, Kobayashi T, Oshita A, Amano H, Ohdan H. No impact of perioperative blood transfusion on recurrence of hepatocellular carcinoma after hepatectomy. *World J Surg*. 2012;36(3):651–8. https://doi.org/10.1007/s00268-012-1425-3.
41. Yang T, Lu JH, Lau WY, et al. Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma: a propensity score matching analysis. *J Hepatol*. 2016;64(3):583–93. https://doi.org/10.1016/j.jhep.2015.10.012.