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Intraoperative Blood Transfusion and Postoperative Morbidity Following Liver Resection

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Background: Blood transfusion is common during liver resection (LR). The objective of the present study was to investigate the effects of intraoperative transfusion of different blood components on post-LR morbidity.

Material/Methods: We included 610 patients undergoing LR and grouped them according to intraoperative transfusion of different blood components: packed red blood cells only (PRBC, n=81); frozen fresh plasma, platelets, and cryoprecipitate (FPC, n=38); transfusion only with PRBC + FPC transfusion (n=244); and no blood transfusion (n=247). Propensity score matching (PSM) analysis was used to mitigate selection bias in comparisons.

Results: The overall blood transfusion rate was 59.5%. In comparison with the no blood transfusion group, PRBC-only and PRBC + FPC transfusion were more common in patients with lower preoperative hemoglobin, worse liver function, larger tumor size, and undergoing a major LR, and thus were associated with increased postoperative morbidity. In contrast, FPC-only transfusion was more frequent in patients with a liver function of Child-Pugh B and lower preoperative albumin *vs.* the no blood transfusion group. In the propensity model, transfusion of PRBC (PRBC-only and PRBC+FPC) and FPC (FPC-only and FPC+PRBC) were significantly associated with increased postoperative complications *vs.* the no blood transfusion group (OR and 95% CI, 1.9 [1.2–2.7], p=0.002; OR and 95% CI, 1.6 [1.0–2.4], p=0.029). In contrast, intraoperative PRBC-only or FPC-only transfusion showed no significant adverse effects on postoperative morbidity.

Conclusions: Allogenic transfusion of PRBC and FPC blood components was associated with increased postoperative morbidity after liver surgery. Different blood components should be used only when absolutely necessary.

MeSH Keywords: Blood Transfusion • General Surgery • Liver Neoplasms • Morbidity

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Background

Liver resection (LR) is the treatment of choice for a wide variety of liver tumors, including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and hepatic metastatic tumors [1]. With advancements in surgical techniques and improvements in perioperative critical care, in-hospital mortality after LR has decreased significantly (<5%) [2–5]. However, postoperative morbidity still remains as high as 60% [4,6–8]. The liver is an organ with dual blood supply from the portal vein and hepatic artery. Moreover, the majority of patients in Asia with liver tumors present with liver fibrosis and cirrhosis, mainly due to hepatitis B or C virus (HBV or HCV) infection, and thus have impaired liver function, fragile coagulation function, hypoalbuminemia, and even anemia and thrombocytopenia [9–12]. Therefore, LR is still one of the most technically demanding and high-risk procedures, and blood transfusion is commonly needed during LR.

Blood transfusion is a life-saving procedure for critically ill patients with massive blood loss or anemia. Particularly in patients undergoing major operations, transfusion of packed red blood cell (PRBC), fresh frozen plasma (FFP), platelets, or cryoprecipitate is critical in maintaining hemostasis, correcting abnormal coagulation, and ensuring adequate tissue perfusion and oxygenation [13]. However, some studies strongly advocated a restrictive PRBC transfusion in surgery patients, since perioperative blood transfusion is associated with increased postoperative morbidity [14–17].

The "yellow" blood products, including FFP, platelets, and cryoprecipitate (FPC), are largely used in patients undergoing liver surgery to correct coagulopathy and promote microvascular hemostasis. However, overutilization of FPC is common, since there is no consensus on the optimal indication and threshold for utilization of FPC. Perioperative or intraoperative transfusion of FFP and platelet has been found to increase the risk of postoperative complications in several studies but not in others [13,18–20].

There is still no strong evidence of the potential influence of intraoperative PRBC and FPC transfusion on immediate outcome of patients following LR. Moreover, most patients in the previous studies enrolled as PRBC or FFP transfusion groups were probably transfused with both [16–20], since most patients undergoing liver surgery needed transfusion with both PRBC and the "yellow" blood products. Therefore, the results might reflect a dual influence of "red" and "yellow" blood products on postoperative morbidity. The objective of the present study was to assess the separate and combined impacts of PRBC and FPC blood products transfusion on postoperative complications after LR.

Material and Methods

Study population

We included all patients undergoing hepatic resection for liver malignancies from January 2008 to December 2015 in our hospital. Patients with laparoscopic or emergent surgeries were excluded from the study. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. A waiver of informed consent was obtained because the data were analyzed from electronic medical records and reported without personal identifiers.

Data collection and definition

The demographic, laboratory, imaging, surgical, and pathological data of the patients were obtained from the medical records and computer database. All the laboratory data were documented prior to surgery. The total volume of intraoperative blood loss and blood transfusion were documented in the anesthesia records, including PRBC, FFP, platelets, and cryoprecipitate. The PRBC transfusion group was defined as intraoperative transfusion of PRBC with or without transfusion of FPC and the FPC transfusion group was defined as intraoperative transfusion of FPC with or without transfusion of PRBC.

The postoperative complications were evaluated for each patient during the hospital stay and within 30 days after surgery. The complications were defined as we previously reported [16]. The severity of all complications was classified according to Clavien-Dindo classification of surgical complications [21]. Resection of 3 or more liver segments was defined as major hepatectomy, while resection of 2 or less was classified as minor hepatectomy [22].

Statistical analysis

Data are expressed as mean ± standard deviation for numerical variables and number (percentages) for nominal variables. Numerical data were compared with one-way ANOVA or Kruskal-Wallis test among the groups, and with the *t* test or Mann-Whitney U test for comparisons between the 2 groups. Comparison of categorical data was performed with the chi-squared test or Fisher's exact test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated by using logistic regression. A p value <0.05 was considered statistically significant. Statistical analysis was carried out using SPSS 22.0 (Chicago, IL, USA).

To eliminate the selection bias, we introduced propensity score matching (PSM) analysis into the present study to balance the baseline characteristics associated with postoperative complications [23–26] and thereby simulated random

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group allocation [27]. Propensity scores were estimated using a logistic regression model based on baseline patient characteristics, including age, sex, body mass index (BMI), comorbidities, presence of hepatitis, liver function, American Society of Anesthesiologists (ASA) classification, intraoperative hepatic inflow occlusion, and surgery types. We performed 1: 1 matching without replacement using a caliper with a width 0.1 of the standard deviation to generate matched pairs of patients.

Results

Baseline characteristics

In total, 610 patients undergoing liver resection for treatment of HCC (n=513, 84.1%), ICC (n=58, 9.5%), combined HCC-ICC (n=3, 0.5%), and other liver malignancies (n=36, 5.9%) were included: 442 (72.5%) patients were HBV- and/or HCV-positive and 363 (59.5%) patients were transfused with autologous blood products intraoperatively. Among the whole cohort, 325 (53.3%) patients received at least 1 unit of PRBC intraoperatively, and 282 (46.2%) patients were transfused with at least 100 ml FFP, 10 U platelets, or 1U cryoprecipitate intraoperatively. The patients were divided into 4 groups depending on the intraoperative transfusion of different blood components: group A was PRBC-only transfusion (n=81), group B was PRBC and FPC transfusion (n=244), group C was FPC-only transfusion (n=38), and group D was no blood transfusion (n=247).

Patients in the 4 groups were similar in age, sex, BMI, cigarette smoking, diabetes, and cardiovascular disease before surgery (Table 1). PRBC-only transfusions were more common in HBV/HCV-negative patients than in the other 3 groups (all $p<0.05$). Not surprisingly, in comparison with the no blood transfusion group, PRBC-only and PRBC + FPC transfusion were more likely indicated because of lower preoperative hemoglobin and worse liver function, and thus were more commonly needed in patients with larger tumor size and in those experiencing a major LR with longer operation time and larger volume of intraoperative blood loss (Table 1). In contrast, FPC-only transfusion was more frequent in patients with a liver function of Child-Pugh B and lower preoperative albumin *vs.* the no blood transfusion group. However, the tumor status and surgical procedures were not significantly different between the FPC-only and no blood transfusion groups.

Complications associated with blood transfusion

The influence of different blood components transfusion on postoperative complications is shown in Table 2, indicating that the overall complications were significantly higher in the PRBC-only and PRBC + FPC transfusion groups than in the no blood transfusion group (OR and 95% CI, 1.8 [1.1–3.0], 2.3 [1.6–3.3], respectively, both $p<0.05$, Table 2). Specifically, patients in the PRBC+FPC transfusion group had higher incidence of peritoneal effusion and liver failure than in the no blood transfusion group (both $p<0.05$, Table 2). PRBC-only transfusion was associated with increased wound infection risk *vs.* no blood transfusion ($p<0.05$, Table 2). However, no significant difference was identified between the single FPC transfusion and no blood transfusion groups in overall morbidity (OR and 95% CI, 1.1 [0.5–2.2], $p>0.05$, Table 2) or any complications (all $p>0.05$, Table 2).

Complications after PRBC transfusion in propensity model

Due to the significant difference of patients at baseline, 204 pairs of patients were generated by PSM from 325 PRBC-transfused patients (with or without FPC transfusion) and 247 non-transfused patients. The patients in the 2 groups were well matched with age, sex, comorbidities, liver function, ASA classification, and surgical procedures (all $p>0.05$, Supplementary Table 1). In the propensity model, the overall morbidity after LR was significantly higher in PRBC-transfused than in non-transfused patients (OR and 95% CI, 1.9 [1.2–2.7], $p=0.002$, Table 3). Moreover, more patients in the PRBC transfusion group developed severe complications than in the no blood transfusion group (Clavien-Dindo III–V, 30.6% *vs.* 17.5%, p=0.039, Table 3). Specifically, peritoneal effusion and liver failure were more common in PRBC-transfused *vs.* non-transfused patients (32.8% *vs.* 24%, $p=0.048$, and 6.4% *vs.* 1%, $p=0.06$, Table 3).

Complications after FPC transfusion in propensity model

Similarly, 188 pairs of patients were generated from 287 FPC-transfused patients (with or without PRBC transfusion) and 247 no blood transfusion patients by PSM and who were well matched for age, sex, comorbidities, liver function, ASA classification, and surgical procedures (all $p>0.05$, Supplementary Table 2). In the propensity model, the overall complications and liver failure were found to be higher in the FPC transfusion group compared to the no blood transfusion group (OR and 95% CI, 1.6 [1.0–2.4], $p=0.029$, and 7.5 [1.7–33.4], $p=0.03$, Table 4).

Complications after PRBC- or FPC-only transfusion

To exclude the possible synergistic effects of PRBC and FPC, we entered all 81 patients with PRBC-only transfusion (no FPC transfusion) and 247 no blood transfusion patients into PSM analysis, and finally generated 79 pairs of patients who were equivalent in age, sex, comorbidities, liver function, ASA classification, and surgical procedures (all $p>0.05$, Supplementary Table 3). In this propensity model, no difference was identified in overall complications or severity of postoperative complications, or in any complications between the 2 groups (all $p>0.05$, Table 5).

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Table 1. Baseline characteristics of all eligible patients in each group depending on intraoperative blood components transfusion.

Variable	Group a, PRBC only (n=81)	Group b, PRBC+FPC (n=244)	Group c, FPC only (n=38)	Group d, no transfusion (n=247)	*p* Value
Male gender	55 (67.9%)	195 (79.9%)	31 (81.6%)	193 (78.1%)	0.136
Age (year)	52±13	52±12	52±11	54±12	0.555
Body mass index (kg/m^2)	22.4±3.0	22.8±3.5	22.2±2.8	23.1±3.1	0.151
Cigarette smoking	32 (39.5%)	104 (42.6%)	19 (50%)	99 (40%)	0.662
Diabetes mellitus	9 (11.1%)	19 (7.8%)	4 (10.5%)	25 (10.1%)	0.744
HBV/HCV positive	48 (59.3%) ab,ac,ad	178 (73%)	32 (84.2%)	184 (74.5%)	**0.017**
Cardiovascular disease	14 (17.3%)	34 (13.9%)	5 (13.2%)	43 (17.4%)	0.693
Child-Pugh class					**0.002**
A	74 (91.4%) ad	224 (91.8%) bd	34 (89.5%) cd	244 (98.8%)	
B	7 (8.6%)	20 (8.2%)	4 (10.5%)	3 (1.2%)	
ASA classification					0.098
1	3 (3.7%)	8 (3.3%)	1 (2.6%)	9 (3.6%)	
2	61 (75.3%)	168 (68.9%)	28 (73.7%)	199 (80.6%)	
3	17 (21%)	68 (27.9%)	9 (23.7%)	39 (15.8%)	
ICG 15min retention (%)	11.1±14.6	10.9±9.2	12.7±11.5	9.5±14.1	0.827
Prothrombin time (s)	13.5±1.3	13.7±1.3	13.9±1.5	13.6±1.1	0.123
Hemoglobin (g/L)	128.2±21.3 ad	130.3±18.8 bd	132.9±18.8	137.5±18.0	**<0.001**
Platelet count (×10^9/L)	161.8±81.7	152.7±87.2	132.6±71.9	147.3±64.2	0.220
White blood cells (×10^9/L)	5.6±2.1	5.8±2.9	4.8±1.7	5.5±2.3	0.109
Aspartate aminotransferase (U/L)	43.5±26.4 ab	66.7±66.5 bd	53.7±42.8	42.1±45.9	**<0.001**
Alanine aminotransferase (U/L)	23.8±39.1	27.9±56.3	24.2±27.0	16.4±22.8	0.078
Total bilirubin (μmol/L)	23.8±39.1	27.9±56.3 bd	24.2±27.0	16.4±22.8	**0.023**
Albumin (g/L)	39.3±5.2 ab	37.8±5.6 bd	37.7±5.5 cd	39.5±4.5	**0.001**
Alpha-fetoprotein (ng/ml)	3786.7±1383.4	8071.3±1192.6	7153.3±2636.1	5695.5±1096.4	0.200
Operation time (min)	264±90 ac,ad	284±97 bc,bd	199±75	185±69	**<0.001**
Intraoperative blood loss (ml)	776.9±453.5 ab,ac,ad	1243.5±1033.8 bc,bd	423.8±335.8	391.8±282.1	**<0.001**
Hepatic inflow occlusion	50 (61.7%)	175 (71.7%) bd	23 (60.5%)	141 (57.1%)	**0.008**
Maximal tumor size (cm)	6.4±3.2 ab,ac,ad	7.8±3.8 bc,bd	5.0±2.9	5.2±2.8	**<0.001**

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Table 1 continued. Baseline characteristics of all eligible patients in each group depending on intraoperative blood components transfusion.

Variable	Group a, PRBC only (n=81)	Group b, PRBC+FPC (n=244)	Group c, FPC only (n=38)	Group d, no transfusion (n=247)	*p* Value
Tumor location					**0.007**
Left lobe	36 (44.4%) ad	75 (30.7%) bd	10 (26.3%)	54 (21.9%)	
Right lobe	43 (53.1%)	159 (65.2%)	27 (71.1%)	187 (75.7%)	
Bilobar involvement	2 (2.5%)	10 (4.1%)	1 (2.6%)	6 (2.4%)	
Primary disease*					**0.011**
Hepatocellular carcinoma	59 (72.8%) ab,ac,ad	204 (83.6%)	36 (94.7%)	217 (87.9%)	
Intrahepatic cholangiocarcinoma	17 (21%)	26 (10.7%)	1 (2.6%)	17 (6.9%)	
Other liver malignancies	5 (6.2%)	15 (6.2%)	2 (5.3%)	14 (5.7%)	
Surgical procedures					**<0.001**
Minor hepatectomy	52 (64.2%) ac,ad	131 (53.7%) bc,bd	35 (92.1%)	214 (86.6%)	
Major hepatectomy	29 (35.8%)	113 (46.3%)	3 (7.9%)	33 (13.4%)	

PRBC – packed red blood cells; FPC – frozen fresh plasma, platelet and cryoprecipitate; HBV – hepatitis B virus; HCV – hepatitis C virus; ASA – the American Society of Anesthesiologists; ICG – indocyanine green; * Three cases of combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma. ab – $p<0.05$ when compared between group a and b; ac – $p<0.05$ when compared between group a and c; ad – $p<0.05$ when compared between group a and d; bc – $p<0.05$ when compared between group b and c; bd – $p<0.05$ when compared between group b and d; cd – $p<0.05$ when compared between group c and d.

Table 2. Comparison of the postoperative morbidity among different groups w/n intraoperative blood components transfusion following liver resection.

Complications	Group a, PRBC only (n=81)	Group b, PRBC+FPC (n=244)	Group c, FPC only (n=38)	Group d, no transfusion (n=247)	*p* Value
Peritoneal effusion	23 (28.4%)	91 (37.3%)bd	11 (28.9%)	53 (21.5%)	**0.002**
Hydrothorax	15 (18.5%)	30 (12.3%)	2 (5.3%)	27 (10.9%)	0.163
Liver failure	2 (2.5%) ab	24 (9.8%) bd	2 (5.3%)	2 (0.8%)	**<0.001**
Biliary fistula	3 (3.7%)	17 (7%)	0	9 (3.6%)	0.144
Peritoneal infection	3 (3.7%)	8 (3.3%)	0	6 (2.4%)	0.642
Pulmonary infection	2 (2.5%)	11 (4.5%)	1 (2.6%)	8 (3.2%)	0.784
Intraperitoneal bleeding	4 (4.9%)	5 (2%)	1 (2.6%)	3 (1.2%)	0.250
Renal failure	1 (1.2%)	4 (1.6%)	0	0	0.110
Systemic sepsis	1 (1.2%)	3 (1.2%)	0	4 (1.6%)	0.873
Wound infection	2 (2.5%) ad	1 (0.4%)	0	0	**0.048**
Other complications	3 (3.7%)	16 (6.6%)	1 (2.6%)	6 (2.4%)	0.139

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Table 2 continued. Comparison of the postoperative morbidity among different groups w/n intraoperative blood components transfusion following liver resection.

Complications	Group a, PRBC only (n=81)	Group b, PRBC+FPC (n=244)	Group c, FPC only (n=38)	Group d, no transfusion (n=247)	*p* Value
Clavien-Dindo classification					0.070
Grade I–II	29 (69%)	95 (67.9%)	13 (86.7%)	75 (81.5%)	
Grade III–V	13 (31%)	45 (32.1%)	2 (13.3%)	17 (18.5%)	
All complications	42 (51.9%) ad	140 (57.4%) bc,bd	15 (39.5%)	92 (37.2%)	**<0.001**
OR (95% CI)	1.8 (1.1–3.0) ad	2.3 (1.6–3.3) bd	1.1 (0.5–2.2)	1 (reference)	

PRBC – packed red blood cells; FPC – frozen fresh plasma, platelet and cryoprecipitate; OR – odds ratio; CI – confidence interval; ab – $p<0.05$ when compared between group a and b; ac – $p<0.05$ when compared between group a and c; ad – $p<0.05$ when compared between group a and d; bc – $p<0.05$ when compared between group b and c; bd – $p<0.05$ when compared between group b and d.

Table 3. Postoperative complications in patients of PRBC transfusion group and no blood transfusion group in a propensity score model.

Complications	PRBC group (n=204)	No transfusion group (n=204)	p Value
Peritoneal effusion	67 (32.8%)	49 (24%)	**0.048**
Hydrothorax	31 (15.2%)	23 (11.3%)	0.306
Liver failure	13 (6.4%)	2 (1%)	**0.006**
Biliary fistula	12 (5.9%)	8 (3.9%)	0.493
Peritoneal infection	4 (2%)	5 (2.5%)	1.000
Pulmonary infection	8 (3.9%)	7 (3.4%)	1.000
Intraperitoneal bleeding	7 (3.4%)	3 (1.5%)	0.338
Renal failure	1 (0.5%)	0	1.000
Systemic sepsis	1 (0.5%)	4 (2%)	0.372
Wound infection	1 (0.5%)	0	1.000
Other complications	12 (5.9%)	4 (2%)	0.071
Clavien-Dindo classification			**0.039**
Grade I–II	77 (69.4%)	66 (82.5%)	
Grade III–V	34 (30.6%)	14 (17.5%)	
All complications	111 (54.4%)	80 (39.2%)	**0.002**
OR (95% CI)	1.9 (1.2-2.7)	1 (reference)	**0.002**

PRBC – packed red blood cells; OR – odds ratio; CI – confidence interval.

The small number of patients receiving FPC-only transfusion (n=38) limited the PSM analysis in the present study. However, although more patients presented with liver function of Child-Pugh class B in the single FPC transfusion group than in the no blood transfusion group (10.5% *vs.* 1.2%, $p<0.05$, Table 1), the overall incidence and severity of postoperative complications and the incidence of each complication were similar between the 2 groups (all $p>0.05$, Table 2).

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Table 4. Postoperative complications in patients of FPC transfusion group and no blood transfusion group in a propensity score model.

Complications	FPC group (n=188)		No transfusion group (n=188)		p Value
Peritoneal effusion	60	(31.9%)	48	(25.5%)	0.171
Hydrothorax	21	(11.2%)	19	(10.1%)	0.738
Liver failure	14	(7.4%)	2	(1.1%)	**0.003**
Biliary fistula	9	(4.8%)	8	(4.3%)	1.000
Peritoneal infection	4	(2.1%)	5	(2.7%)	1.000
Pulmonary infection	6	(3.2%)	6	(3.2%)	1.000
Intraperitoneal bleeding	4	(2.1%)	3	(1.6%)	1.000
Renal failure	2	(1.1%)	0		0.499
Systemic sepsis	1	(0.5%)	2	(1.1%)	1.000
Wound infection	1	(0.5%)	0		1.000
Other complications	11	(5.9%)	4	(2.1%)	0.111
Clavien-Dindo classification					0.100
Grade I–II	68	(71.6%)	61	(82.4%)	
Grade III–V	27	(28.4%)	13	(17.6%)	
Total complications	95	(50.5%)	74	(39.4%)	**0.029**
OR (95% CI)	1.6	(1.0-2.4)	1	(reference)	**0.030**

FPC – frozen fresh plasma, platelet and cryoprecipitate; OR – odds ratio; CI – confidence interval.

Table 5. Postoperative complications in patients of single PRBC transfusion group and no blood transfusion group in a propensity score model.

Complications	PRBC only group (n=79)		No transfusion group (n=79)		p Value
Peritoneal effusion	22	(27.8%)	19	(24.1%)	0.586
Hydrothorax	15	(19.0%)	9	(11.4%)	0.184
Liver failure	2	(2.5%)	1	(1.3%)	1.000
Biliary fistula	3	(3.8%)	5	(6.35)	0.719
Peritoneal infection	3	(3.8%)	1	(1.3%)	0.620
Pulmonary infection	2	(2.5%)	3	(3.8%)	1.000
Intraperitoneal bleeding	4	(5.1%)	2	(2.5%)	0.681
Renal failure	0		0		–
Systemic sepsis	1	(1.3%)	0		1.000
Wound infection	2	(2.5%)	0		0.497
Other complications	3	(3.8%)	3	(3.8%)	1.000
Clavien-Dindo classification					0.092
Grade I–II	28	(68.3%)	28	(87.5%)	
Grade III–V	13	(31.7%)	4	(12.5%)	
All complications	41	(51.9%)	32	(40.5%)	0.151

PRBC – packed red blood cells.

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Discussion

Severe anemia and massive bleeding are critical condition associated with various unfavorable outcomes, and allogenic blood transfusion is the most common treatment [20,28–30]. However, numerous studies have found that PRBC transfusion was associated with adverse short- and long-term outcomes, especially in surgery patients when transfused perioperatively or intraoperatively [12–15]. However, studies on potential impacts of "yellow" blood products on postoperative outcomes are extremely limited, the results of which are conflicting [13,18,19,31]. Therefore, blood transfusion seems to be "good" in some situations but "bad" in other situations.

Although previous studies have mostly reported that overutilization of blood products can induce adverse outcomes in low-risk or surgically-treated patients [11–15,22], there are still some critical points remaining undetermined. Firstly, there have been few studies on the association of blood transfusion with postoperative morbidity following LR with compromised liver function. The liver is the main organ involved in synthesis of albumin and many pro-coagulant factors. However, most patients with HCC and ICC are complicated with coagulopathy due to HBV-, HCV-, or alcohol-related cirrhosis, as well as anemia and thrombocytopenia secondary to portal hypertension and hypersplenism. In the present study, 72.5% of patients were complicated with HBV/HCV infection. Therefore, transfusion of blood components, including PRBC, FFP, platelets, and cryoprecipitate, are more common during LR than in other selective surgeries. LR is mostly performed for hepatic colorectal metastases in Western countries, so most of the patients in these studies had normal hepatic and coagulant function [13,32–34]. Secondly, whether the "red" and "yellow" blood products have different or synergistic influences on postoperative outcomes remains unclear. Previous studies ignored whether the PRBC-transfused patients were transfused with FPC or whether the FPC-transfused patients were transfused with PRBC concomitantly. Given that most patients with liver disease could be transfused with both, the adverse impacts on postoperative morbidity might be a result of both "red" and "yellow" blood transfusion rather than a single component.

One of the strongest merits of the present study is that the patients were divided into 4 groups: PRBC-only transfusion, FPC-only transfusion, PRBC + FPC transfusion, and no blood transfusion. PRBC-only and PRBC + FPC transfusion was more common in patients with worse liver function and larger tumor burden, and thus were associated with increased postoperative morbidity. Consistent with other studies [11,17], the propensity model used in the present study with mitigation of those confounding factors showed that transfusion of PRBC (with or without FPC transfusion) and FPC (with or without PRBC transfusion) were significantly associated with increased postoperative complications *vs.* the no blood transfusion group. In contrast, intraoperative PRBC-only and FPC-only transfusion showed no significantly adverse effects on postoperative morbidity. Therefore, intraoperative PRBC-only and FPC-only transfusion might have limited impacts on postoperative outcome but might have significant effects when both PRBC and FPC are transfused.

The synergistic effects of "red" and "yellow" blood transfusion on postoperative morbidity might be a dual effect both quantitatively and qualitatively. Consistently, some previous studies found that FFP transfusion did not affect postoperative outcome among patients undergoing LR for HCC or colorectal liver metastasis [18,19,35]. In contrast, a more comprehensive study with enrollment of 3027 patients undergoing pancreatic, hepatic, and colorectal resections demonstrated that FFP and platelet transfusion were both associated with worse postoperative outcomes [13]. Interestingly, similar to our study, Kaibori et al. found increased postoperative complications in patients undergoing LR for HCC when transfused with both PRBC and FFP than in those transfused with only FFP or no blood, but no found difference in postoperative morbidity between FFP-transfused patients and non-transfused patients [19]. However, the significant difference in preoperative conditions among different groups limited reliability of the results [19]. In fact, it could be argued that the higher complication rate is due to the severity of disease in patients with more transfusions, rather than due to the transfusion itself. The present study used PSM analysis to match the patients with the pre- and intraoperative characteristics. As a result, much more transfusion of "yellow" blood product increased the total volume and complexity of blood in addition to PRBC, which might amplify the deleterious effects of blood transfusion on postoperative outcome.

There are several limitations of the present study. First, the nature of the retrospective study could not exclude selection bias. As presented above, the preoperative conditions of the patients in different blood transfusion groups were different. Therefore, we then performed PSM analysis to generate well-matched patients in each group with equal baseline characteristics and preoperative liver function. However, some influential factors might be difficult to document and control in a retrospective study. Therefore, the direct influence of severity of disease itself on postoperative morbidity, rather than blood transfusion, could not be excluded in the present study. Second, combined PRBC and FPC transfusion are common in LR for HCC. Therefore, there were few patients with PRBC- or FPC-only transfusion in our study, which might have caused further bias and be insufficient to generate a statistically significant difference. Therefore, many more studies with larger cohorts of patients are needed in the future.

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Conclusions

In conclusion, concurrent "red" and "yellow" blood transfusion is common during LR, which is associated with a significantly higher risk of postoperative morbidity. In contrast, transfusion with PRBC- or FPC-only blood products showed no obvious deleterious impacts on postoperative outcome. The present study supports the possibly synergistic effects of "red" and "yellow" blood cells on postoperative morbidity. Therefore, different blood components should be considered separately and strictly used for different medical treatments.

Conflict of interest

None.

Supplementary Table

Supplementary Table 1. Baseline characteristics of patients in PRBC transfusion group and no blood transfusion group in a propensity score model.

Variable	PRBC group (n=204)		No transfusion group (n=204)		*p* Value
Male gender	158	(77.5%)	160	(78.4%)	0.811
Age (year)	52±12		53±12		0.856
Body mass index (kg/m^2)	22.6±3.4		23.0±3.0		0.263
Cigarette smoking	82	(40.2%)	82	(40.2%)	1.000
Diabetes mellitus	18	(8.8%)	19	(9.3%)	1.000
HBV/HCV positive	147	(72.1%)	153	(75%)	0.575
Cardiovascular disease	27	(13.2%)	32	(15.7%)	0.574
Child-Pugh class					0.724
A	199	(97.5%)	201	(98.5%)	
B	5	(2.5%)	3	(1.5%)	
ASA classification					0.141
1	6	(2.9%)	7	(3.4%)	
2	149	(73%)	164	(80.4%)	
3	49	(24%)	33	(16.2%)	
ICG 15min retention (%)	9.7±9.9		9.9±14.8		0.938
Hepatic inflow occlusion	142	(69.6%)	141	(69.1%)	1.000
Tumor location					0.108
Left lobe	57	(27.9%)	44	(21.6%)	
Right lobe	137	(67.2%)	155	(76%)	
Bilobar involvement	10	(4.9%)	5	(2.5%)	
Primary disease					0.762
Hepatocellular carcinoma	175	(85.8%)	178	(87.3%)	
Intrahepatic cholangiocarcinoma	19	(9.3%)	15	(7.4%)	
Other liver malignancies	10	(4.9%)	11	(5.4%)	
Surgical procedures					0.892
Minor hepatectomy	173	(84.8%)	171	(83.8%)	
Major hepatectomy	31	(15.2%)	33	(16.2%)	

PRBC – packed red blood cells; HBV – hepatitis B virus; HCV – hepatitis C virus; ASA – the American Society of Anesthesiologists; ICG – indocyanine green.

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Supplementary Table 2. Baseline characteristics of patients in FPC transfusion group and no blood transfusion group in a propensity score model.

Variable	FPC group (n=188)	No transfusion group (n=188)	*p* Value
Male gender	153 (81.4%)	149 (79.3%)	0.604
Age (year)	53±12	54±12	0.367
Body mass index (kg/m^2)	22.7±3.4	22.9±3.0	0.623
Cigarette smoking	78 (41.5%)	76 (40.4%)	0.834
Diabetes mellitus	18 (9.6%)	18 (9.6%)	1.000
HBV/HCV positive	128 (68.1%)	143 (76.1%)	0.107
Cardiovascular disease	25 (13.3%)	30 (16%)	0.466
Child-Pugh class			0.337
A	181 (96.3%)	185 (98.4%)	
B	7 (3.7%)	3 (1.6%)	
ASA classification			0.117
1	7 (3.7%)	6 (3.2%)	
2	133 (70.7%)	150 (79.8%)	
3	48 (25.5%)	32 (17%)	
ICG 15min retention (%)	9.9±8.2	10.3±15.1	0.895
Hepatic inflow occlusion	136 (72.3%)	131 (69.7%)	0.570
Tumor location			0.247
Left lobe	48 (25.5%)	44 (23.4%)	
Right lobe	129 (68.6%)	139 (73.9%)	
Bilobar involvement	11 (5.9%)	5 (2.7%)	
Primary disease			0.778
Hepatocellular carcinoma	164 (87.2%)	167 (88.8%)	
Intrahepatic cholangiocarcinoma	13 (6.9%)	13 (6.9%)	
Other liver malignancies	11 (5.9%)	8 (4.3%)	
Surgical procedures			0.578
Minor hepatectomy	159 (84.6%)	155 (82.4%)	
Major hepatectomy	29 (15.4%)	33 (17.6%)	

FPC – frozen fresh plasma, platelet and cryoprecipitate; HBV – hepatitis B virus; HCV – hepatitis C virus; ASA – the American Society of Anesthesiologists; ICG – indocyanine green.

Supplementary Table 3. Baseline characteristics of patients in single PRBC transfusion group and no blood transfusion group in a propensity score model.

Variable	PRBC group (n=79)	No transfusion group (n=79)	*p* Value
Male gender	53 (67.1%)	56 (70.9%)	0.606
Age (year)	52±14	53±13	0.659
Body mass index (kg/m^2)	22.4±3.0	23.1±3.3	0.127

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Variable	PRBC group (n=79)		No transfusion group (n=79)		*p* Value
Cigarette smoking	32	(40.5%)	26	(32.9%)	0.322
Diabetes mellitus	9	(11.4%)	3	(3.8%)	0.130
HBV/HCV positive	47	(59.5%)	58	(73.4%)	0.064
Cardiovascular disease	14	(17.7%)	11	(13.9%)	0.513
Child-Pugh class					0.719
A	74	(93.7%)	76	(96.2%)	
B	5	(6.3%)	3	(3.8%)	
ASA classification					0.680
1	2	(2.5%)	1	(1.3%)	
2	61	(77.2%)	65	(82.3%)	
3	16	(20.2%)	13	(16.5%)	
ICG 15min retention (%)	11.1±14.6		16.5±21.5		0.354
Hepatic inflow occlusion	49	(62.0%)	41	(51.9%)	0.199
Tumor location					0.066
Left lobe	35	(44.3%)	21	(26.6%)	
Right lobe	42	(53.2%)	55	(69.6%)	
Bilobar involvement	2	(2.5%)	3	(3.8%)	
Primary disease					0.876
Hepatocellular carcinoma	67	(84.8%)	70	(88.6%)	
Intrahepatic cholangiocarcinoma	7	(8.9%)	6	(7.6%)	
Other liver malignancies	5	(6.3%)	3	(3.8%)	
Surgical procedures					0.866
Minor hepatectomy	52	(65.8%)	53	(67.1%)	
Major hepatectomy	27	(34.2%)	26	(32.9%)	

PRBC – packed red blood cells; HBV – hepatitis B virus; HCV – hepatitis C virus; ASA – the American Society of Anesthesiologists; ICG – indocyanine green.

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