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Association of intra-operative red blood cell transfusion on the systemic immune index and recovery in patients undergoing cesarean section: a large propensity score-matched study

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Abstract

Background Post-partum hemorrhage (PPH) is a leading cause of maternal death worldwide. However, the effect of blood transfusion in patients undergoing cesarean section remains unclear.

Materials and methods The analysis was based on the retrospective evaluation of the pre- and post-operative data for 1231 patients who underwent a cesarean section at our hospital between January 2016 and June 2020. Patients were classified into the blood transfusion group (BT) and the no blood transfusion group (NBT) based on their intra-operative blood transfusion status.

Results After propensity score matching, 322 patients were included in both groups and between-group differences in length of hospital stay (LOS), perioperative systemic inflammation indicators, and post-operative complications were evaluated. The LOS was longer in the BT (median, 6.6 days) than the NBT (median, 4.2 days) group ($P=0.026$). The post-operative complication rate was higher for the BT than NBT group, as follows: vomiting, 3.2% vs. 4.9%, $P=0.032$; fever, 5.41% vs. 2.24%, $P=0.032$; wound complications, 15.44% vs. 10.45%, $P=0.028$; and intestinal obstructions, 5.88% vs. 2.75%, $P=0.034$. Systemic inflammation indicators increased significantly, from the pre-operative baseline, for both groups at post-operative day (POD) 1 and POD3. On multivariate analysis, intra-operative blood transfusion was associated with a longer LOS (hazard ratio, 1.52; 95% confidence interval, 1.07–2.25).

Conclusion Intraoperative blood transfusion for cesarean section was associated with increased levels of systemic inflammation indicators, higher post-operative complication rates, and prolonged hospital stay.

Keywords Blood transfusion, Immune indicator, Length of stay, Propensity score matching, Cesarean section

Introduction

Post-partum hemorrhage (PPH) is a leading cause of maternal death worldwide (Shaylor et al. 2017). Generally defined as blood loss volume > 500 mL within the first 24 h post-partum (Nathan 2019), PPH accounted for 34% of the 275,000 estimated maternal deaths globally in 2015 (Quantitative Blood Loss in Obstetric Hemorrhage 2019). Accordingly, the American College of Obstetricians and Gynecologists (ACOG) issued recommendations emphasizing the importance of an organized and systematic process for better coordination of the response and

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management of PPH (O'Brien et al. 2018). Of these, red blood cell (RBC) transfusion is one of the most important treatment options for PPH (Muñoz et al. 2019). However, the effect of intra-operative red blood cell transfusion on post-operative recovery from deliveries via cesarean section remains unclear.

Blood transfusion may be lifesaving in cesarian sections associated with large volume loss of blood resulting in anemia (Muñoz et al. 2019 Mar; Sultan et al. 2021). However, it is important to consider the evidence of adverse short-term clinical outcomes that have been associated with intra-operative blood transfusion in patients undergoing surgery (Kim et al. 2020). Retrospective studies have reported an increased risk of post-operative complications in patients who received blood transfusions during major surgery, including increased systemic inflammation indicators, post-operative grade II complication rates, prolonged length of hospital stay (LOS), and 30-day all-cause readmission rate (Connor et al. 2018). Results from a study revealed that intra-operative blood transfusion, which indicated a decrease in hemoglobin (Hb) level < 7 g/dL, was associated with an increased risk for post-operative complications (Zhang et al. 2020). There is also evidence that the transfusion of allogeneic blood inhibits immune responses, which can adversely impact prognosis in the peri-operative period (Zhang et al. 2020). To date, however, the association between intra-operative blood transfusion and post-operative recovery in patients with PPH has not been clearly established. Additionally, the association between intra-operative blood transfusion and post-operative complications has not been specifically evaluated in obstetric patients. Accordingly, our aim in this study was to perform a retrospective analysis of the association between intra-operative blood transfusion and post-operative recovery in patients who underwent a cesarean section. We hypothesized that intra-operative blood transfusion during the cesarian section would be associated with LOS. As a secondary outcome, we evaluated the association between peri-operative blood transfusion and peri-operative systemic inflammatory indicators, post-operative recovery parameters, fatigue severity score, post-operative complication rate, and readmission rate.

Materials and methods

Study design and statement of ethics

After obtaining approval from the Shanghai First Maternity and Infant Hospital Institutional Review Board. We retrospectively collected data from 1426 patients who underwent a cesarean section between January 2016 and June 2020.

The inclusion criteria were pregnant women with elective term single pregnancy. Exclusion criteria were as follows: emergency cesarean section; twin pregnancy; use of anti-inflammatory drugs or immunosuppressants for > 1 month prior to the cesarean section; chronic inflammatory diseases; and incomplete medical records. The pregnancy characteristics, medical history, operative details, and post-operative course were extracted from the medical records.

All pregnant women, or a relative as appropriate, provided informed consent for the use of their clinical data for research prior to the cesarean section. This study was reviewed and approved by the Shanghai First Maternity Ethics Committee (protocol: #2020–049).

Primary outcome

The primary outcome of this study was the LOS, defined as the time from the date of the cesarian section to the date of discharge.

Secondary outcomes

The secondary endpoints included peri-operative systemic inflammation indicators, the rate of post-operative complication, wound complications, the fatigue severity score, the admission rate to the intensive care unit (ICU), and the 30-day all-cause readmission rate. The systemic inflammatory indicators included neutrophil, lymphocyte, monocyte, and platelet counts recorded 3 days prior to the cesarian section and on post-operative days (POD) 1 and 3. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and the neutrophil-to-lymphocyte ratio (SII). Complications were evaluated using the Clavien-Dindo classification which is suitable to describe the incidence and grade the severity of surgical complications, as follows: grade I, any deviation from the expected post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological intervention; grade II, complications require pharmacological treatment with drugs other, than those allowed for grade I complications, blood transfusion, and total parenteral nutrition; grade III, complications require surgical endoscopic or radiological intervention; grade IV, life-threatening complication; and grade V, patient death.

Exposure variable

The exposure variable is the use of blood transfusion with the following criteria used as clinical indicators for the need for transfusion: intra-operative blood loss volume > 500 ml and an intra-operative decrease in Hb level < 8 g/dl. The type of blood products used—red blood cells or fresh frozen plasma—and the number of units transfused were recorded.

Anesthesia care

Upon entering the operating room, a pre-operative pregnancy screening was performed as per the American Society of Anesthesiologists (ASA) standards. Spinal anesthesia is the first choice for cesarean sections in patients without contraindications to this type of anesthesia. For spinal anesthesia induction, patients were placed in the right recumbent position and the subarachnoid puncture was performed at the L3–L4 or L2–L3 inter-vertebral space. After observing the free flow of cerebrospinal fluid at the puncture site, 0.5% hyperbaric ropivacaine, consisting of 2 mL of 0.75% hyperbaric ropivacaine in 1 mL of saline, was administered. An epidural indwelling catheter, 4 cm in length, was placed in the epidural space. At 5-min post-induction, the extent of anesthesia was evaluated at the T4 to T6 level. When the anesthetic effect was unsatisfactory, an additional 5 ml of 0.5% ropivacaine was injected into the epidural space. For patients with contraindications to spinal anesthesia, such as coagulation dysfunction, lumbar disease, or physiological shock, general anesthesia was administered. General anesthesia was induced using propofol (target-controlled infusion, effect-site concentration 3.0–4.0 μg/ml), remifentanil (0.3–0.5 μg/kg), and rocuronium (0.6 mg/kg). After induction, endotracheal intubation was performed and general anesthesia was maintained using propofol, sufentanil, and remifentanil. Repeated bolus injections of sufentanil and rocuronium were administered throughout the surgery.

Statistical analysis

Continuous variables were reported as the mean ± standard deviation and categorical variables as frequencies and percentages. To control for the effects of selection bias, propensity score matching was performed, and differences in study outcomes between groups "with" (BT) and "without" (NBT) intra-operative blood transfusion were evaluated for the matched groups. Matching was performed using a 5-to-1 digit greedy match algorithm. On univariate analyses, between-group differences were evaluated using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the independent samples *t*-test or Wilcoxon signed-rank test, as appropriate, for continuous variables. Statistical analyses were performed using SPSS software (version 28.0; SPSS Inc., Chicago, IL, USA), with significance set at a *P*-value < 0.05.

Results

Eligible were 1426 patients who underwent cesarean section within the study period. After screening on the exclusion criteria, 322 patients were included in the BT group and 909 in the NBT group (Fig. 1). In the total cohort, between-group differences were identified in the ASA pre-operative screening status ($P=0.005$), fetal birth weight ($P<0.001$), operative time ($P<0.001$), volume of blood loss ($P<0.001$), and pre-operative Hgb level ($P<0.001$). After propensity score matching, 312 patients were included in both groups, with no between-group

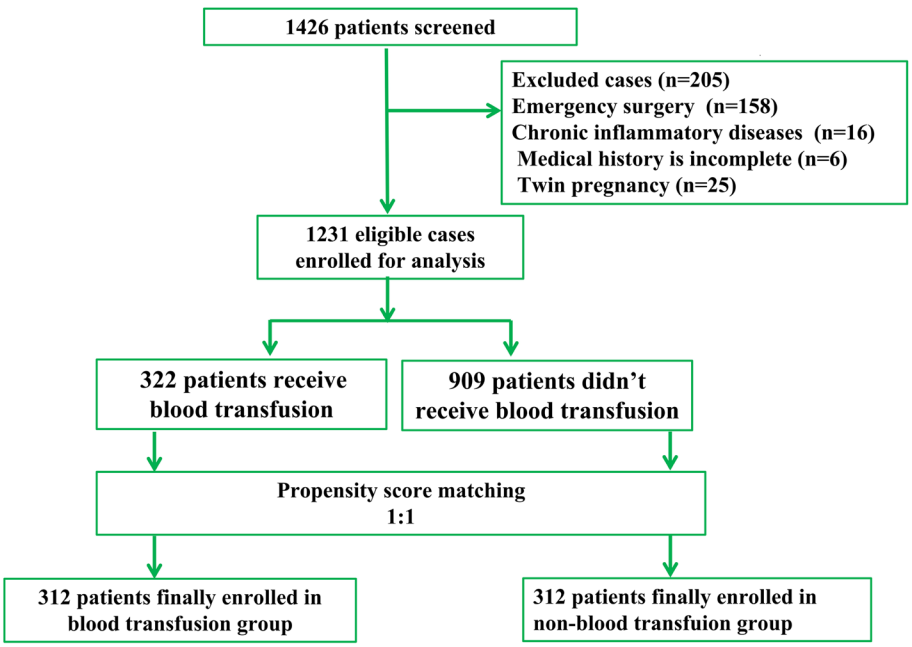

Fig. 1 Flowchart of the trials

difference in the distribution of age ($P=0.139$), body mass index (BMI, $P=0.526$), ASA pre-screening status ($P=0.811$), gestational age at delivery ($P=0.363$), fetal birthweight ($P=0.262$), primary mode of anesthesia ($P=0.893$), primary cause of PPH ($P=0.993$), and level of experience of the attending obstetrician ($P=0.878$). There were between-group differences in operative time ($P<0.001$), volume of blood loss ($P<0.001$), and pre-Hgb level ($P<0.001$; Table 1).

Primary outcome

The LOS was significantly shorter in the NBT (mean, 4.2 days) than in the BT (mean, 7.1 days) group ($P=0.026$; Fig. 2A).

Secondary outcome

The rate of post-operative adverse outcomes was generally higher for the BT than NBT group, respectively, as follows (Fig. 3A): vomiting, 4.9% vs. 3.2%, $P=0.032$; fever, 5.41% vs. 2.24%, $P=0.032$; wound complications, 15.44% vs. 10.45%, $P=0.02$; and intestinal obstruction, 5.88% vs. 2.75%, $P=0.034$. There was no difference in the incidence rate of pneumonia between the BT and NBT groups, respectively: 3.2% vs. 3.4%, $P=0.563$ (Fig. 3A). NBT yielded an advantage over BT on the following outcomes (Fig. 3B): lower 30-day day all-cause readmission rate, 4.40% vs. 7.14% ($P=0.018$) and ICU admission rate, 1.70% vs. 4.10% ($P=0.034$). Additionally, the Clavien-Dindo classification of adverse events was lower for the NBT than BT group (Fig. 3C): grade 1, 4.7% vs.8.4% ($P=0.031$) and grade II, 10.7% vs.18.3% ($P=0.023$).

On univariate analyses, the following factors were not associated with LOS (Table 2): age (hazard ratio (HR), 1.02; 95% confidence interval (CI), 0.98–1.21; $P=0.258$); BMI (HR, 1.11; 95%CI, 0.72–1.52; $P=0.324$); ASA pre-screening status (HR, 1.05; 95%CI, 0.70–1.46; $P=0.159$); gestational age at delivery (HR, 1.15; 95%CI, 0.64–1.20; $P=0.258$); pre-Hgb (HR = 1.45, 95%CI, 0.93–1.71, $P=0.254$); and experience of obstetrician (HR, 1.12; 95%CI, 0.94–1.46; $P=0.078$). The following factors were associated with a longer LOS (Table 2): fetal birthweight (HR, 2.10; 95%CI, 1.71–2.76; $P<0.001$); a longer operative time (HR, 1.52; 95%CI, 1.24–1.75; $P<0.001$); and blood transfusion (HR, 1.56; 95%CI, 1.15–1.98; $P=0.032$) (Table 2). On multivariable analysis, fetal birthweight (HR, 1.65; 95%CI, 1.06–2.32; $P=0.019$), operative time (HR = 1.51; 95%CI, 1.13–1.61; $P=0.042$); low pre-Hb level (HR, 1.42; 95%CI, 1.02–1.78; $P=0.045$) and blood transfusion (HR, 1.52; 95%CI, 1.07–2.25; $P=0.024$) were retained as independent factors of a longer LOS (Table 3).

Table 1 Baseline characteristics in the BT group and NBT group

	Original cohort		*P*	Matched cohort		*P*
	BT group ($n=322$)	NBT group ($n=909$)		BT group ($n=312$)	NBT group ($n=312$)	
Age (mean ± SD, years)	33.49 ± 4.51	32.97 ± 4.23	0.066	33.49 ± 4.51	32.97 ± 4.26	0.139
BMI (kg/m^2)	27.5 (23.5–35.3)	26.0 (21.7–33.6)	0.425	27.5 (23.5–35.3)	26.0 (20.7–32.6)	0.526
ASA (*n*,%)						0.811
I–II	283(87.5%)	842(92.6%)	0.005	273(87.5%)	271(86.9%)	
III	39(12.5%)	67(7.4%)		39(12.5%)	41(13.1%)	
Age at delivery (mean ± SD, days)	273.11 ± 22.11	272.66 ± 20.66	0.745	273.11 ± 22.11	274.66 ± 20.36	0.363
Birthweight (mean ± SD, g)	3488.31 ± 1006.69	3073.16 ± 1078.84	< 0.001	3488.31 ± 1006.69	3423.16 ± 1086.85	0.262
Mode of anesthesia (*n*,%)			0.192			0.893
General	41(10%)	69(7.6%)		31(10%)	30(9.6%)	
Neuraxial	281(90%)	840(92.4%)		281(90%)	282(90.4%)	
Primary cause of PPH (*n*,%)			0.987			0.993
Uterine atony	128(41%)	378(41.8%)		128(41.0%)	127(40.8%)	
Placenta accreta	80(22.4%)	195(21.5%)		70(22.4%)	68(21.9%)	
Retained placenta	102(32.6%)	300(33%)		102(32.6%)	104(33.2%)	
Others	12(4%)	36(3.7%)		12(4%)	13(4.1%)	
Operation time (mean ± SD, min)	55.20 ± 8.54	42.64 ± 7.83	< 0.001	55.20 ± 8.54	40.64 ± 7.13	< 0.001
Blood loss (mean ± SD, ml)	831.65 ± 78.35	241.39 ± 83.61	< 0.001	831.65 ± 78.35	236.39 ± 80.21	< 0.001
Pre-Hgb (mean ± SD, g/dl)	101.72 ± 33.28	119.67 ± 25.33	< 0.001	101.72 ± 33.28	112.67 ± 45.33	< 0.001
Obstetrician experience			0.427			0.878
< 5 years	39(9%)	69(7.6%)		29(9%)	27(8.6%)	
5 years or more	283(91%)	840(92.4%)		283(91%)	285(91.4%)	

BMI body mass index, *IQR* inter-quartile range, *ASA* American Society of Anesthesiologists score, *PPH* postpartum hemorrhage

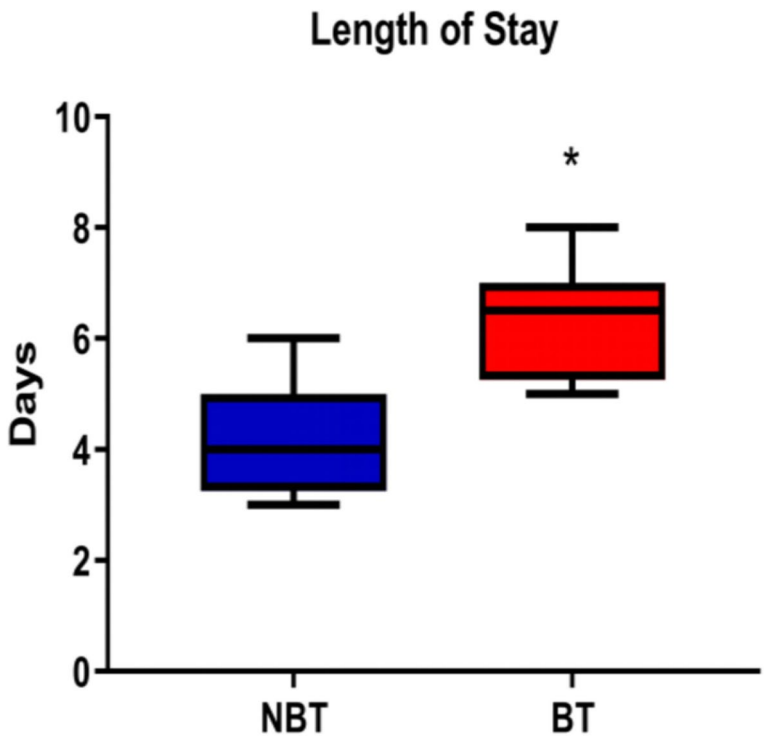

Fig. 2 Measure outcomes between the groups. Length of stay between blood transfusion group and non-blood transfusion group

After matching, there were no between-group differences in the preoperative NLR, LMR, or SII (Fig. 4A–C). Compared to pre-operative levels, the NLR and SII increased and the LMR decreased at POD1 and POD3 for both groups ($P < 0.001$; Fig. 4B). Of note, the NLR and SII values were lower on POD3 than on POD1 but remained higher than pre-operative values ($P < 0.001$; Fig. 4A–C). The NLR and SII at POD1 and POD3 were lower for the NBT than the BT group ($P < 0.001$; Fig. 4A–C), with the LMR being higher for the NBT than the BT group ($P < 0.001$; Fig. 4B). Fatigue scores were significantly lower in the NBT than BT group at 2 h and 48 h post-operatively ($P < 0.001$; Fig. 4D).

Discussion

In this study, our results showed that intra-operative red blood cell transfusion during the cesarian section significantly increased LOS, the rate of post-operative vomiting, and wound complications, as well as increased levels of post-operative systemic inflammation indicators, namely the NLR and SII. These results indicate a significant association between the post-operative inflammatory response and intra-operative blood transfusion in obstetric care.

Allogeneic blood transfusions induce important biological alterations in the immune system, providing a potential mechanism for increased risk of infections and post-transfusion graft-versus-host disease (Surbek et al. 2020; Zdanowicz et al. 2021; Thurn et al. 2019; Semple et al. 2019). Selected hematological markers, including the NLR, LMR, and SII, can comprehensively show the balance of the host immune system (Yuan et al. 2020) and, therefore, have been considered prognosis-related indicators in malignant diseases (Owusu-Agyemang et al. 2017; Papageorge et al. 2017; Tai et al. 2018), with an increase in NLR or SII and decreased LMR being associated with poor prognosis in patients undergoing surgery (Selvaggio et al. 2020; Hirahara et al. 2019; Zhang et al. 2018).

In addition, the NLR is a biomarker for pregnancy-related complications, including gestational diabetes (Papageorge et al. 2017), pre-eclampsia (Tai et al. 2018), and acute pancreatitis during pregnancy (Selvaggio et al. 2020 Sep). In addition, the NLR has been shown to provide a more accurate proxy of placental inflammatory status than serum C-reactive protein (CRP) levels, with a high NLR being predictive of impending pre-term birth in the presence of normal CRP levels (Hirahara et al. 2019). The NLR is also a recognized marker of significant risk for post-operative complications in other conditions (Zhang et al. 2018). Our study is the first to evaluate the relationship between post-operative inflammatory biomarkers and intra-operative blood transfusion specifically in women who underwent cesarean section.

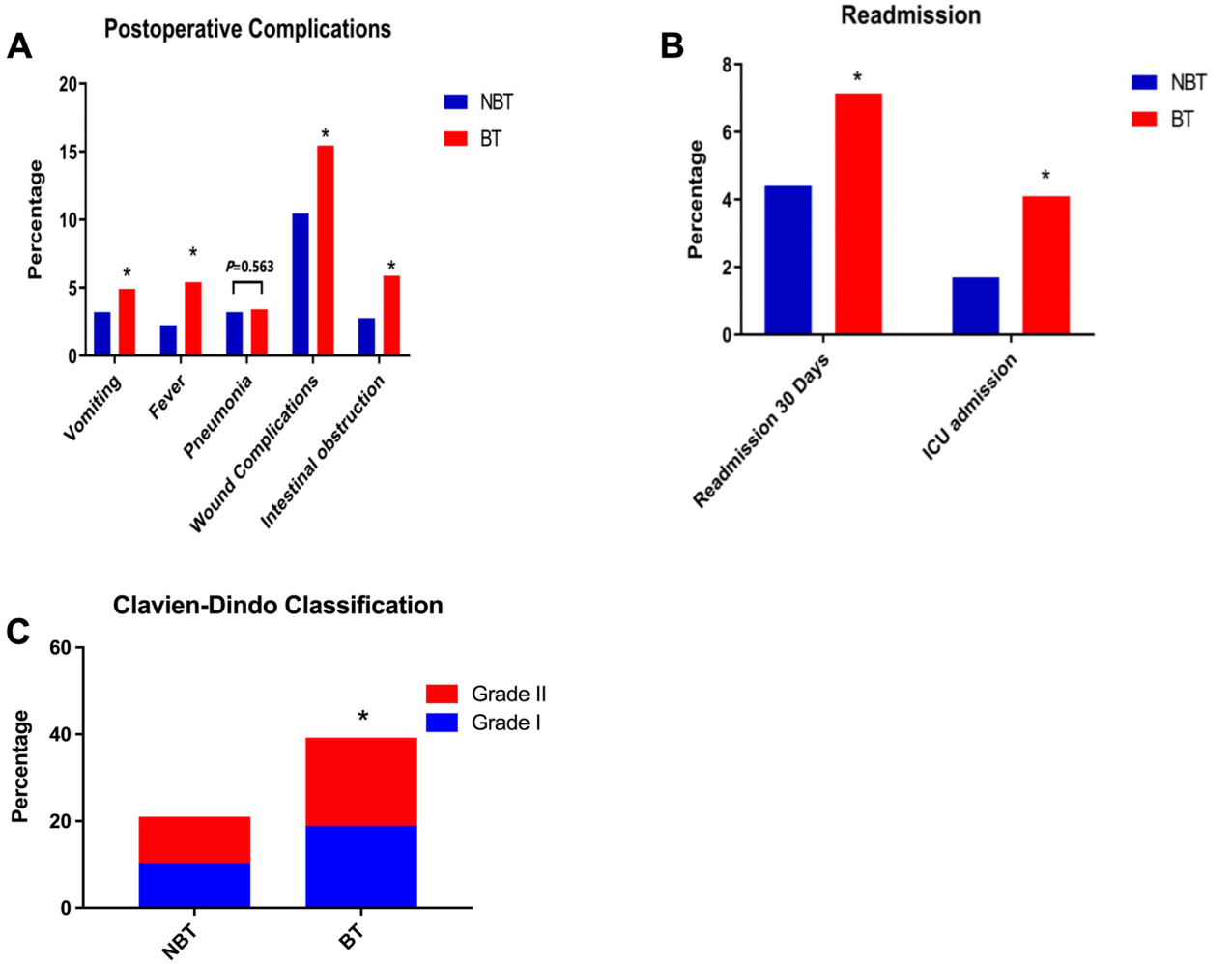

Fig. 3 **A** Postoperative complications between blood transfusion group and non-blood transfusion group. **B** Readmission between blood transfusion group and non-blood transfusion group. **C** Clavien-Dindo Classification between blood transfusion group and non-blood transfusion group

Table 2 Univariate analysis of length of stay

Variables	LOS	
	HR (95%CI)	*P*-value
Age (years)	1.02(0.98,1.21)	0.258
BMI (kg/m^2)	1.11 (0.72,1.52)	0.324
ASA	1.05(0.70,1.46)	0.159
Gestational age at delivery (days)	1.15(0.64,1.20)	0.267
Birthweight (g)	2.10(1.71,2.76)	< 0.001
Operation time(min)	1.52(1.24,1.75)	< 0.001
Pre-Hgb (g/dl)	1.45(0.93,1.71)	0.254
Pre-Hct (%)	1.42(1.29,1.58)	< 0.001
Experience of obstetrician	1.12(0.94,1.46)	0.078
Blood transfusion (yes)	1.56(1.15,1.98)	0.032

Table 3 Multivariable Cox proportional of LOS

Variables	LOS	
	HR (95%CI)	*P*-value
Birthweight (g)	1.65(1.06,2.32)	0.019
Operation time (min)	1.51(1.13,1.61)	0.042
Pre-Hgb (g/dl)	1.42(1.02,1.78)	0.045
Blood transfusion (yes)	1.52(1.07,2.25)	0.024

We identified that an increase in the NLR or SII and a decrease in the LMR were associated with adverse prognoses in women who underwent cesarean section (Thurn et al. 2019; Semple et al. 2019; Yuan et al. 2020). Our findings of increased levels of systemic inflammation indicators in patients who received intra-operative red blood

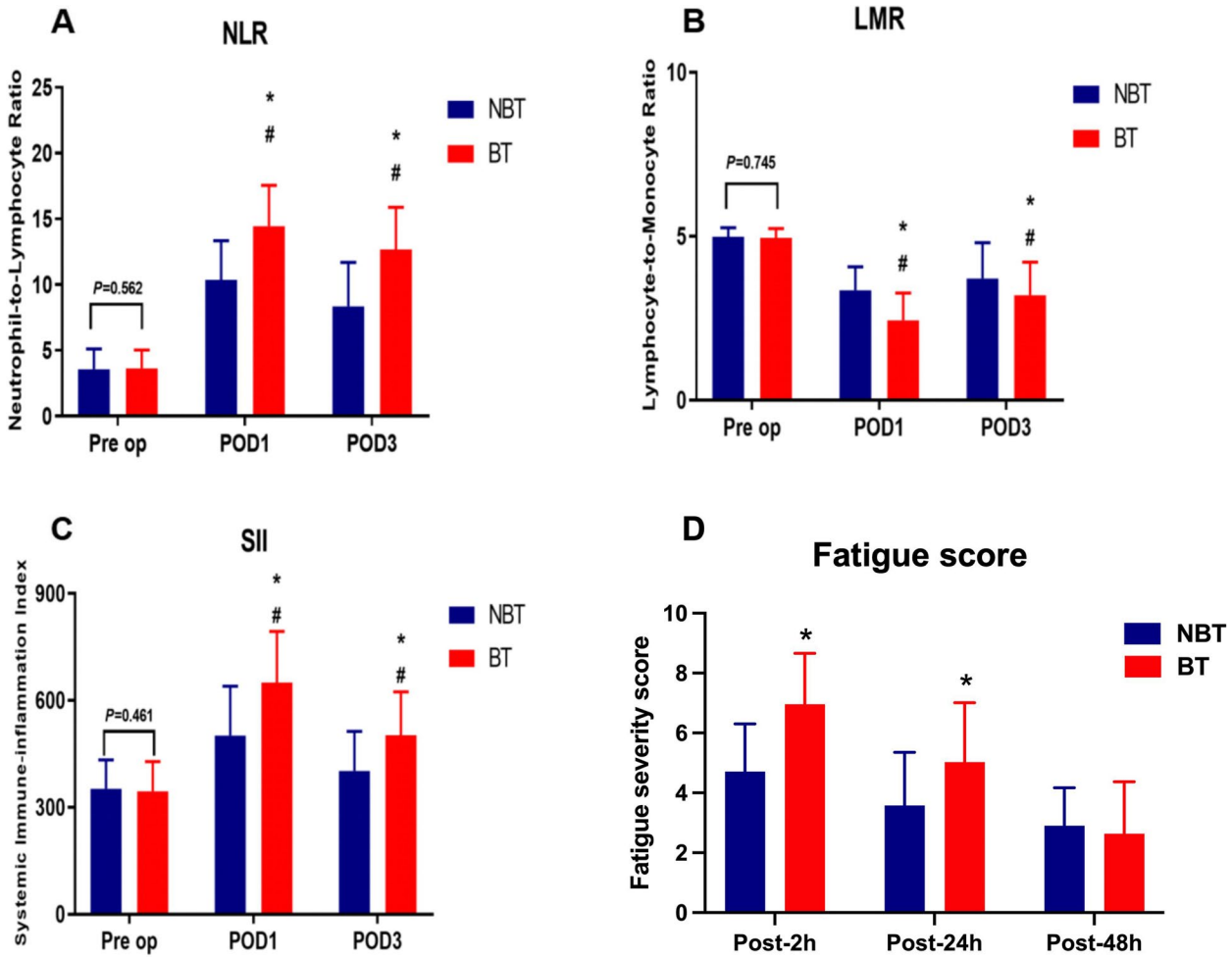

Fig. 4 System inflammatory indicators between blood transfusion group and non-blood transfusion group

cell transfusion are suggestive of a dysregulation of the inflammatory response, which may be associated with a higher rate of complications and longer LOS.

There is evidence that allogeneic blood transfusions significantly increase the incidence of post-operative complications, such as blood transfusion-related lung injury and surgical site infections (Owusu-Agyemang et al. 2017; Tai et al. 2018; Selvaggio et al. 2020). This is consistent with our findings of a higher incidence of post-operative complications in the BT than NBT group. Zhang et al. (Zhang et al. 2020) also demonstrated that peri-operative blood transfusion may increase the risk of post-operative complications and, therefore, increase the LOS.

The limitations of our study need to be acknowledged. Foremost is the retrospective design for which selection bias cannot be denied. The data were also obtained from a single center. Second, even with propensity score matching for relevant factors associated with post-partum hemorrhage, the possibility of bias due to unmeasured confounding factors cannot be denied.

Conclusion

In our study cohort, intra-operative blood transfusion during the cesarian section was significantly associated with increased post-operative systemic inflammation indicators, a prolonged LOS, and a higher rate of post-operative complications, compared to patients who did not receive intra-operative blood transfusion. Future well-designed, prospective studies are warranted to explore the relationship between allogeneic blood transfusions and outcomes in patients undergoing cesarean section.

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None.

Authors' contributions
YL.Z and ZD.X wrote the main manuscript text and ZQ.L prepared figures.All authors reviewed the manuscript.

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Availability of data and materials
The data was implemented by Shanghai First Maternity and Infant Hospital. According to relevant regulations, the data could not be shared, but could request from correspondence author.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Shanghai First Maternity and Infant Hospital, Tongji University (protocol: #2020–049). Informed consent was obtained from all subjects and/or their legal guardian(s) by telephone.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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