Effects of perioperative red blood cell transfusion on systemic immune indicators and postoperative recovery in patients undergoing cesarean section: A propensity score matching analysis

Yilu Zhou
Tongji University
Yiyi Tao
Tongji University
Zhendong Xu
Tongji university
Zhiqiang Liu (eliteromes@126.com)
Shanghai First Maternity and Infant Hospital

Research

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Abstract

Background

Postpartum hemorrhage (PPH) is one of the leading causes of maternal death in all regions of the world. Intra-operative red blood cell transfusion is one of the most effective strategies to treat PPH. However, the effect of blood transfusion on patients undergoing cesarean section remains unclear. The aim of this study was to investigate the effects of a intra-operative blood transfusion on systemic immune indicators and postoperative recovery in patients undergoing cesarean section.

Methods

This retrospective study enrolled patients undergoing cesarean section between January 2016 and June 2020. We divided these patients into two groups according to whether they received a intraoperative blood transfusion. Baseline characteristics were compared between groups. After propensity score matching, the length of stay (LOS), perioperative systemic inflammation-based scores, and postoperative complications were compared. Univariate and multivariable Cox proportional hazard models were used to evaluate the associations between covariates and outcomes.

Results

A total of 1221 patients were enrolled. After propensity score matching, a significant difference in LOS was observed between groups (4.2days vs. 6.6days, P=0.026). The postoperative complication rate in the blood transfusion (BT) group was significantly higher than that in the non-blood transfusion(NBT) group (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; intestinal obstructions, 5.88% vs. 2.75%, P=0.034, respectively). The systemic inflammatory indicators fluctuated significantly in the BT group compared with the NBT group on POD1 and POD3. The multivariate analysis indicated that intra-operative blood transfusion was associated with a longer LOS (hazard ratio: 1.52, 95% confidence interval: 1.07, 2.25).

Conclusions

A intra-operative blood transfusion was associated with fluctuations in systemic inflammatory indicators, higher postoperative complication rates and a prolonged length of stay.

Introduction

Postpartum hemorrhage (PPH) is one of the leading causes of maternal death in all regions of the world, and the definition of PPH is controversial(1). Generally, blood loss of 500 ml or more, blood loss with related physical signs regardless of the mode of delivery, and symptoms of hypovolemia after delivery are considered indicators of PPH(2). In addition, the American College of Obstetricians and Gynecologists (ACOG) issued recommendations that emphasize the importance of an organized and systematic process to help coordinate the response and management of PPH(3). Red blood cell transfusion is one of the most important treatments for PPH(4). However, the effect of intra-operative red blood cell transfusion on postoperative recovery remains unclear.

For patients undergoing cesarean section with bleeding and anemia, blood transfusion can save lives(5, 6).Intraoperative strategies for red blood transfusions may affect short-term clinical outcomes in patients undergoing surgery(7). Several retrospective studies have shown that transfused patients have an increased risk of developing infectious and noninfectious postoperative complications after major surgery(8). In addition, the results from a recent randomized controlled trial (RCT) indicate that a restrictive approach in which transfusions were triggered by hemoglobin (Hb) levels lower than 7 g/dL increased the risk of postoperative complications. Furthermore, some studies have found that the infusion of allogeneic blood inhibits the immune function of patients, which is not conducive to improving the prognosis in the perioperative period (9).

The association of intraoperative blood transfusion and postoperative recovery in patients suffering from PPH remains unclear. Additionally, studies examining whether receiving blood transfusion during surgery will promote postoperative complications and the effect of the duration of hospitalization on obstetric patients are still lacking. Therefore, we conducted a retrospective study to assess the association between intraoperative blood transfusion and postoperative recovery in patients undergoing cesarean section. We

hypothesized that intraoperative blood transfusion is associated with a longer length of stay. Furthermore, we investigated the association between perioperative blood transfusion and perioperative systemic inflammatory indicators, postoperative recovery parameters, postoperative complication rates and readmission rates.

Materials And Methods

Patients

Patients who underwent cesarean section at Shanghai First Maternity and Infant Health Hospital from January 2016 to June 2020 were enrolled in this study. This study was reviewed and approved by the Shanghai First Maternity Ethnics Committee (Protocol: #2020-049). All pregnant women or their relatives signed an informed consent form for research data use before undergoing cesarean section. The exclusion criteria were emergency surgery, twin pregnancy, patients treated with anti-inflammatory drugs or immunosuppressants for more than one month before cesarean section, patients with chronic inflammatory diseases, and incomplete medical records. Pregnancy characteristics, medical history, and operative details were reviewed and recorded.

Primary outcome

The primary outcome of this study was the LOS. LOS was defined as the interval between the date of surgery and the date of discharge.

Secondary outcome

Secondary endpoints included perioperative systemic inflammation-based scores (NLR, LMR, and SII). The counts of neutrophils, lymphocytes, monocytes and platelets were recorded three days before surgery (pre-surgery), the first day after surgery (POD1) and the third day after surgery (POD3). NLR was defined as the neutrophil to lymphocyte ratio, LMR was defined as the lymphocyte to monocyte ratio, and SII was defined as neutrophil*platelet/lymphocyte ratio. Postoperative complications, wound complications, ICU admission rates and readmission rates within 30 days were reviewed and recorded.

Anesthesia Care

Upon entering the operating room, pregnancy was monitored according to the American Society of Anesthesiologists (ASA) monitoring standards. Spinal anesthesia was the first choice for all cesarean sections in patients without contraindications. Patients were placed in the right recumbent position and punctured in L3-L4 or L2-L3 space. After observing the free flow of the cerebrospinal fluid after subarachnoid puncture, 0.5% hyperbaric ropivacaine (2 mL of 0.75% hyperbaric ropivacaine and 1 mL of 10% glucose) was administered. An epidural indwelling catheter with a length of 4 cm was used in the epidural space. Five minutes later, the anesthetic plane was evaluated at the T4-T6 level. When the effect was not satisfactory, 5 ml of 0.5% ropivacaine were injected into the epidural space. When the patient presented with contraindications to spinal anesthesia (coagulation dysfunction, lumbar disease, shock, etc.), general anesthesia was administered. General anesthesia was induced with 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). The patients were then endotracheally intubated, and general anesthesia was maintained with propofol, sufentanil and remifentanil. Repeated bolus injections of sufentanil and rocuronium were administered as necessary throughout the operation.

Statistical Analysis

We compared different clinical factors between the blood transfusion group and the non-blood transfusion group. Descriptive statistics, including the means and standard deviations, were reported for continuous variables. Frequency counts and percentages were calculated for categorical variables such as the ASA physical status, gestational age at delivery, birthweight, operation time, blood loss, and pre–Hgb levels. Univariate Cox proportional hazards models were fitted to evaluate the effects of continuous variables on time-to-event outcomes. Multivariable Cox proportional hazard models were used for the multivariate analysis to include important and significant covariates. We performed a propensity score matching analysis to reduce selection bias by building a matched group of patients to compare LOS between patients with a blood transfusion and those without a blood transfusion. Patients were matched using a 5-to-1 digit greedy match algorithm. Statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

A total of 1426 patients who underwent cesarean section were enrolled in this study. After reviewing the exclusion criteria, 329 patients were included in the BT group, and 909 were included in the NBT group (Figure 1). After propensity score matching, no significant differences in age (P=0.139), BMI (P=0.526), ASA status (P=0.811), gestational age at delivery (P=0.363), birthweight (P=0.262), primary mode of anesthesia (P=0.893), primary cause of PPH (P=0.993), and experience of the attending obstetrician (P=0.878) were observed between groups. However, significant differences in the operation time (P<0.001), blood loss (P<0.001) and pre-Hgb levels (P<0.001) were identified (Table 1).

Primary outcome

The LOS was defined as the date of surgery to the date of discharge. The LOS in the NBT group was significantly shorter than that in the BT group (mean time (days): 4.2 vs. 7.1, P=0.026,Fig. 2A).

Secondary outcome

Regarding postoperative complications, the incidence of postoperative vomiting was higher in the BT group than in the NBT group (3.2% vs. 4.9%, P=0.032,Fig. 2B). The incidence of postoperative fever was higher in the BT group than in the NBT group (5.41% vs. 2.24%, P=0.032,Fig. 2B). For postoperative pneumonia, no significant differences were observed between the two groups (3.2% vs. 3.4%, P=0.563,Fig. 2B). Furthermore, the incidence of wound complications in the BT group was higher than that in the NBT group (15.44% vs. 10.45%, P=0.028,Fig. 2B). The incidence of intestinal obstructions in the BT group was significantly higher than that in the NBT group (5.88% vs. 2.75%, P=0.034,Fig. 2B). However, the NBT group had significantly lower 30-day and ICU admission rates than the BT group (4.40% vs. 7.14%, 1.70% vs. 4.10%, P=0.018 and P=0.034, respectively,Fig. 2C). According to the univariate analysis, birthweight, a longer operation time, low pre-Hb levels and blood transfusion were associated with a longer LOS. The multivariable analysis showed that birthweight, operation time, low pre-Hb levels and blood transfusion were associated with a longer LOS. After matching, blood transfusion was still associated with a longer LOS.

After matching, no significant differences in the preoperative NLR, LMR or SII were observed between the two groups (Fig. 3). Compared with preoperative assessments, the NLR and SII in the two groups increased significantly and the LMR was significantly decreased in all patients on POD1 and POD3 (P<0.001, Fig. 3B). The NLR and SII values were slightly lower on POD3 than on POD1 but were still higher than the preoperative values (P<0.001, Fig. 3A-C). The NLR and SII values in the NBT group on POD1 and POD3 were significantly lower than those in the BT group (P<0.001, Fig. 2A-C), whereas a significantly higher LMR was detected in the NBT group than in the BT group (P <0.001, Fig. 3B).

Discussion

In this large retrospective cohort study, our results showed that the hospital stay of patients who received a blood transfusion was significantly longer, the incidence of postoperative vomiting and wound complications was higher than that of patients without a blood transfusion, and the postoperative inflammatory index fluctuated more drastically in patients who received a blood transfusion.

The main bleeding site in postpartum hemorrhage is the uterus(10). When postpartum hemorrhage occurs, the uterine muscle tissue is hypoxic and does not contract well, and the sensitivity of oxytocin receptors decreases. Repeated hemostasis operations increase further damage to the uterine muscles(10). At the same time, the sinusoids on the dissected surface of the placenta cannot be closed, and fibrinogen deposition and thrombosis do not play a role(10). Therefore, obstetric hemorrhage has the characteristics of a fast speed, large volume, difficult evaluation, and difficulty of stopping bleeding quickly.

Blood transfusion is the most common method for the clinical treatment of patients with obstetric hemorrhage. It effectively solve the patient's anemia caused by excessive blood loss, helps maintain blood volume and blood pressure, exerts a certain preventive effect on patients with shock, and improves the prognosis of patients(11, 12). However, a large number of clinical practices have found that after patients with obstetric hemorrhage receive a large transfusion of blood, although their life and safety are guaranteed, they also experience certain side effects, mainly manifested as abnormal blood coagulation(13). Due to the long-term storage of blood, platelets and coagulation factors are destroyed to a certain extent. After entering the patient's body, the active coagulation factors will be reduced, which will lead to coagulation dysfunction.

In terms of postoperative complications, a large number of allogeneic blood transfusions will significantly increase the incidence of postoperative complications, such as blood transfusion-related lung injury (14) and surgical site infections (15). In the present study,

the incidence of postoperative complications in patients receiving blood transfusion increased significantly during the perioperative period. Zhang et al reported that a perioperative blood transfusion potentially increases the risk of postoperative complications and is associated with a prolonged LOS(9). Furthermore, another study reported that perioperative blood transfusion may be associated with worse outcome in patients undergoing surgery(16). After blood transfusion, the immune system changes significantly. These changes have been shown to be potential mechanisms that increase the risk of infection, graft-versus-host disease and postoperative complications after blood transfusion(17). According to recent studies, the suppression of perioperative immune function may promote postoperative metastasis and recurrence in patients with cancer(18). A large number of studies have also shown that certain markers of blood components, such as NLR, LMR and SII, comprehensively indicate the balance of the host immune system and have been considered indicators related to the prognosis(19, 20). An increased NLR or SII and decreased LMR are associated with a poor prognosis in patients undergoing surgery(21, 22). Based on our results, patients undergoing a blood transfusion exhibit greater fluctuations in these systemic inflammatory markers after surgery. Thus, blood transfusion is related to the strong suppression of immune function and/or inflammatory response disorders, such as a higher complication rate and longer hospital stay, in patients receiving a blood transfusion. (23)

Our research has limitations.The limitations include the following: the study was a retrospective study rather than a random controlled trial, and the data were obtained from a single center. Second, even if we perform a propensity score matching analysis, considering the various factors related to postpartum hemorrhage, we still cannot avoid the possibility of biased results due to unmeasured confounding factors.

Conclusion

In summary, the transfusion of a large amount of blood can save the life and ensure the safety of patients with PPH, but it will exert certain effects on the levels of inflammatory factors and postoperative recovery of the patients. During the treatment period, clinicians should focus on actively implementing measures to avoid risks, prevent complications, and improve patients' long-term prognoses.

Abbreviations

PPH
Postpartum hemorrhage
LOS
length of stay
BT
blood transfusion
Hb
hemoglobin
NLR
neutrophil to lymphocyte ratio
LMR
lymphocyte to monocyte ratio
SII
System immune indicator

Declarations

Anknowledgements:None

Author Contributions

ZYL, and TYY: conception and design. LZQ,XZD: acquisition, statistical analysis, or interpretation of the data. All authors: drafting of the manuscript, reviewed, and approved the final version of the manuscript.

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Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics approved consent to participate

The studies involving human participants were reviewed and approved by the Shanghai First Maternity Ethnics Committee (Protocol: #2020-049). Written informed consent for participation was required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication:Not applicable

Informed consent:Informed consent was obtained from all individuals participants included in the study

Competing Interest:None

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Tables

Table1. Baseline characteristics in BT group and NBT group

	Original cohort		*P*	Matched cohort		*P*	Standard difference (%)
	BT group(n=312)	NBT group(n=909)		BT group(n=312)	NBT group(n=312)		
Age (years)	33.49±4.51	32.97±4.23	0.066	33.49±4.51	32.97±4.26	0.139	3.52
BMI (kg/m2)	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	2.44
ASA							1.98
I-II	273(87.5%)	842(92.6%)	0.005	273(87.5%)	271(86.9%)	0.811	
III	39(12.5%)	67(7.4%)		39(12.5%)	41(13.1%)		
Gestational age at delivery (days)	273.11±22.11	272.66±20.66	0.745	273.11±22.11	274.66±20.36	0.363	
Birthweight (g)	3488.31±1006.69	3073.16±1078.84	<0.001	3488.31±1006.69	3423.16±1086.85	0.262	2.56
Primary Mode of Anesthesia			0.192			0.893	4.42
General	31(10%)	69(7.6%)		31(10%)	30(9.6%)		
Neuraxial	281(90%)	840(92.4%)		281(90%)	282(90.4%)		
Primary cause of PPH			0.987			0.993	
Uterine atony	128(41%)	378(41.8%)		128(41.0%)	127(40.8%)		
Placenta accreta	70(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(min)	55.20±8.54	42.64±7.83	<0.001	55.20±8.54	40.64±7.13	<0.001	6.58
Blood Loss(ml)	831.65±78.35	241.39±83.61	<0.001	831.65±78.35	236.39±80.21	<0.001	7.45
Pre Hgb (g/dl)	101.72±33.28	119.67±25.33	<0.001	101.72±33.28	112.67±45.33	<0.001	7.98
Experience of attending obstetrician							3.14
5 years	28(9%)	69(7.6%)	0.427	28(9%)	27(8.6%)	0.878	
5 years or more	283(91%)	840(92.4%)		283(91%)	285(91.4%)		

Abbreviations: BMI: Body Mass Index; IQR: Inter Quartile Range; ASA: American Society of Anesthesiologists score; PPH: Postpartum haemorrhage

Table 2. Univariate analysis Length Of Stay

Variables	LOS	
	HR (95% CI)	*P*-value
Age (years)	1.02(0.98,1.21)	0.258
BMI (kg/m2)	1.11 (0.72,1.52)	0.324
ASA	1.05(0.70,1.46)	0.159
Gestational age at delivery	1.15(0.64,1.20)	0.267
Birthweight	2.10(1.71,2.76)	<0.001
Operation time(min)	1.52(1.24,1.75)	<0.001
Pre Hgb	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	1.56(1.15,1.98)	0.032

Table 3. Multivariable Cox proportional of LOS

Variables	LOS (Before matching)		LOS (After matching)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Birthweight	1.73(1.10,2.40)	0.034	1.65(1.06,2.32)	0.019
Operation time(min)	1.60(1.13,1.76)	0.012	1.51(1.13,1.61)	0.042
Pre Hgb	1.51(1.01,1.98)	<0.001	1.42(1.02,1.78)	0.045
Blood transfusion	1.93(1.03,2.45)	0.004	1.52(1.07,2.25)	0.024

Figures

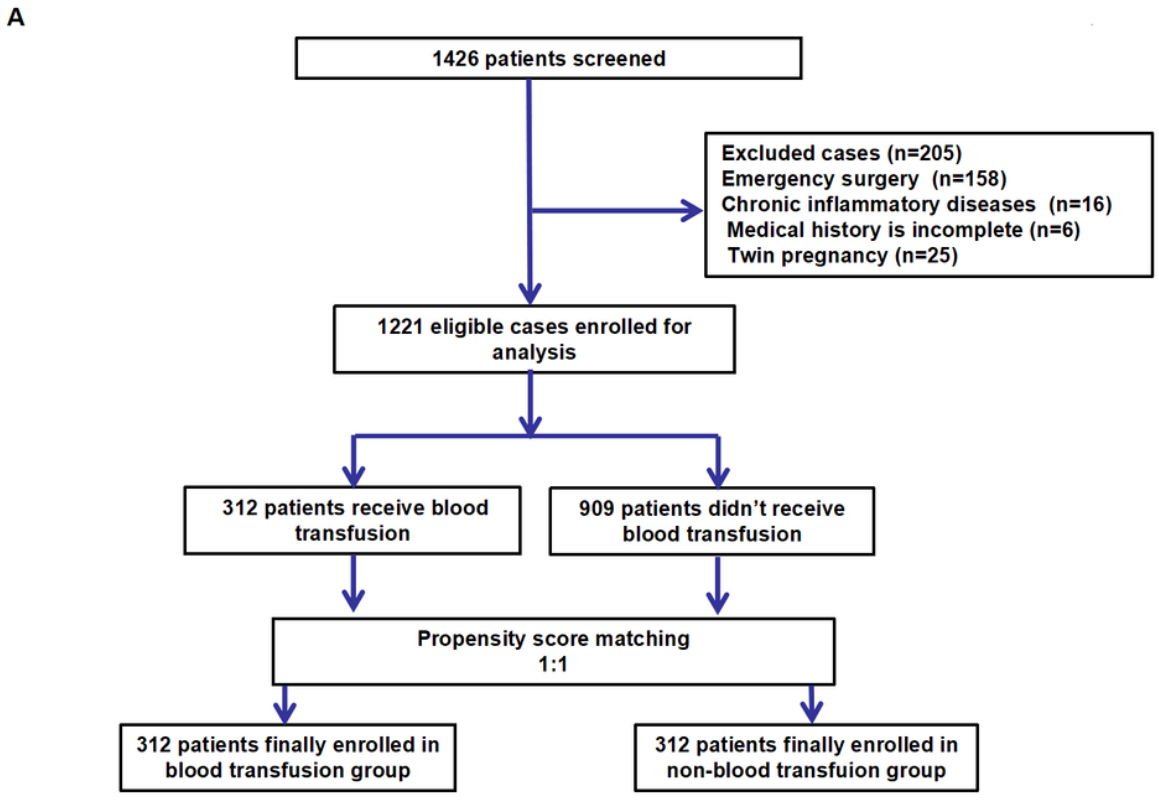

Figure.1

Figure 1

Flowchart of patients enrolled in the study

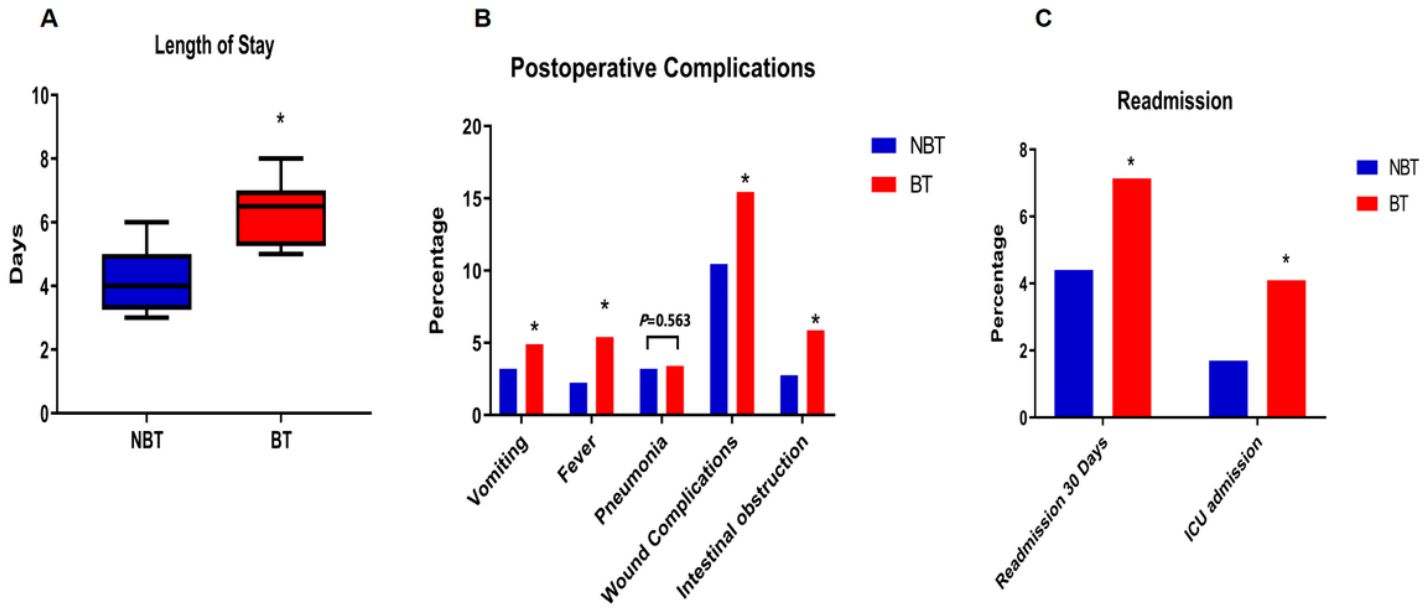

Figure.2

Figure 2

Primary outcome of the study.(A).Length of Stay,(B).Postoperative complication,(C) Readmission rate between the groups.

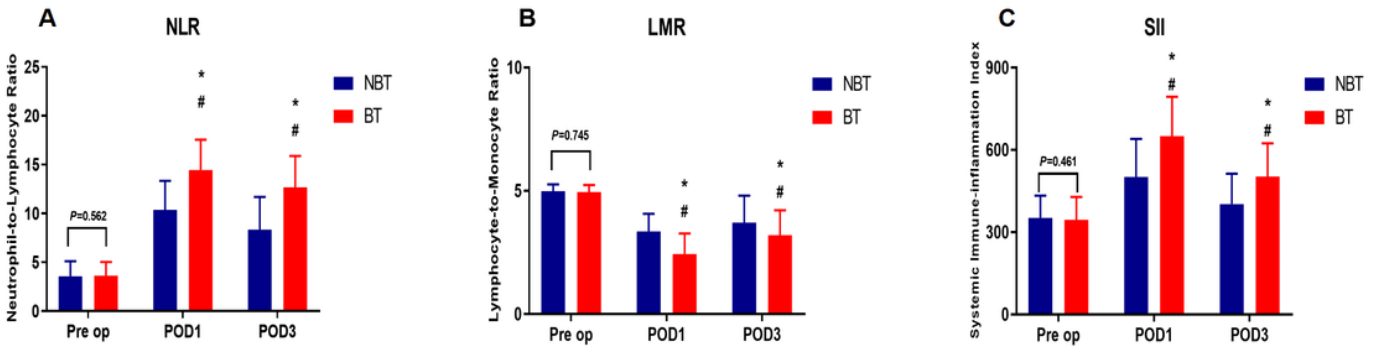

Figure.3

Figure 3

Perioperative System immune indicators.(A),NLR, (B)LMR, (C) SII