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Perioperative blood transfusion does not affect recurrence-free and overall survivals after curative resection for intrahepatic cholangiocarcinoma: a propensity score matching analysis

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Abstract

Background: Whether perioperative blood transfusions (PBTs) adversely influence oncological outcomes for intrahepatic cholangiocarcinoma (ICC) patients after curative resection remains undetermined.

Methods: Of the 605 patients who underwent curative liver resection for ICC between 2000 and 2012, 93 received PBT. We conducted Cox regression and variable selection logistic regression analyses to identify confounding factors of PBT. Propensity score matching (PSM) and Cox regression analyses were used to compare the overall survival (OS) and disease-free survival (DFS) between the patients with or without PBT.

Results: After exclusion, 93 eligible patients (15.4%) received PBT, compared with 512 (84.6%) who did not receive PBT; the groups were highly biased in terms of the propensity score (PS) analysis (0.096 ± 0.104 vs. 0.479 ± 0.372, $p < 0.001$). PBT was associated with an increased risk of OS (HR: 1.889, 95% CI: 1.446–2.468, $p < 0.001$) and DFS (HR: 1.589, 95% CI: 1.221–2.067, p < 0.001) in the entire cohort. After propensity score matching (PSM), no bias was observed between the groups (PS,0.136 ± 0.117 VS. 0.193 ± 0.167, $p = 0.785$). In the multivariate Cox analysis, PBT was not associated with increased risks of OS (HR: 1.172, 95% CI: 0.756–1.816, $p = 0.479$) and DFS (HR: 0.944, 95% CI: 0.608–1.466, $p = 0.799$). After propensity score adjustment, PBT was still not associated with OS or DFS after ICC curative resection.

Conclusions: The present study found that PBT did not affect DFS and OS after curative resection of ICC.

Keywords: Intrahepatic cholangiocarcinoma, Hepatectomy, Perioperative blood transfusion, Overall survival, Disease-free survival

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Background

Cholangiocarcinoma is the second most prevalent primary liver tumor worldwide, and its 3-year survival rate ranges from 20% to 60% in different regions due to difficulties in its diagnosis and poor responses to current therapies [1–5]. Surgical resection is the only feasible treatment modality that has a curative outcome for patients. Despite fast-paced improvements in surgical technique and experience, there is still a risk of massive blood loss and a subsequent need for blood transfusion. Blood transfusion is a double-edged clinical weapon that maintains blood volume to control hemorrhagic shock, supplies blood components to improve oxygen carrying capacity of blood, and regulates hemostasis by increasing blood coagulation factors. However, transfusions may cause short or severe complications including allergic reactions, hemolytic reactions, and immunosuppression. Several recent studies found PBT may be associated with worse postoperative outcomes for cancer patients [6–8]. However, without random controlled trials, it was debated whether systemic and statistic bias existed that led to this unreliable sign. Indeed, some reports argued that PBT has no impact on tumor recurrence and long-term mortality [9–12]. In this study, we summarize more than a decade of data at our institute and implemented a propensity score matching system to investigate the association between PBT and long-term outcome in ICC patients.

Methods

Participants and criteria

The study enrolled 758 consecutive ICC patients who underwent curative surgery between 2000 and 2012 at the Liver Cancer Institute, Zhongshan Hospital, Fudan University. All resections were performed or supervised by experienced hepatobiliary surgeons and used standardized procedures [13]. Additionally, all surgical specimens were confirmed by pathologic histology [2]. The following exclusion criteria were used: pre-interventional therapy before liver surgery ($n = 35$, 27 underwent transcatheter arterial chemoembolization (TACE), 1 underwent radiofrequency ablation(RFA), 2 underwent radiotherapy, and 5 underwent RFA plus TACE); hemoglobin less than 70 g/L ($n = 1$); widespread metastasis ($n = 4$); TNM staging IVb ($n = 89$); missing data of hemoglobin before surgery ($n = 14$); missing data of blood transfusion ($n = 5$); and clinical source loss (n = 5) (Fig. 1). The eligible 605 patients included 93 cases who received perioperative allogeneic blood transfusion and 512 cases without transfusion. We defined the perioperative period as the time between the third preoperative day and the seventh postoperative day.

Data source

All data on the patients' demographics, morbidity, postoperative mortality, and histological results were obtained from the hospital medical system. The TNM classification
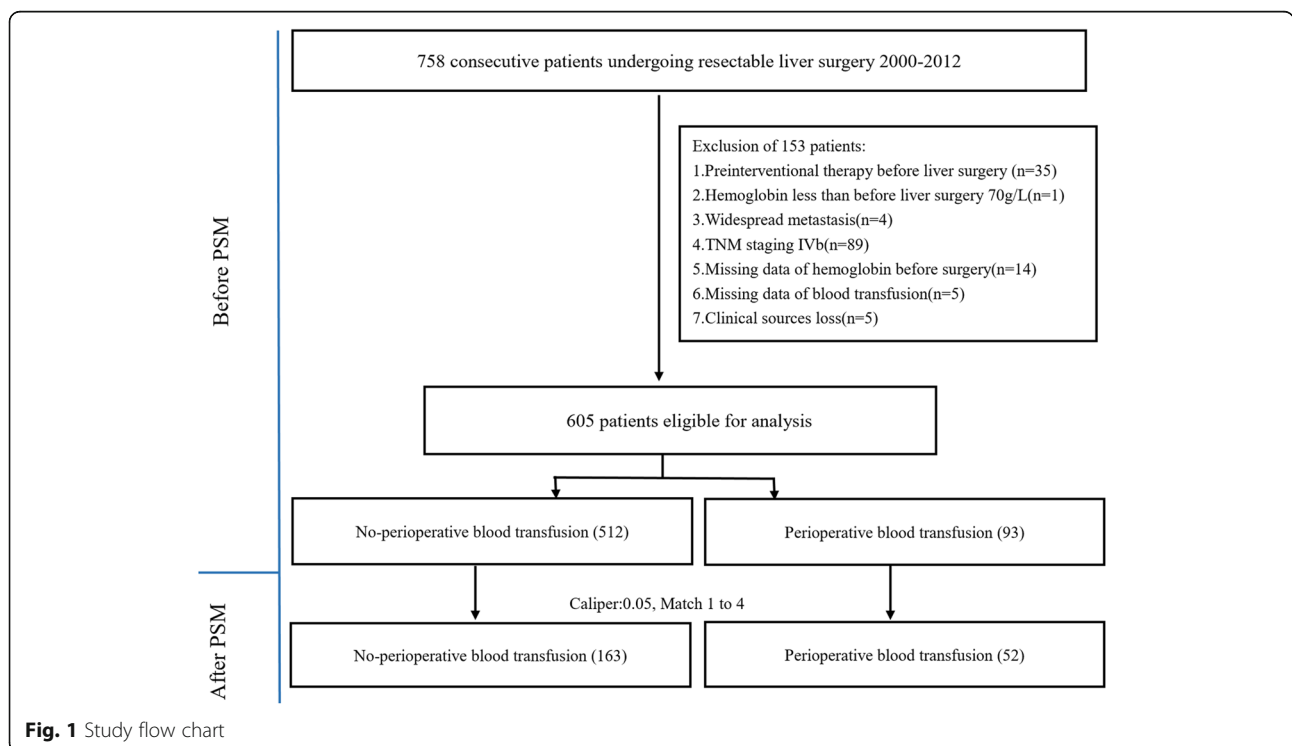

Fig. 1 Study flow chart

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was based on the AJCC Cancer Staging Manual, Seventh edition (2010) by springer New York, Inc. All patients were followed-up regularly at outpatient clinics and the Liver Cancer Institute, Zhongshan Hospital, Fudan University. The follow-up results were obtained via telephone by an experienced researcher working in the Liver Cancer Institute. All patients were regularly followed in the outpatient department and tumor markers were measured every 3 months during the first 3 years and thereafter every 6 months until the study end or loss of follow-up. An abdominal ultrasound was performed every 3 months, and abdominal computed tomography or MRI was performed 6 months postoperatively or upon suspected recurrence. The median follow-up time was 20 months (range 0–134 months), and the end follow-up time was November 2015. The primary research endpoint was the death of patient or the end follow-up time, and the secondary endpoint was follow-up dropout. The OS was defined as the period from surgery until death due to any cause. DFS was defined as the duration from surgery until the date of intrahepatic cholangiocarcinoma recurrence. The transfusion of any blood visible components including red blood cells and blood plasma were considered blood transfusion. Blood management, including processing, testing, and transporting, were quality controlled by Shanghai Blood Center. The ABO and Rh status as well as blood cross matching were conducted by the blood department of Zhongshan hospital [14].

Variables and statistics

The categorical variables are shown as whole numbers and proportions, and the continuous variables are described as the means with standard deviation as appropriate. Two-sided p values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 22 and R statistical software. To compare continuous variables that followed Gaussian distributions, t tests were used; the K-Independent-Samples Test (Kruskal Wallis H(K) test) was used for those variables did not follow Gaussian distributions. To compare proportional variables, a Two-Independent-Samples Test (Mann-Whitney U test) was used, and a Two-Related-Samples Test (Wilcoxon Signed Ranks Test) was applied to matched propensity scores [15]; all missing data are reflected in the available data [16]. We examined the following parameters: age, gender, preoperative hemoglobin (Hb), platelets (PLT), aspartate aminotransferase (AST), alanine transaminase (ALT), alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA19–9), prothrombin time (PT), international normalized ratio (INR), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (Anti-HCV), tumor maximum dimension (TMD), tumor node metastasis (TNM), intraoperative blood loss (IBL), degree of differentiation (DD), and transcatheter arterial chemoembolization (TACE). The confounders were

measured accurately using univariate Cox regression through an enter variable selection procedure. The full variable selection logistic regression was used to specify a mathematical relationship for the variables related to blood transfusion [17]. The regression models were based on Akaike's information criterion. We then adjusted for further confounding parameters in the propensity score analysis. This is a useful technique that focuses on the relationship between confounders and the treatment [18, 19]. The "PS MATCHING 3.03" and "SPSS Statistics R Essentials 22.0" and "R-2.15.3-win" R packages [20] were used to perform the matching propensity score analysis. The matching confounders was estimated by the regression models described above, and balance matching showed the values of absolute standard mean difference (SMD). The demographics and characteristics of the matched patients were compared to ensure that there were no significant differences in the baseline settings. We used univariate and multivariate Cox regressions to assess the prognostic value of blood transfusion through balanced data. The GraphPad Prism 6 software was used to draw the survival curves depicting OS and DFS.

Results

Demographics and clinical characteristics of the 605 eligible patients before PSM

Of these patients, 93 (15.37%) received blood transfusion, and 512 (84.63%) did not. We described the patient demographics and clinical characteristics for the two groups separately (Table 1). The clinical data for 9 of the 21 variables differed significantly ($P < 0.05$) as a result of a conspicuous bias with pre-described PS (0.096 ± 0.104 vs. 0.479 ± 0.372 $P < 0.001$).

Confounding factors between the PBT groups and outcome

To investigate whether the existing confounders led to any bias, a univariate Cox regression was conducted to filter out the 8 variables that were associated with the outcome without considering treatment. In the OS Cox regression model, the preoperative Hb, total bilirubin, ALT, CA19–9, anti-HCV, TMD, TNM stage, intraoperative blood loss variables were selected as independent prognostics for ICC patients. In the DFS Cox regression model, CEA, which was an extended prognostic, was picked out. Then, a univariate logistic regression was performed between patients who received blood transfusion and those who did not; the gender, preoperative Hb, PLT, total bilirubin, CA19–9, HBsAg, and intraoperative blood loss differed significantly. After multivariate analysis, only the preoperative Hb, total bilirubin, and intraoperative blood loss were left and were thus considered confounders that had to be adjusted to synthesize all of the regression models (Table 2).

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Table 1 Demographics and clinical characteristics of 605 eligible patients before PSM

Characteristic	Variable	Before PSM		
		No-PBT	PBT	*P* value
		(*n* = 512)	(*n* = 93)	
Age	Y ± SD	57.42 ± 10.815	56.54 ± 11.801	0.176[a]
Gender	female/ male	190/322	48/45	0.008[c]
Preoperative Hb	g/L ± SD	132.53 ± 16.22	118.63 ± 17.68	0.329[a]
Platelet	1 × 10^9/L ± SD	179.25 ± 64.02	201.30 ± 97.35	0.038[a]
Total bilirubin	available data	510(99.61%)	92 (98.92%)	
	umol /L ± SD	24.98 ± 55.35	86.79 ± 134.47	<0.001[b]
AST	available data	502(98.05%)	90 (96.77%)	
	U/L ± SD	44.56 ± 87.09	56.21 ± 57.45	<0.001[b]
ALT	available data	509 (99.41%)	92 (98.92%)	
	U/L ± SD	50.40 ± 95.22	57.90 ± 67.28	0.002[b]
AFP	available data	497 (97.07%)	91 (97.85%)	
	ng/mL ± SD	95.28 ± 953.72	93.02 ± 585.95	0.982[b]
CEA	available data	489 (95.51%)	87 (93.55%)	
	ng/mL ± SD	22.42 ± 154.07	61.84 ± 330.14	0.060[b]
CA19–9	available data	486 (94.92%)	86 (92.47%)	
	U/mL ± SD	1152.16 ± 3116.14	2698.09 ± 4923.75	<0.001[b]
PT	available data	506 (98.83%)	91 (97.85%)	
	s ± SD	11.20 ± 9.23	11.87 ± 3.11	0.093[b]
INR	available data	502 (98.05%)	89 (95.70%)	
	Value ±SD	0.98 ± 0.11	0.98 ± 0.14	0.910[b]
HBsAg	available data	506 (98.83%)	93 (100.00%)	
	(−)/(+)	302/204	71/22	0.002[c]
Anti-HCV	available data	502 (98.05%)	93 (100.00%)	
	(−)/(+)	493/9	91/2	0.814[c]
Tumor number	available data	511 (99.80%)	92 (98.92%)	
	1/>1	426/85	81/11	0.259[c]
TMD	available data	509 (99.41%)	93 (100.00%)	
	cm	6.48 ± 3.16	6.92 ± 3.44	0.284[b]
TNM stage	available data	489 (95.51%)	74 (79.57%)	
	I/II/III/IVa	294/80/17/98	47/15/0/12	0.433[c]
Cirrhotic nodule	available data	512 (100.00%)	91 (97.85%)	
	no/ yes	344/168	70/21	0.065[c]
DD	available data	412 (80.47%)	76 (81.72%)	
	I/II-III/IV	2/408/2 (0.49%)	0/76/0 (0.00%)	1.000[c]
IBL	available data	503 (98.24%)	93 (100.00%)	
	<1 L/≥1 L	499/4 (99.20%)	61/32 (65.59%)	<0.001[c]
Preventive TACE	no/yes	474/38 (92.58%)	86/7 (92.47%)	0.972[c]
Propensity Score	available data	501 (84.49%)	92 (15.51%)	
		0.096 ± 0.104	0.479 ± 0.372	<0.001[b]

[a]t test
[b]K-Independent-Samples Test (Kruskal Wallis H(K) test)
[c]Two-Independent-Samples Test (Mann-Whitney U test)
Values are presented as n (%) or mean ± standard deviation(SD)
Hb: hemoglobin; AST: aspartate aminotransferase; ALT: alanine transaminase; AFP: alpha fetoprotein; CEA: carcinoembryonic antigen; CA19–9: carbohydrate antigen 19–9; PT: prothrombin time; INR: international normalized ratio; HBsAg: hepatitis B surface antigen; Anti-HCV: anti-hepatitis C virus; TMD: tumor maximum dimension; TNM: tumor node metastasis; IBL: intraoperative blood loss; DD: The degree of differentiation;
TACE: transcatheter arterial chemoembolization. PSM: propensity score matching; No-PBT: no-perioperative transfusion; PBT: perioperative transfusion

Table 2 A univariate Cox regression and a variable selection logistic regression for confounding factors based on Transfusion and No-transfusion

Characteristic	Variables	Before PSM Univariate (OS, COX Regression) HR (95% CI)	P value[a]	Univariate (DFS, COX Regression) HR (95% CI)	P value[a]	Univariate (Logistic Regression) OR (95% CI)	P value[a]	Multivariate (Logistic Regression) OR (95% CI)	P value[a]
Age	Y ± SD	1.007 (0.998–1.017)	0.131	1.006 (0.997–1.014)	0.219	0.993 (0.973–1.013)	0.477		
Gender	female	reference		reference		reference		reference	
	male	1.184 (0.956–1.466)	0.121	1.163 (0.949–1.425)	0.145	0.553 (0.355–0.863)	0.009	0.790 (0.393–1.585)	0.506
Preoperative Hb	g/L ± SD	0.988 (0.981–0.994)	<0.001	0.990 (0.985–0.996)	0.001	0.951 (0.937–0.965)	<0.001	0.947 (0.927–0.967)	<0.001
Platelet	1×10^9/L ± SD	1.001 (1.000–1.003)	0.177	1.001 (0.999–1.002)	0.222	1.004 (1.001–1.007)	0.006	1.001 (0.997–1.006)	0.537
Total bilirubin	umol/L + SD	1.003 (1.002–1.004)	<0.001	1.002(1.001–1.003)	0.001	1.007 (1.005–1.010)	<0.001	1.006 (1.003–1.009)	<0.001
AST	U/L ± SD	1.000 (0.999–1.002)	0.487	1.001 (1.000–1.002)	0.205	1.001 (0.999–1.003)	0.24		
ALT	U/L ± SD	1.001 (1.000–1.002)	0.029	1.001 (1.000–1.002)	0.049	1.001 (0.999–1.003)	0.472		
AFP	ng/mL ± SD	1.000 (1.000–1.000)	0.379	1.000 (1.000–1.000)	0.451	1.000 (1.000–1.000)	0.983		
CEA	ng/mL ± SD	1.000 (1.000–1.000)	0.745	1.001 (1.000–1.001)	0.01	1.001 (1.000–1.002)	0.108		
CA19–9	U/mL ± SD	1.000 (1.000–1.000)	<0.001	1.000 (1.000–1.000)	<0.001	1.000 (1.000–1.000)	<0.001	1.000 (1.000–1.000)	0.903
PT	s ± SD	1.000 (0.988–1.012)	0.99	1.008 (0.994–1.022)	0.28	1.007 (0.986–1.028)	0.507		
INR	Value ±SD	2.307 (0.949–5.605)	0.065	1.692 (0.742–3.855)	0.211	0.714 (0.095–5.388)	0.744		
HBsAg	(−)	reference		reference		reference		reference	
	(+)	0.912 (0.737–1.130)	0.401	0.882 (0.718–1.084)	0.232	0.459 (0.275–0.764)	0.003	0.552 (0.258–1.183)	0.126
Anti-HCV	(−)	reference		reference		reference			
	(+)	0.395 (0.163–0.956)	0.04	0.507 (0.240–1.073)	0.076	1.204 (0.256–5.663)	0.814		
Tumor number	1	reference		reference		reference			
	>1	1.122 (0.835–1.507)	0.446	1.088 (0.821–1.441)	0.559	0.681 (0.348–1.332)	0.261		
TMD	cm	1.052 (1.017–1.087)	0.003	1.057 (1.025–1.090)	<0.001	1.041 (0.975–1.113)	0.229		
TNM stage	I	reference		reference		reference			
	II	1.105 (0.804–1.518)		1.192 (0.882–1.611)		1.173 (0.624–2.206)			
	III	2.167 (1.104–4.255)		1.823 (0.961–3.455)		0.000(0.000-.)			
	IVa	2.088 (1.592–2.739)	<0.001	1.657 (1.273–2.157)	0.001	0.766 (0.390–1.503)	0.784		
Cirrhotic nodule	no	reference		reference		reference			
	yes	1.127 (0.910–1.397)	0.274	1.028 (0.834–1.266)	0.799	0.614 (0.365–1.035)	0.067		
DD	I	reference		reference		reference			
	II-III	2997.401 (0.000-.)		8142.694 (0.000-.)		300,921,742.177 (0.000-.)			
	IV	2632.881 (0.000-.)	0.982	8450.077 (0.000-.)	0.997	1.000 (0.000-.)	1.000		

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Table 2 A univariate Cox regression and a variable selection logistic regression for confounding factors based on Transfusion and No-transfusion *(Continued)*

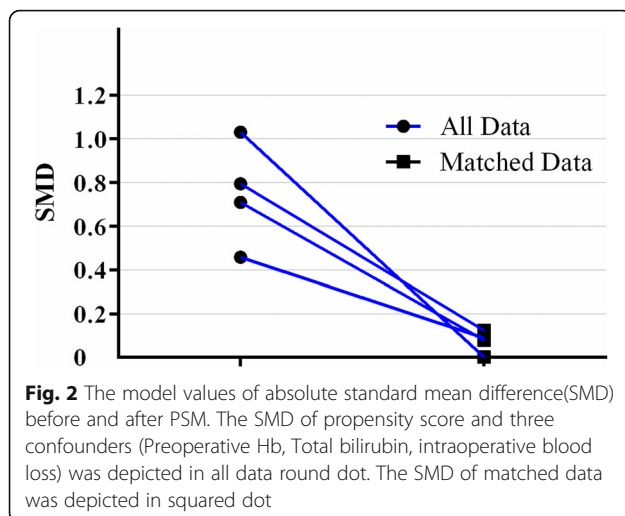| Characteristic	Variables	Before PSM				Univariate (Logistic Regression)		Multivariate (Logistic Regression)	
		Univariate (OS, COX Regression)		Univariate (DFS, COX Regression)					
		HR (95% CI)	P value[a]	HR (95% CI)	P value[a]	OR (95% CI)	P value[a]	OR (95% CI)	P value[a]
IBL	<1000 mL	reference		reference		reference		reference	
	≥1000 mL	1.733 (1.184–2.535)	0.005	1.816 (1.243–2.652)	0.002	65.443 (22.383–191.341)	<0.001	168.205 (43.249–654.184)	<0.001
Preventive TACE	no	reference		reference		reference			
	yes	0.841 (0.585–1.209)	0.349	1.300 (0.914–1.848)	0.144	1.015 (0.439–2.348)	0.972		

OS: overall survival; DFS: disease-free survival; OR: odd ratio; HR: hazard ratio; "": indicate the exceeded value
[a]likelihood ratio test

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Demographics and clinical characteristics of 215 matched patients after PSM

Before performing propensity score matching analysis, we used a calculation called "PS Power and Sample Size Calculations(Version 3.0, January 2009)" [21, 22] to estimate the ideal sample size. We are planning a study with 1 PBT subject matched to 4 no-PBT subjects, an accrual interval of 1 month, and additional follow-up after the accrual interval of 133 months. Prior data indicate that the median survival time on the no-PBT is 26 months. If the true median survival times on the PBT and no-PBT are 26 and 12 months, respectively, we will need to study 31 PBT subjects and 124 no-PBT subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) $0.9(\beta = 0.1)$. The Type I error probability associated with this test of this null hypothesis is $0.01(\alpha)$.

The propensity score matching procedure was performed to reduce confounding variables based on the three identified factors. The caliper was set at 0.05, and we used an optimal match ratio of 1:4. We found 52 of the 93 transfused patients were matched with 163 of the 512 no-transfused patients, which is more than the ideal sample size we calculated previously to obtain the significant conclusion. The propensity score suggests there were no biases in the matched groups (0.136 ± 0.117 vs. 0.193 ± 0.167, $P = 0.785$). Figure 2 shows the matched data absolute standardized mean difference (SMD), and the SMD of all three confounders and PS decreased to less than 0.2. In Table 3, the matched patient characteristics were compared, and no significant differences were shown between the groups, considering all 21 variables.

Fig. 2 The model values of absolute standard mean difference(SMD) before and after PSM. The SMD of propensity score and three confounders (Preoperative Hb, Total bilirubin, intraoperative blood loss) was depicted in all data round dot. The SMD of matched data was depicted in squared dot

Perioperative blood transfusion has no effect on OS and DFS after PSM

The univariate Cox proportional hazards regression analysis indicated PBT has a poor effect on OS and DFS before propensity score matching, which forebodes an 88.9% risk of overall mortality (HR: 1.889, 95% CI: 1.446–2.468, $p < 0.001$) and 58.9% risk of DFS (HR: 1.589, 95% CI: 1.221–2.067, $p < 0.001$). Additionally, the Kaplan-Meier curve of OS showed the no-transfused group has a significant benefit compared with transfused group ($p < 0.0001$) (Fig. 3), the median survival months(MSMs) of PBT (12 months) is obviously less than non-PBT (26 months), Of note, no difference was found in DFS ($p = 0.3807$), same as the MSMs (PBT = 15 months, non-PBT = 16 months). However, after performing a multivariate risk dependent Cox regression we found that neither OS (HR: 1.172, 95% CI: 0.756–1.816, $p = 0.479$) nor DFS (HR: 0.944, 95% CI: 0.608–1.466, $p = 0.799$) was significantly different due to blood transfusion. Our findings suggest it was not a statistically independent prognostic risk. After propensity score matching, PBT had no significant effect on the risk of OS (HR: 1.429, 95% CI: 0.972–2.103, $p = 0.070$) and DFS (HR: 1.262, 95% CI: 0.858–1.856, $p = 0.238$) (Table 4). Furthermore, the Kaplan-Meier plot showed similar trends for OS ($P < 1.000$) and DFS ($P < 0.230$). Both PBT and non-PBT MSMs to OS is 21 months and no significant difference (PBT = 12 months, non-PBT = 15 months) to DFS.

Discussion

Several studies have focused on how PBT affects gastrointestinal carcinomas and other tumors [6–8, 10, 11, 14, 23, 24], and some concluded that PBT led to a poor outcome and increased the probability of recurrence [6–8, 25, 26]]. However, others reported that PBT was not an independent prognostic factor for tumor recurrence and OS [24]. Müller et al. reached the same conclusion in a study of 128 advanced cholangiocarcinoma patients [9]: the small number of sources and heterogeneity from a mixture of intrahepatic, hilar, and distal cholangiocarcinoma may result an unconvincing selection bias. In our consecutive retrospective cohort study with 758 patients, we only recruited those who had intrahepatic cholangiocarcinoma without metastasis, and we found that PBT had no prognosis-related effect on OS and DFS.

We first explored the variables in 605 patients and found a significant bias between the two groups, which is consistent with previous reports. The survival analysis showed transfusion was an independent prognostic cause of OS and DFS. Moreover, we tried to determine which variables interacted with the outcome and treatment, using a combination of logistic and Cox regressions, and we found three interference factors: preoperative Hb, total bilirubin, and intraoperative blood loss. The propensity score matching was performed to reduce the confounding influence

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Table 3 Demographics and clinical characteristics of 215 patients after PSM

Characteristic	Variable	After PSM		
		No-PBT (n = 163)	PBT (n = 52)	P value
Age	Y ± SD	57.67 ± 10.77	56.90 ± 12.34	0.114[a]
Gender	female/male	72/91	27/25	0.330[c]
Preoperative Hb	g/L ± SD	125.38 ± 15.90	120.25 ± 18.72	0.232[a]
Platelet	1×10^9/L ± SD	180.29 ± 65.50	193.38 ± 93.35	0.350[a]
Total bilirubin	umol/L ± SD	31.34 ± 62.77	60.36 ± 115.37	0.070[b]
AST	available data	161 (98.77%)	50 (96.15%)	
	U/L ± SD	46.25 ± 81.74	47.92 ± 62.24	0.763[b]
ALT	U/L ± SD	51.14 ± 80.64	53.35 ± 77.74	0.374[b]
AFP	available data	158 (96.93%)	52 (100.00%)	
	ng/mL ± SD	196.77 ± 1590.50	123.49 ± 741.51	0.994[b]
CEA	available data	157 (96.32%)	49 (94.23%)	
	ng/mL ± SD	22.66 ± 149.81	95.03 ± 437.78	0.375[b]
CA19–9	available data	156 (95.71%)	48 (92.31%)	
	U/mL ± SD	1170.62 ± 3041.71	1491.47 ± 3691.9	0.439[b]
PT	available data	161 (98.77%)	51 (98.08%)	
	s ± SD	10.76 ± 4.65	11.96 ± 3.59	0.075[b]
INR	available data	158 (96.93%)	50 (96.15%)	
	Value ±SD	0.98 ± 0.13	0.98 ± 0.15	0.997[b]
HBsAg	available data	160 (98.16%)	52 (100.00%)	
	(−)/(+)	100/60	39/13	0.100[c]
Anti-HCV	available data	159 (97.55%)	52 (100.00%)	
	(−)/(+)	157/2	51/1	0.726[c]
Tumor number	1/>1	140/23	43/9	0.574[c]
TMD	cm	6.84 ± 3.39	6.83 ± 3.38	0.967[c]
TNM stage	available data	155(95.09%)	44 (84.62%)	
	I/II/III/IVa	92/24/5/34	25/11/0/8	0.968[c]
Cirrhotic nodule	available data	163 (100%)	50 (96.2%)	
	no/yes	112/51	40/10	0.123[c]
DD	available data	126 (77.30%)	43 (82.70%)	
	I/ II-III	2/124 (1.59%)	0/43 (0.00%)	0.407[c]
IBL	<1 L/≥1 L	161/2 (98.77%)	52/0 (100.00%)	0.423[c]
Preventive TACE	no/yes	153/10 (93.87%)	47/5 (90.38%)	0.392[c]
Propensity Score		0.136 ± 0.117	0.193 ± 0.167	0.785[d]

[a] t test
[b] K-Independent-Samples Test (Kruskal Wallis H(K) test)
[c] Two-Independent-Samples Test (Mann-Whitney U test)
[d] Two-Related-Samples Test (Wilcoxon Signed Ranks Test)
Values are presented as n (%) or mean ± standard deviation

based on the three factors. To obtain the optimal matching data, the match ratio of 1:4 and a general caliper value of 0.05 were applied based on Abadie's research [17]. We matched 52 transfused patients to 163 no-transfused patients, and all SMD values were less than 0.2, which suggests that the matching model was well adjusted [27]. A further exploration of all variables was performed using the same statistical method, and no significant bias persisted between the groups in terms of the *P* value and PS. The survival analysis of OS and DFS also revealed that PBT had no effect on OS or DFS. Admittedly, we could not deny its effect on delaying the duration of the hospital stay, a higher

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Fig. 3 Kaplan-Meier survival plot of OS and DFS before and after PSM. The survival curve of overall survival and disease-free survival in unadjusted model (**a**, **b**). The survival curve of overall survival and disease-free survival after matched (**c**, **d**). Median survival months were showed in each figure
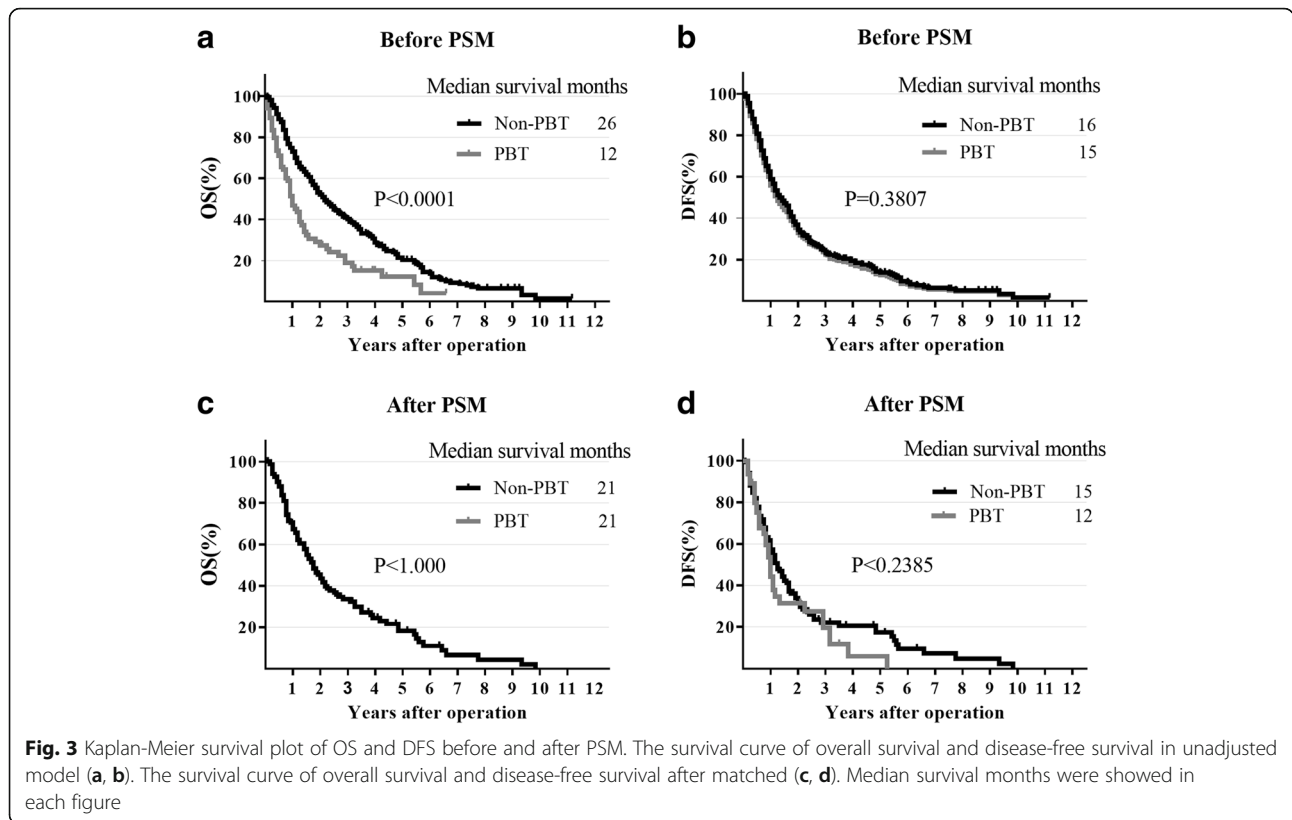
probability of complication such as febrile reaction, allergic reaction, graft-vs. -host disease (GVHD), hemolytic reaction, and other long-term results like virus infection and immunosuppression.

Fundamental confounding factors and inappropriate statistical methods may result in the illusion that PBT may lead to poor survival. Lian X et al. demonstrated the positive viewpoint by using a large gastric adenocarcinoma data set [6]. They revealed that PBT resulted in poor prognosis but not an independent prognostic factor based on a univariate and multivariate Cox analysis. The explanation might be different distribution of clinicopathological features between two groups and some confounder existed, such as TNM stage and intraoperative blood loss. Our ICC data set indeed found that intraoperative blood loss is an important confounder, in fact, it is more likely to transfuse blood for

those massively bleeding patients. Norihisa Kimura et al. concluded that PBT was a strong risk factor for both recurrence and poor survival based on 66 HCCA after aggressive surgical resection [8], they also kindly pointed out their limit of the small sample size may have resulted in a loss of statistical power. Finding that such confounders could adversely cover up the truth. Therefore, an appropriate technique such as PSM must be performed to avoid the bias before the final analysis, and ideal sample size of matched pairs may be necessary to strength the conclusion.

There are several limitations in this study. First, although the propensity score matching analysis is an acceptable method of simulating a random controlled trial, but it is still not sufficient to make up for the value of RCTs in circumstances with ethical challenges. Second, our study only recruited patients within China, and the results may

Table 4 Univariate and multivariate Cox analysis predicting OS and DFS based on Transfusion and No-transfusion

Characteristic	Variable	Before PSM				After PSM	
		univariate		multivariate		univariate	
		HR (95% CI)	P value[a]	HR (95% CI)	P value[a]	HR (95% CI)	P value[a]
PBT(OS)	no	reference	<0.001	reference	0.479	reference	0.070
	yes	1.889 (1.446–2.468)		1.172 (0.756–1.816)		1.429 (0.972–2.103)	
PBT(DFS)	no	reference	0.001	reference	0.799	reference	0.238
	yes	1.589 (1.221–2.067)		0.944 (0.608–1.466)		1.262 (0.858–1.856)	

[a]likelihood ratio test

not be applicable to other countries especially western states. Third, the exclusion of patients in the propensity score matching analysis reduced the statistical power. Finally, unknown or unobserved confounding factors may contribute to potential bias because the missing source collection and available data may result in information bias.

Conclusions

In conclusion, our data suggest that PBT was not associated with the long-term outcome of ICC. Inappropriate statistical analyses may lead to variable results, and risk adjustments can eliminate the detrimental effect.

Abbreviations

AFP: alpha fetoprotein; ALT: alanine transaminase; Anti-HCV: anti-hepatitis C virus; AST: aspartate aminotransferase; CA19–9: carbohydrate antigen 19–9; CEA: carcinoembryonic antigen; DD: The degree of differentiation; DFS: disease-free survival; Hb: hemoglobin; HBsAg: hepatitis B surface antigen; HR: hazard ratio; IBL: intraoperative blood loss; ICC: intrahepatic cholangiocarcinoma; INR: international normalized ratio; MSMs: median survival months; No-PBT: no-perioperative transfusion; OR: odd ratio; OS: overall survival; PBT: perioperative blood transfusion; PBT: perioperative transfusion; PS: propensity score; PSM: propensity score matching; PT: prothrombin time; RCT: random controlled trials; SMD: absolute standardized mean difference; TACE: transcatheter arterial chemoembolization; TMD: tumor maximum dimension; TNM: tumor node metastasis

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
PYZ, ZT, WRL conceived of the project and designed the research and drafted the manuscript. WRL, MXT, XFJ, LJ, PYZ, HW, CYT collected and organized the data, PYZ, ZT carried out the research, ZBD, YFP, SJQ, ZD, JZ, JF supervised the research, discussed its integrity and revised each parts critically for publication, YHS were responsible for quality control and managed the experimental design, reviewed the manuscript and provided funding support. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study with clinical data was approved by the Ethics Committee of the Zhongshan Hospital, Fudan University (Y2017–279). We clarify that all clinical data in this study was collected in patients who had given written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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