

Perioperative Transfusion is Related to the Length of Hospital Stays in Primary Liver Cancer Patients

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Purpose: Blood loss may be corrected with red blood cell transfusion, but may ultimately contribute to negative impacts. This study was a retrospective analysis to assess the impact of perioperative blood transfusion on hospital stay days in liver cancer patients.

Methods: We retrospectively examined data from patients with primary liver cancer who underwent curative resection. Patients were divided into perioperative blood transfusion (PBT) and non-PBT groups. Data were given as means and SDs for continuous variables and as counts and percentage for categorical variables. The correlation between blood transfusion and hospital stay days was analyzed by Fisher's exact test. Multivariable logistic regression analyses were used to identify independent predictors of length of hospital stays.

Results: Totally 206/1031 patients (20.3%) were given perioperative transfusion. The mean length of hospital stay was 17.8 days in PBT and 13.9 days in non-PBT groups. Our multivariable logistic regression showed transfusion, total bilirubin, indirect bilirubin, and the ratio of albumin to bilirubin were all indicators of the length of hospital stay days. Perioperative transfusion was also associated with prolonged length of hospital stays (95% CI: 0.395–0.811, $p = 0.002$). Transfusion also affected intrinsic coagulation factors (activated partial thromboplastin time, fibrinogen, platelet), inflammatory index (neutrocyte to lymphocyte ratio, monocyte), albumin and bilirubin levels.

Conclusion: Perioperative transfusion of blood was associated with a significantly increased length of hospital stays probably via changing intrinsic coagulation and inflammatory factors and bilirubin levels in plasma.

Keywords: primary liver cancer, transfusion, length of hospital stays, bilirubin, coagulation factor, inflammatory factor

Introduction

It has been reported that millions of units of blood products are transfused annually.¹ Complications are more likely to take place after transfusion of blood products² and transfusion can significantly increase the risk of morbidity and death in critically ill patients.³ Previous studies suggested that the storage time of red blood cells (RBCs) may lead to immunosuppression.^{4,5} RBCs undergo morphologic and functional changes during the duration for storage⁶ (what is called “storage lesions”), including imbalance of the cell membrane expression of CD47 and phosphatidylserine, which can contribute to activate the immune system.⁷ Moreover, during storage, cytokines and other immunomodulatory substances accumulate in the supernatant and trigger the activation of immune cells. Studies suggested that transfusions of storage-damaged red cells were likely to cause increased morbidity and mortality.^{2,8} Otherwise, researchers pointed that mortality increased linearly associated with the amount of blood transfused.^{9,10} Most

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studies focused on the index of patients' mortality to assess the clinical effect of blood utilization.^{11,12} The secondary outcomes included complications of pneumonia, adverse reactions and sequentially hospital duration. It can be understandable that in-hospital day's prolongation may make a potential and negative difference on the long-term maintenance of patients.

Primary liver cancer (PLC) is one of the most common malignant tumors worldwide, for which resection surgically and transplantation are the primary choices for the treatment. Due to the rich blood supply and the fragility of the texture, intraoperative bleeding is unavoidable in resection of liver cancer, and clinical transfusion is usually required to correct anemia and maintain the stability of vital signs. Whether perioperative transfusion of red blood cell has a negative effect on patients with PLC by extending in-hospital days remains controversial.^{13–17} Based on this, the aim of our study is to evaluate the impact of transfusion on length of hospital stay (LOHS) in PLC patients who have received perioperative transfusion.

Patients and Methods

Patients

The retrospective study included PLC patients who underwent complete liver resection in Hua Shan Hospital of Fudan University of Shanghai, China from December 2015 to December 2018. All of the patients were made a definite diagnosis of PLC by the combination of epidemiologic history, clinical situation, laboratory tests, and imaging examination according to the Asian Pacific Association for the Study of the Liver guideline. We included neither patients who died during the hospitalization or had incomplete documentation within the medical records nor patients less than 18 years old. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Clinical Research Ethics Committee of the Huashan Hospital of Fudan University of Shanghai, China.¹⁸ Because of the retrospective nature of the study, patient consent for inclusion was waived. But patient's personal information was appropriately anonymized and de-identified prior to analysis.

Data Collection and Outcomes

All of the patients were divided into two groups including perioperative blood transfusion (PBT) and non-PBT groups (Figure 1). All RBCs are prepared in accordance with international standards and supplied by the hospital blood bank

according to applicable local regulations. Perioperative blood transfusion was defined as at least 1 unit of allogeneic red blood cell transfusion either during operation or within 24 hours after operation. Blood transfusion during operation was decided according to the institution's clinical protocol¹⁹ (hemoglobin <70 g/L). Patients' clinical data were obtained by medical record review within 48 hours after transfusion. Variables included prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, white blood cell (WBC), hemoglobin, hematocrit (hct), neutrocyte, lymphocyte, neutrocyte to lymphocyte ratio (NLR), monocyte, platelet, total bilirubin (tbil), direct bilirubin (dbil), indirect bilirubin (ibil), albumin, globulin, albumin to globulin ratio (AG), albumin/total bilirubin (alb/tbil), albumin/direct bilirubin (alb/dbil), albumin/indirect bilirubin (alb/ibil). The main study outcomes were the length of hospital stay of patients.

Statistical Analysis

Data were given as means and SDs for continuous variables and as counts and percentage for categorical variables. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of death in the patients were calculated, respectively, using univariate and multivariate logistic regression analyses. The differences in several groups were compared by independent *t* test and chi-square test. The data analysis software was SAS for windows version 9.4 (SAS Institute, Cary, NC, USA), IBM SPSS Statistic for windows version 25.0 (SPSS Inc., Armonk, NY, USA) and R for windows (Version 3.4.4). *P* values <0.05 was considered as statistically significant.

Results

The Pathological Baseline of Patients with PLC

The patient demographics and baseline clinical variables according to transfusion are shown in Table 1. The mean hospital stay was 14.7 ± 6.5 days, including 13.9 ± 5.5 days for no transfusion group and 17.8 ± 8.8 days for transfusion group. Patients receiving perioperative red cell transfusion had increased hospital stay days.

Red Cell Transfusion Prolonged Hospital Stay Days of PLC Patients

To identify the relationship between transfusion and LOHS, subjects were separated into two groups (Figure 1). Fisher's exact tests revealed that red cell transfusion was associated with the short-term outcomes

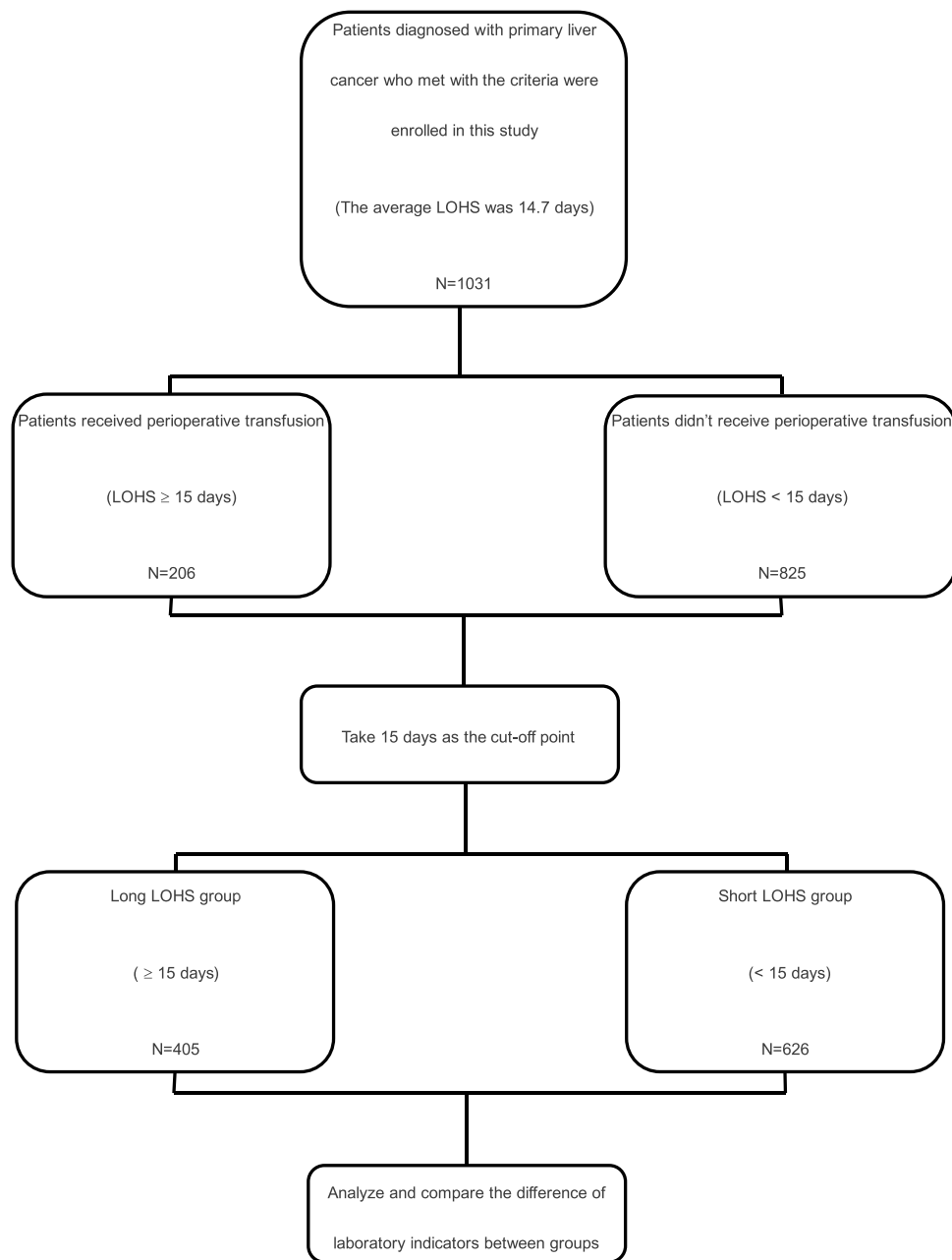


Figure 1 The flow chart of grouping in the study.

($p < 0.05$). In the group less than 15 days, 14.1% of the patients were with RBCs transfusion, compared with 29.1% of the group over 15 days, which indicated that the proportion of blood transfusion was increased by one time in accordance with the duration in hospital (Table 2).

Relevant Clinical Indicators of the LOHS

To seek the reason why the transfusion patients' hospital stay days were different from that of the non-transfusion patients', we observed the postoperative indicators related

to inflammation and coagulation between different hospital stay groups. The level of postoperative monocytes was the only inflammatory index of statistical difference (7.5 ± 3.6 vs 7.3 ± 3.7 , $p = 0.038$). These coagulation indicators' significant differences in patients was also detected, including fibrinogen (2.4 ± 0.9 vs 2.6 ± 1.4 , $p < 0.001$), and platelet (148.3 ± 67.6 vs 159.3 ± 85.9 , $p < 0.001$). Besides, we discovered that post contents of several kinds of bilirubin and albumin (alb) were significantly different between the two groups (Table 3).

Table I Patients' Clinicopathological Characteristics

	Total	PBT Group	None-PBT Group	P value
N	1031 (100.0)	206 (20.0)	825 (80.0)	
Age				0.052
≤50	339 (32.9)	56 (5.4)	283 (27.4)	
>50	692 (67.1)	150 (14.5)	542 (52.6)	
Gender				0.136
Male	777 (75.4)	147 (14.3)	630 (61.1)	
Female	254 (24.6)	59 (5.7)	195 (18.9)	
BMI	23.3 (3.1)	22.9 (3.3)	23.4 (3.0)	0.091
Co-illnesses	132 (12.8)	38 (3.7)	94 (9.1)	0.007
ASA scores				<0.001
≤2	992 (96.2)	187 (18.1)	805 (78.1)	
>2	39 (3.8)	19 (1.8)	20 (1.9)	
HBsAg (+)	700 (68.0)	121 (11.7)	579 (56.2)	0.002
Anti-HCV (+)	18 (1.7)	8 (0.8)	10 (1.0)	0.009
Cirrhosis (+)	661 (64.1)	132 (12.8)	529 (51.3)	0.991
ECOG performance status				0.059
0	953 (92.4)	184 (17.8)	769 (74.6)	
I–2	78 (7.6)	22 (2.1)	56 (5.4)	
Repeat hepatectomy	186 (18.0)	37 (3.6)	149 (14.5)	0.974
Child-Pugh grade				0.112
A	1021 (99.0)	202 (19.6)	819 (79.4)	
B	10 (1.0)	4 (0.4)	6 (0.6)	
TNM stage				<0.001
I	370 (35.9)	47 (4.6)	323 (31.3)	
II	384 (37.2)	86 (8.3)	298 (28.9)	
III	243 (23.6)	60 (5.8)	183 (17.7)	
IV	34 (3.3)	13 (1.3)	21 (2.0)	
Tumor differentiation				0.272
I	18 (1.7)	2 (0.2)	16 (1.6)	
II	691 (67.0)	129 (12.5)	562 (54.5)	
III	312 (30.3)	73 (7.1)	239 (23.2)	
IV	10 (1.0)	2 (0.2)	8 (0.8)	
Tumor size				<0.001
≤5	689 (66.8)	105 (10.2)	584 (56.6)	
>5	342 (33.20)	101 (9.8)	241 (23.4)	
Tumor number				0.994
Solitary	836 (81.1)	167 (16.2)	669 (64.9)	
Multiple	195 (18.9)	39 (3.8)	156 (15.1)	
Satellites	179 (17.4)	57 (5.5)	122 (11.8)	<0.001
Extent of hepatectomy				<0.001
Minor	764 (74.1)	120 (11.6)	644 (52.5)	
Major	267 (25.9)	86 (8.3)	181 (17.6)	

(Continued)

Table 1 (Continued).

	Total	PBT Group	None-PBT Group	P value
Pringle maneuver	423 (41.0)	76 (7.4)	347 (33.7)	0.177
Vascular invasion	120 (11.6)	34 (3.3)	86 (8.3)	0.015
Portal hypertension (+)	101 (9.8)	35 (3.4)	66 (6.4)	<0.001
Hospital-stay days	14.7 (6.5)	17.8 (8.8)	13.9 (5.5)	<0.001
Intraoperative blood loss, mL	389.7 (421.1)	820.2 (693.0)	282.2 (209.7)	<0.001

Notes: Co-illnesses: comorbid illnesses include hypertension, diabetes, cardiovascular disease, appendicitis, cholecystitis and renal dysfunction.

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Table 2 The Relationship Between Transfusion and Hospital Duration

	LOHS < 15 Days		LOHS ≥ 15 Days		P value
	Number	Percentage Within LOHS Group	Number	Percentage Within LOHS Group	
Transfusion	88	14.1%	118	29.1%	<0.05
Non-transfusion	538	85.9%	287	70.9%	< 0.05
Total	626	100.0%	405	100.0%	< 0.05

Table 3 Comparisons of Patients' Postoperative Parameters Between the Different Hospital Stays Groups

	Total	Hospital Stays < 15 Days	Hospital Stays ≥ 15 Days	P value
PT, s	13.8 (9.1)	13.6 (9.1)	14.2 (9.2)	0.806
APTT, s	31.8 (13.0)	31.2 (11.8)	32.7 (14.7)	0.048
Fibrinogen, g/L	2.5 (1.1)	2.4 (0.9)	2.6 (1.4)	<0.001
WBC	16.5 (74.8)	14.9 (42.2)	18.8 (107.0)	0.210
Hemoglobin, g/L	121.7 (20.7)	123.3 (20.1)	119.2 (21.3)	0.132
Hct	38.3 (21.3)	38.3 (20.1)	38.4 (23.0)	0.330
Neutrocyte	85.9 (26.2)	86.3 (33.3)	85.4 (7.2)	0.522
Lymphocyte	7.4 (5.0)	7.5 (4.4)	7.1 (5.7)	0.178
NLR	16.4 (12.7)	16.1 (13.4)	16.8 (11.6)	0.732
Monocyte	7.4 (3.6)	7.5 (3.5)	7.3 (3.7)	0.038
Platelet count, × 10 ⁹ /L	152.7 (75.5)	148.3 (67.6)	159.3 (85.9)	<0.001
Tbil	27.6 (37.8)	23.5 (23.7)	33.9 (52.0)	<0.001
Dbil	14.6 (29.3)	11.3 (18.7)	19.6 (40.0)	<0.001
Ibil	12.9 (11.7)	12.1 (8.8)	14.1 (15.0)	<0.001
Albumin, g/L	36.6 (4.4)	37.1 (4.3)	35.8 (4.6)	0.02
Globulin, g/L †	23.6 (8.3)	24.0 (9.8)	22.8 (5.3)	0.458
AG	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	0.105
Alb/Tbil	2.0 (1.0)	2.1 (1.0)	1.8 (0.9)	0.934
Alb/Dbil	4.4 (2.6)	4.7 (2.6)	4.0 (2.7)	0.831
Alb/Ibil	3.4 (11.4)	3.3 (14.5)	3.6 (1.9)	0.525

To further confirm the independent factor for LOHS, we used univariate and multivariate regression analysis as follows (Table 4). The data suggested that perioperative RBCs transfusion did impact the patients' hospital stay days. Meanwhile, the results showed that the indicators

of total bilirubin (tbil), indirect bilirubin (ibil), and the ratio of albumin to total bilirubin (alb/tbil) and albumin to indirect bilirubin (alb/ibil) could be used to estimate the LOHS of PLC patients.

Transfusion Has an Effect on Hospital Stay Days Probably Through Affecting Functional Indexes

To explain the cause of why transfusion led to prolong patients' hospital duration, we evaluated clinical laboratory test results between the transfusion and non-transfusion groups (Table 5). Significant differences existed among the postoperative factors of APTT, fibrinogen, hct, neutrocyte to lymphocyte ratio (NLR), monocyte, platelet, tbil, dbil, ibil, alb, the albumin and globulin ratio (AG), the albumin and direct bilirubin ratio (alb/dbil) between the two groups (all $p < 0.05$). This suggests that the intrinsic coagulation pathway and inflammatory index were changed in patients receiving a transfusion. Transfusion also affect bilirubin levels, which are independent factors for LOHS.

Discussion

Primary liver cancer (PLC) is one of the most common tumors worldwide.²⁰ In China, the annual incidence and mortality of PLC are estimated to continue to increase.²¹ Although surgical resection and transplantation are the

Table 4 Univariate and Multivariate Analysis of LOHS

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	HR P value	Hazard Ratio (95% CI)	HR P value
PT, s	1.007 (0.993–1.021)	0.335	1.005 (0.991–1.020)	0.493
APTT, s	1.010 (0.997–1.024)	0.139	1.004 (0.994–1.014)	0.458
Fibrinogen, g/L	1.131 (1.001–1.278)	0.049	1.136 (0.982–1.315)	0.087
WBC	1.001 (0.999–1.003)	0.451	1.001 (0.999–1.003)	0.338
Hemoglobin, g/L	0.990 (0.984–0.996)	0.002	0.997 (0.990–1.005)	0.494
Hct	1.000 (0.994–1.006)	0.961	1.001 (0.995–1.008)	0.719
Neutrocyte	0.998 (0.992–1.005)	0.616	0.993 (0.968–1.019)	0.599
Lymphocyte	0.983 (0.955–1.011)	0.223	0.990 (0.954–1.028)	0.604
NLR	1.005 (0.995–1.015)	0.376	1.002 (0.985–1.020)	0.824
Monocyte	0.986 (0.949–1.024)	0.468	0.988 (0.949–1.028)	0.550
Platelet count, ×10 ⁹ /L	1.002 (1.000–1.004)	0.026	1.002 (1.000–1.004)	0.048
Tbil	1.010 (1.005–1.006)	<0.001	1.013 (1.005–1.021)	0.002
Dbil	1.013 (1.006–1.021)	<0.001	0.990 (0.970–1.010)	0.307
Ibil	1.017 (1.003–1.030)	0.013	1.013 (1.005–1.021)	0.001
Albumin, g/L	0.934 (0.906–0.963)	<0.001	0.978 (0.934–1.024)	0.335
Globulin, g/L	0.968 (0.946–0.992)	0.008	0.955 (0.909–1.002)	0.062
AG	1.034 (0.735–1.454)	0.849	0.828 (0.383–1.791)	0.631
Alb/Tbil	0.701 (0.608–0.809)	<0.001	0.483 (0.265–0.880)	0.017
Alb/Dbil	0.881 (0.835–0.931)	<0.001	1.069 (0.934–1.223)	0.331
Alb/Ibil	1.003 (0.989–1.017)	0.667	1.235 (1.021–1.492)	0.029
Transfusion	0.400 (0.292–0.547)	<0.001	0.566 (0.395–0.811)	0.002

Table 5 Comparisons of Patients' Postoperative Parameters Between PBT and Non-PBT Groups

	Total	PBT Group	None-PBT Group	P value
PT, s	13.8 (9.1)	14.6 (8.6)	13.7 (9.2)	0.678
APTT, s	31.2 (6.1)	35.2 (19.2)	30.9 (10.7)	0.002
Fibrinogen, g/L	2.5 (1.1)	2.5 (1.7)	2.5 (0.9)	<0.001
WBC	16.5 (74.8)	13.9 (5.9)	17.1 (83.9)	0.425
Hemoglobin, g/L	121.7 (20.7)	110.2 (19.5)	124.6 (20.0)	0.652
Hct	38.3 (21.3)	37.3 (31.2)	38.6 (17.6)	0.011
Neutrocyte	85.9 (26.2)	86.8 (6.1)	85.7 (29.3)	0.53
Lymphocyte	7.4 (5.0)	6.5 (6.7)	7.6 (4.4)	0.398
NLR	16.4 (12.7)	19.3 (12.5)	15.6 (12.7)	0.038
Monocyte	7.4 (3.6)	7.3 (5.0)	7.5 (3.1)	0.038
Platelet count, × 10 ⁹ /L	152.7 (75.4)	150.3 (92.2)	153.3 (70.6)	0.001
Tbil	27.6 (37.8)	41.8 (63.6)	23.9 (26.6)	<0.001
Dbil	14.6 (29.3)	24.5 (48.4)	12.1 (21.1)	<0.001
Ibil	12.9 (11.7)	17.0 (19.0)	11.9 (8.6)	<0.001
Albumin, g/L	36.6 (4.4)	34.4 (5.0)	37.2 (4.1)	<0.001
Globulin, g/L †	23.6 (8.3)	22.7 (6.6)	23.8 (8.7)	0.093
AG	1.6 (0.4)	1.6 (0.45)	1.6 (0.34)	<0.001
Alb/Tbil	2.0 (1.0)	1.4 (0.9)	2.1 (1.0)	0.061
Alb/Dbil	4.4 (2.6)	3.1 (2.3)	4.8 (2.6)	0.001
Alb/Ibil	3.4 (11.4)	3.1 (1.9)	3.5 (12.7)	0.587

main treatment options, it is still a challenge with a high risk of massive blood loss. And the long-term prognosis remains unsatisfactory because of recurrence and

metastasis after curative resection.²² The outcome is reported to be influenced probably by many clinical factors, such as liver cirrhosis, tumor size, surgical margin,

vascular invasion and perioperative blood transfusion.^{23,24} PBT has already been reported to negatively affects survival time of patients in many neoplasms.^{25–29}

The current study showed a clear connection between PBT and in-hospital days in PLC, and found that transfusion prolonged in-hospital days. Multivariate regression analysis demonstrates the LOHS is related to serum tbil, ibil, alb/tbil, alb/ibil and transfusion. Researchers have pointed that elevated bilirubin could lead to irreversible damage to the brains and neurons, especially the increased indirect bilirubin with strong toxicity.^{30,31} And the bilirubin-albumin ratio level was related to the bilirubin encephalopathy, which could be a potential predictor in neonates' patients. The imbalance of oxidation and antioxidation is associated with varieties of inflammatory conditions. ROS may promote the release of inflammatory cytokines, which may weaken antioxidant defenses and lead to oxidative stress. It was reported that Ibil exerted anti-ROS properties. Thus, we suppose that bilirubin as endogenous antioxidants which have been shown to inhibit the production of proinflammatory cytokine,³² and therefore had protective effects.³³ Bilirubin may be over-consumed and destructed during the inflammatory process and due to prolong in-hospital days.

To further explain why RBCs transfusion leads to prolonged in-hospital days, we estimated postoperative clinical laboratory parameters. When patients were given perioperative RBCs transfusion, the time of APTT increased, the levels of fibrinogen changed and the amount of platelet decreased respectively. This suggested that the transfused red blood cell had certain effects on coagulation function.³⁴ The altered NLR and the quantity of monocyte showed that PLC patients inclined to get bacterial infection and the immune defense weakened,³⁵ which probably caused longer hospital stays in the PBT group. Besides, other different post indicators including all kinds of bilirubin, albumin, albumin/globulin and albumin/bilirubin indicated the degree of liver function recovery and Impaired renal function after RBCs transfusion.³⁶ As we all know, after the rupture of red blood cells transfused in spleens, heme is released to bind the globin in serum and thus transform into indirect bilirubin.³⁷ The more red blood cells are destroyed, the more indirect bilirubin with toxicity. The decreased albumin showed impaired liver function and the less ability to detoxify. In our study, both the levels of bilirubin and bilirubin-albumin ratio changed a lot in different hospital duration or transfusion groups. This may provide a new perspective on that transfusion could impact the in-hospital days of PLC patients through changing bilirubin and albumin in plasma.

However, the results may not be generalized to all of the liver cancers due to several potential limitations in our study. First, the retrospective nature determines it is not a randomized controlled trial and all of the data were come from a single medical center. Second, although 1031 patients underwent curative liver resection in this study, only 206 of them received red blood cell transfusion, and the small sample size limited us from drawing conclusions about the correlation between transfusion and in-hospital maintenance. Thus, a large-scale prospective study in multicenter is needed for further confirmation.

In conclusion, the relationship between transfused RBCs transfusion and the length of hospital stays of PLC patients after curative resection was evaluated in this retrospective study. We found that transfusion prolonged in-hospital maintenance of patients with primary liver cancer via changing intrinsic coagulation and inflammatory factors and bilirubin levels in plasma.

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Disclosure

The authors report no conflicts of interest in this work.

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