

RESEARCH ARTICLE

Study on perinatal-related factors of maternity and newborn in parturients with intrapartum fever in part of Eastern China: A cross-sectional study

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Abstract

Background: Maternal intrapartum fever has a serious impact on mother and child. However, the corresponding study seems to be in short.

Methods: The role of inflammatory cells in patients who were diagnosed with intrapartum fever lived in part of Eastern China was evaluated. The obstetrics outcomes, complete blood cell count (CBC) and thereby converted neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio, monocyte to lymphocyte ratio (MLR), and vaginal secretion were compared in different groups.

Results: Prepartum values of white blood cell (WBC), red blood cell (RBC), and hemoglobin (Hb) were all a little higher in the febrile group than in the afebrile group, and postpartum WBC in the afebrile group was still higher while postpartum RBC and Hb were inferior to non-fever maternity. Postpartum NLR and MLR were all higher in the fever group but not preferred overtly difference before delivery. Additionally, the comparison of WBC, RBC, Hb, platelets, neutrophils, and monocytes in prepartum and postpartum all showed significant differences.

Conclusion: The parturition could bring about the value change of CBC and intrapartum fever might aggravate or alleviate this change. Besides, the intrapartum fever might not be caused mainly by infection and the difference between bacteria and fungus could reflect in the CBC.

KEYWORDS

intrapartum fever, monocyte to lymphocyte ratio, neutrophil to lymphocyte ratio, perinatal period, platelet to lymphocyte ratio, vaginal discharge

1 | INTRODUCTION

Maternal intrapartum fever is a common obstetric complication during labor, usually defined as a temperature higher than or equal to

38°C,¹⁻³ but another few defined as over 37.4°C,⁴ occurred in 1.6%–34% parturients.¹ A variety of causes contribute to the etiology of intrapartum fever, including infective and non-infective reasons. Infectious factors, the least common explanation, mainly associate

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with clinical chorioamnionitis, urinary tract infection, and upper respiratory tract infection.⁴⁻⁶ Additionally, most febrile patients during childbirth are secondary to non-infectious agents, involving epidural analgesia, environmental temperature during labor, prolonged labor time, and maternal underlying diseases.^{4,6-8} Fever during labor could trigger adverse obstetric effects, including postpartum hemorrhage, dystocia, and cesarean delivery.^{3,9} In addition to the obstetric outcomes, adverse neonatal sequelae contain low Apgar scores, neonatal sepsis, hypotonia, neonatal encephalopathy, epileptic seizure, respiratory distress or asphyxia, and even infants death.^{6,9-11} Thus, intrapartum fever deserves more attention because of its high incidence and severe consequences.

Traditionally, general fever is often diagnosed by complete blood cell count (CBC),^{12,13} this is because the value of CBC before and after fever alters. However, hardly publications describe the change of CBC in parturients who suffered from intrapartum fever during the whole labor. Apart from this, some other new biomarkers, such as neutrophil-to-lymphocyte ratio (NLR),¹⁴ platelet-to-lymphocyte ratio (PLR),¹⁵ as well as monocyte-to-lymphocyte ratio (MLR),¹⁶ are increasingly emerged as effective markers linked to the measure of inflammation and expected to use for judging if a person has a fever. Besides, NLR has also been applied as an inflammatory marker in various conditions, including type 2 diabetes mellitus,¹⁷ irritable bowel syndrome,¹⁸ thyroiditis,¹⁹ cancer,²⁰ Corona Virus Disease 2019 infection,²¹ and ulcerative colitis.²² As for PLR, it also has been proposed as a novel inflammatory predictor in different diseases, such as thyroid nodules²³ and diabetes mellitus.²⁴ In addition, MLR has been associated with hepatosteatosi²⁵ and diabetic nephropathy.²⁶ Similarly, this field also does not extend to the study of intrapartum fever. Therefore, we focused on the pre-, intra-, and postpartum changing situation of patients with intrapartum fever during the birth process in this article. In addition, the possibility of NLR, PLR, and MLR act as biomarkers was explored. Furthermore, the results of vaginal discharge culture in febrile mother were also observed.

2 | PATIENTS AND METHODS

2.1 | Study population

This study was approved by the Medical Ethics Committee of Nanjing Maternity and Child Health Care Hospital. We recruited a retrospective cohort of patients diagnosed with intrapartum fever (defined as temperature over 37.5°C) from January 1, 2018 to December 31, 2018 at Nanjing Maternity and Child Health Care Hospital. And most of the parturients in this hospital were from Eastern China. The women with intrapartum fever was included in the study group, and we parturients who were afebrile was included in the control group. All parturients selected in this study received epidural analgesia.

2.2 | Data collection

Data were acquired from our electronic records system retrospectively. For each woman included in this research, we collected maternal age, gestational weeks at delivery, gravidity and parity, the volume of intrapartum hemorrhage, the volume and turbidity of the amniotic fluid, newborn sex, birth weight of the newborn, degree of perineal laceration, oxytocic manner, time of the first, the second, and the third stage of labor, the volume of intrapartum hemorrhage, prenatal and postnatal data of blood routine examination. Besides, for the study group, we also recorded the intrapartum data of the complete blood count.

As for the data of the blood routine examination, we analyzed the differences between the study group and the control group. In addition, we analyzed the pre- and postnatal differences between these two groups. Moreover, we calculated the NLR, PLR, and MLR defined as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), respectively.

For maternity with intrapartum fever, vaginal secretion specimens were collected in pyretic time and then diagnosed by an experienced doctor. We documented the results of secretion culture, including *Escherichia coli*, *Candida albicans*, *Staphylococcus aureus*, and so forth.

2.3 | Statistical analysis

After the normality test through the Kolmogorov-Smirnov test, a *t* test was performed for calculating the differences in the numerical variables between two normally distributed groups and Mann-Whitney *U* test for non-normally distributed data. And the Kruskal-Wallis test was applied among three non-normally distributed groups. For the classified variables, the chi-square test or Fisher exact test was carried out. All analyses were completed via statistical software SPSS 25.0 (SPSS Inc.) and a two-tailed $p < 0.05$ was treated as statistical significance.

3 | RESULTS

3.1 | Demographic and characteristics

Based on the original data, some data were excluded due to various kinds of reasons as follows. Firstly, we only counted clear and hierarchical color of amniotic fluid. Therefore, pink, bloody, and brown amniotic fluid was excluded. Then, for oxytocic manner, only parturients managed with one mode were recorded to shrug off the effect of interaction between disposing approaches. Besides, parturients over 2 births were excluded because of twins existing.

3.1.1 | Demographic and characteristics for all maternity and newborn

During the whole of 2018, 1797 women in labor suffered from the intrapartum fever in the hospital, and 2850 matched afebrile parturients were also enrolled in this study. And the proportion of the maximum temperature in the fever group from 37.5 to 38.0°C, 38.0 to 38.5°C, and over 38.5°C was 34.60%, 53.09%, and 12.31%, respectively (Figure S1). Table 1 displays the obstetrical characteristics of all included maternity and newborn data and the results demonstrated that the difference between intrapartum fever and afebrile groups exists in maternal age, gestational weeks at delivery, gravidity and parity, the turbidity of the amniotic fluid, birth weight of the

newborn, degree of perineal laceration, oxytocic manner, time of the first and the second stage of labor. The maternity age in the study group was 28.4 ± 2.6 , and up to 29.3 ± 2.8 in the afebrile group ($p < 0.001$). And the gestational weeks in the intrapartum fever and afebrile group were 39.7 ± 1.6 and 39.5 ± 2.6 ($p < 0.001$), respectively. The febrile subjects had lower gravidity and parity, especially for parity. Nearly 95% febrile parturients were nulliparous cases, but <69% nulliparous women in the afebrile group. As for oxytocic manner during delivery, oxytocin regimens represented two-thirds in fever mother-to-be women, nevertheless, more than 60% of parturients without any managements in the afebrile group ($p < 0.001$). Besides, more bleeding (307.6 ± 96.2 vs. 283.2 ± 51.6 , $p < 0.001$) and cloudy amniotic fluid (31.72% vs. 18.21%, $p < 0.001$) occurred

TABLE 1 Characteristics between intrapartum fever and afebrile groups

Variable	Intrapartum fever (n = 1797)	Afebrile (n = 2850)	p
Maternal age	28.4 ± 2.9	29.3 ± 3.8	<0.001
Gestational age (weeks)	39.7 ± 1.3	39.4 ± 1.6	<0.001
Gravidity (%)			<0.001
1	1259 (70.06)	1486 (52.14)	
2-4	527 (29.33)	1312 (46.04)	
≥5	11 (0.61)	52 (1.82)	
Parity (%)			<0.001
1	1706 (94.94)	1957 (68.67)	
2	90 (5.01)	874 (30.67)	
Oxytocic manner (%)			<0.001
No	531 (29.55)	1819 (63.82)	
Propess	13 (0.72)	67 (2.35)	
Oxytocin	1210 (67.33)	914 (32.07)	
Water balloon	0 (0)	3 (0.11)	
Volume of intrapartum hemorrhage (ml)	307.6 ± 96.2	283.2 ± 51.6	<0.001
Amniotic fluid			
Volume (ml)	382.0 ± 53.1	387.7 ± 60.9	0.186
Turbidity (%)			<0.001
Clear	1227 (68.28)	2331 (81.79)	
I	143 (8.12)	204 (7.16)	
II	167 (9.29)	181 (6.35)	
III	250 (13.91)	126 (4.42)	
Degree of perineal laceration (%)			<0.001
No	475 (26.43)	393 (13.79)	
I	966 (53.76)	2042 (71.65)	
II	356 (19.81)	415 (14.56)	
Labor time (min)			
The first stage of labor	632.1 ± 167.1	417.8 ± 240.9	<0.001
The second stage of labor	36.1 ± 17.5	29.0 ± 16.3	<0.001
The third stage of labor	9.2 ± 3.4	9.2 ± 4.1	0.222
Total	677.4 ± 173.2	455.9 ± 248.4	<0.001
Birth weight (g)	3384.2 ± 376.8	3299.3 ± 442.0	<0.001

in fever group, whereas they were less prone to bear the laceration of perineum (73.57% vs. 86.21%, $p < 0.001$). Moreover, in the intrapartum fever group, the newborn birth weight was a little higher (3384.2 ± 376.8 g vs. 3299.3 ± 442.0 g, $p < 0.001$), and the first (632.1 ± 167.1 min vs. 417.8 ± 240.9 min, $p < 0.001$) and the second (36.1 ± 17.5 min vs. 29.0 ± 16.3 min, $p < 0.001$) stage of labor were all longer than the afebrile group. However, the third stage of labor in these two groups had no significant difference. We additionally calculated the labor time after fever between 37.5 and 38.0°C , 38.0 and 38.5°C , and over 38.5°C , and the corresponding results were 256, 242, and 199 min (Figure S2). Similar to the third stage of labor, the volume of amniotic fluid also showed no significant difference.

3.1.2 | Demographic and characteristics for nulliparity and corresponding newborn

For the sake of reducing the impact of the parity, we drew the situation of nulliparity alone (Table 2). After included nulliparity only, the number of parturients in intrapartum fever and afebrile group reduced by 91 (1797 to 1706) and 892 (2850 to 1958), respectively. Afebrile maternal age was above the fever parturients before grouping, yet decreased from 29.3 ± 3.8 to 28.0 ± 2.8 and below the febrile group ($p = 0.005$). In fever and afebrile group, the total, the first, and the second stage of labor time were all extended and the difference ($p < 0.001$) still remained, especially for total labor time (from 455.9 ± 248.4 min to 530.3 ± 239.1 min, $p < 0.001$) and the first stage of labor in afebrile maternity (from 417.8 ± 240.9 min to 487.2 ± 233.3 min, $p < 0.001$). Moreover, the gravidity in the afebrile group was more frequent ($p < 0.001$) but had no significant difference between the two groups in nulliparity ($p = 0.411$).

For neonatal data, the weight difference of newborns became larger due to the birth weight in the fever group unchanged nearly (from 3384.2 ± 376.8 to 3382.9 ± 372.0 g), nonetheless, declined to 3265.0 ± 427.6 g from 3299.3 ± 442.0 g in the afebrile group.

Other variables, including gestational weeks, oxytocic manner, the volume of intrapartum hemorrhage, amniotic fluid turbidity, and the degree of perineal laceration, all of the above altered not notably in both groups after grouping. Besides, the volume of amniotic fluid ($p = 0.924$) and the third stage of labor ($p = 0.539$) still showed no striking difference in the two types of population.

3.2 | The intrapartum fever and afebrile CBCs

In order to reveal the impact of intrapartum fever to maternity, we compared the CBCs and converted NLR, MLR, and PLR between intrapartum fever and afebrile groups. The results (Table 3) demonstrate the difference remains in prepartum white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), and monocytes and postpartum WBC, RBC, Hb, neutrophils, monocytes, NLR, and MLR between fever and afebrile parturients. Prepartum mean value of

WBC ($9.53 \times 10^9/\text{L}$ vs. $9.42 \times 10^9/\text{L}$, $p = 0.010$), RBC ($4.02 \times 10^{12}/\text{L}$ vs. $3.98 \times 10^{12}/\text{L}$, $p < 0.001$), and Hb (119.8 g/L vs. 118.2 g/L, $p < 0.001$) were all a little higher in the febrile group than in the afebrile group, and postpartum WBC in the afebrile group is still higher ($12.48 \times 10^9/\text{L}$ vs. $11.71 \times 10^9/\text{L}$, $p < 0.001$). However, postpartum RBC ($3.70 \times 10^{12}/\text{L}$ vs. $3.81 \times 10^{12}/\text{L}$, $p < 0.001$) and Hb (110.5 g/L vs. 113.6 g/L, $p < 0.001$) in fever parturients were inferior to non-fever women. And for neutrophils, prenatal data did not uncover the significant difference, but postnatal neutrophils in the intrapartum fever group ($10.11 \times 10^9/\text{L}$) were higher than in the afebrile group ($9.19 \times 10^9/\text{L}$, $p < 0.001$). Monocytes between the two groups implied the difference in both prepartum and postpartum. Additionally, postpartum NLR and MLR were all higher in the fever group ($p < 0.001$) while not preferred overtly difference before the delivery. However, PLR in the two groups not presented obviously difference whether it was in prepartum ($p = 0.711$) or postpartum ($p = 0.938$). Correspondingly, platelets (PLT) also showed no discrepancy between the intrapartum fever and the afebrile group.

3.3 | Prepartum and postpartum CBCs and its difference

The results of pre- and postpartum CBC of parturients are shown in Table 4. Almost all displayed data illustrated the significant difference between prepartum and postpartum maternity apart from the lymphocytes in intrapartum fever expectant mother ($p = 0.307$). The elevated value of CBCs after labor included WBC, PLT, neutrophils, monocytes, and lymphocytes in both fever and non-fever parturients. On the contrary, postnatal RBC and Hb fallen remarkably. The mean of postpartum RBC fallen from $4.02 \times 10^{12}/\text{L}$ to $3.70 \times 10^{12}/\text{L}$ ($p < 0.001$) in fever parturients and fallen from $3.98 \times 10^{12}/\text{L}$ to $3.81 \times 10^{12}/\text{L}$ ($p < 0.001$) in afebrile maternity. For Hb, the value fallen from 119.8 g/L to 110.5 g/L ($p < 0.001$) in the fever group and fallen from 118.2 g/L to 113.6 g/L ($p < 0.001$) in the non-fever group.

In order to explore whether intrapartum fever would aggravate or alleviate the change of CBCs before and after delivery, we therefore used postpartum data of maternity CBC minus the corresponding prepartum data (Table 4). Table 4 illustrated that elevated WBC, PLT, and neutrophils, as well as reduced RBC and Hb, remained appreciably difference. The difference value of WBC ($2.95 \times 10^9/\text{L}$ vs. $2.28 \times 10^9/\text{L}$, $p < 0.001$) and neutrophils ($2.95 \times 10^9/\text{L}$ vs. $2.28 \times 10^9/\text{L}$, $p < 0.001$) preferred higher in intrapartum fever group, yet lower for PLT ($10.60 \times 10^9/\text{L}$ vs. $11.91 \times 10^9/\text{L}$, $p = 0.023$) in intrapartum fever subjects. Besides, RBC ($-0.32 \times 10^{12}/\text{L}$ vs. $-0.17 \times 10^{12}/\text{L}$, $p < 0.001$) and Hb (-9.21 g/L vs. -4.68 g/L, $p < 0.001$) descended more obviously in fever maternity. However, monocytes ($p = 0.185$) and lymphocytes ($p = 0.459$) recommend pronounced discrepancy in the intrapartum fever and the afebrile group.

TABLE 2 Characteristics of nulliparity between intrapartum fever and afebrile groups

Variable	Intrapartum fever (n = 1706)	Afebrile (n = 1958)	p
Maternal age	28.2 ± 2.6	28.0 ± 2.8	0.005
Gestational age (weeks)	39.7 ± 1.6	39.5 ± 2.61	<0.001
Gravidity (%)			0.411
1	1258 (73.74)	1479 (75.54)	
2-4	444 (26.03)	476 (24.31)	
≥5	4 (0.23)	3 (0.15)	
Oxytocic manner (%)			<0.001
No	480 (28.14)	1085 (55.41)	
Propess	13 (0.76)	62 (3.17)	
Oxytocin	1171 (68.64)	771 (39.38)	
Volume of intrapartum hemorrhage (ml)	308.64 ± 99.73	286.54 ± 54.12	<0.001
Amniotic fluid			
Volume (ml)	381.1 ± 52.3	384.1 ± 55.4	0.924
Turbidity (%)			<0.001
Clear	1157 (67.82)	1569 (80.13)	
I	137 (8.03)	139 (7.10)	
II	161 (9.44)	135 (6.89)	
III	242 (14.19)	108 (5.52)	
Degree of perineal laceration (%)			<0.001
No	456 (26.73)	281 (14.35)	
I	899 (52.70)	1313 (67.06)	
II	351 (20.57)	364 (18.59)	
Labor time (min)			
The first stage of labor	641.2 ± 163.6	487.2 ± 233.3	<0.001
The second stage of labor	37.0 ± 17.6	33.9 ± 16.6	<0.0001
The third stage of labor	9.1 ± 3.3	9.1 ± 3.5	0.539
Total	687.3 ± 169.4	530.3 ± 239.1	<0.001
Birth weight (g)	3382.9 ± 372.0	3265.0 ± 427.6	<0.001

3.4 | Results of positive vaginal secretion culture

For all 1797 parturients who undergone the fever during childbirth, vaginal secretion culture was performed. Out of 1797 intrapartum fever women in labor, 276 cases (15.36%) were tested with positive vaginal secretion culture (the detailed results of the vaginal secretion culture were presented in Figure S3). We then further subdivided positive section into gram-positive bacteria (G+), gram-negative bacteria (G-), and fungus, as for each group, the number of positive women was 122, 69, and 85, respectively. Table 5 describes the pre-, intra-, and postpartum CBC in three subgroups. From Table 5, we could find the value of the positive test results difference mainly existed in RBC, Hb, and PLT, including prepartum RBC, Hb, and PLT, intrapartum RBC and Hb, as well as postpartum PLT. The value of prepartum RBC was $4.12 \times 10^{12}/L$, $4.10 \times 10^{12}/L$, and $3.93 \times 10^{12}/L$ for subgroup G+, G-, and fungus, respectively ($p = 0.009$). And for intrapartum RBC, the matching value was $4.13 \times 10^{12}/L$, $4.20 \times 10^{12}/L$, and $3.97 \times 10^{12}/L$ ($p = 0.011$). But this

difference did not exist in postpartum ($p = 0.984$). The changing trend of Hb was consistent with RBC ($p = 0.025$, 0.010 , and 0.071 for pre-, intra-, and postpartum RBC, respectively). However, the value of PLT showed different tendency. Prepartum and postpartum PLT manifested difference but not in intrapartum ($p = 0.022$, 0.080 , and 0.014 for pre-, intra-, and postpartum RBC, respectively). In addition, post hoc test (results not shown) suggested that the difference appeared in fungus with G+ or G- but not G+ with G-. In other words, the difference principally occurred in fungus with bacteria rather than different bacteria. Nonetheless, the value of WBC, neutrophils, monocytes, and lymphocytes in three groups presented no significant difference.

4 | DISCUSSION

Maternal intrapartum fever, a usual abnormal status during labor, results in most kinds of adverse outcomes affecting the health of

TABLE 3 Complete blood cell counts of intrapartum fever and afebrile groups

Variable	Intrapartum fever (n = 1786)	Afebrile (n = 1882)	p
Prepartum			
WBC (10 ⁹ /L)	9.53 (7.72–10.89)	9.42 (7.58–10.71)	0.010
RBC (10 ¹² /L)	4.02 (3.77–4.23)	3.98 (3.73–4.22)	<0.001
Hb (g/L)	119.75 (112–127)	118.23 (110–126)	<0.001
PLT (10 ⁹ /L)	192.49 (155–223)	190.41 (153–221)	0.179
Neutrophils (10 ⁹ /L)	7.08 (5.33–8.25)	7.05 (5.20–8.17)	0.103
Monocytes (10 ⁹ /L)	0.59 (0.47–0.69)	0.59 (0.45–0.69)	0.038
Lymphocytes (10 ⁹ /L)	1.73 (1.38–2.06)	1.71 (1.37–2.01)	0.210
NLR (%)	4.60 (2.91–5.36)	4.71 (2.90–5.30)	0.994
MLR (%)	0.37 (0.27–0.43)	0.40 (0.27–0.42)	0.322
PLR (%)	120.20 (89.12–142.58)	122.84 (86.79–143.02)	0.711
Postpartum			
WBC (10 ⁹ /L)	12.48 (10.58–14.02)	11.71 (9.75–13.35)	<0.001
RBC (10 ¹² /L)	3.70 (3.41–3.99)	3.81 (3.52–4.10)	<0.001
Hb (g/L)	110.53 (101–121)	113.55 (104–123)	<0.001
PLT (10 ⁹ /L)	203.09 (166–236)	202.32 (166–234)	0.691
Neutrophils (10 ⁹ /L)	10.11 (8.26–11.56)	9.19 (7.47–10.66)	<0.001
Monocytes (10 ⁹ /L)	0.64 (0.47–0.76)	0.61 (0.46–0.73)	<0.001
Lymphocytes (10 ⁹ /L)	1.75 (1.43–2.01)	1.75 (1.41–2.03)	0.938
NLR (%)	6.26 (4.64–7.05)	5.70 (4.20–6.52)	<0.001
MLR (%)	0.41 (0.27–0.45)	0.38 (0.26–0.43)	<0.001
PLR (%)	124.35 (94.95–143.97)	123.41 (94.12–144.87)	0.938

Abbreviations: Hb, hemoglobin; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelets; RBC, red blood cell; WBC, white blood cell.

mothers and newborns strongly.^{4–8} However, in most cases, fever comes during birth time silently. In other words, intrapartum fever often occurs without obvious pathogens or symptoms. All these problems put clinicians in a dilemma and worth being noticed.

In the present study, we focus on the influence of intrapartum fever to the whole labor. Before the delivery, the value of WBC, RBC, Hb, and monocytes in mother with intrapartum fever were all higher than non-fever parturients. Though the difference reflected not obvious in value between the two groups, the results demonstrated that women with intrapartum fever may have a manifestation in partial CBC in the prenatal. On one hand, these phenomena could make clinicians stay alert. On the other hand, several of these cells play a key role in the development of fever. For example, WBC, one of the vital defense cells to protect the human body, could resist exogenous bacteria, fungal, and virus.^{27,28} Before suffering from the fever, heat-sensitive activators, including pathogens and elevated generation of IL-17, IL-1 β , and IL-1 α in intestinal tissue, increase the release of neutrophils from bone marrow and followed infiltration.²⁹ Besides, fever-related soluble IL-6R α for signal transduction may be supplied by monocytes.³⁰ As is well-known, monocytes and neutrophils were contained in WBC in the test of CBC. Hence, may be due to the pre-activation of the febrile stress response, monocytes and neutrophils, as well as other types of leukocyte, increased slightly

and finally reflected in the change of the value of WBC. Moreover, another latest article demonstrated that the function of RBC not only limited in the oxygen transportation, but also contained the pathogen capture and presentation.³¹ And this may attribute to its change in the blood. Additionally, literature reported that maternal Hb no more than 110 g/L was considered to be associated with maternal fever.⁸ However, in our exploration, mean Hb of intrapartum fever parturients reached 119.75 g/L and even a little bit higher than afebrile subjects. This imparity needs to be deeply investigated by more large clinical trial.

Subsequently, we compared the relative parameter of prepartum and postpartum value for further investigation. Whether in the intrapartum fever or afebrile group, almost all parameters demonstrated difference between prepartum and postpartum status except for lymphocytes in the fever group. These results illustrated that delivery as a stress reaction changed the value of CBC through a set of immune responses. Pioneering studies suggested that delivery is an inflammatory process^{32–34} and our outcomes ulteriorly proved this view. Then, the results of the comparison of the CBC difference manifested that the fever further aggravated the change value of the WBC, RBC, Hb, and neutrophils and alleviated the change value of the PLT caused by parturition. In other words, the blood was concentrated after delivery, and more concentrated in intrapartum

TABLE 4 Prepartum and postpartum complete blood cell count and its difference of intrapartum fever and afebrile groups

Variable	Prepartum	Postpartum	<i>p</i> '	Difference	<i>p</i> ''
Intrapartum fever (<i>n</i> = 1786)					
WBC (10 ⁹ /L)	9.53 (7.72–10.89)	12.48 (10.58–14.02)	<0.001	2.95 (1.02–4.89) ^a	<0.001
RBC (10 ¹² /L)	4.02 (3.77–4.23)	3.70 (3.41–3.99)	<0.001	–0.33 (–0.58 to –0.02) ^b	<0.001
Hb (g/L)	119.75 (112–127)	110.53 (101–121)	<0.001	–9.21 (–17 to 0) ^c	<0.001
PLT (10 ⁹ /L)	192.49 (155–223)	203.09 (166–236)	<0.001	10.60 (–8 to 30) ^d	0.023
Neutrophils (10 ⁹ /L)	7.08 (5.33–8.25)	10.11 (8.26–11.56)	<0.001	3.03 (1.17–4.95) ^e	<0.001
Monocytes (10 ⁹ /L)	0.59 (0.47–0.69)	0.64 (0.47–0.76)	<0.001	0.04 (–0.10 to 0.17) ^f	0.185
Lymphocytes (10 ⁹ /L)	1.73 (1.38–2.06)	1.75 (1.43–2.01)	0.307	0.02 (–0.30 to 0.33) ^g	0.459
Afebrile (<i>n</i> = 1882)					
WBC (10 ⁹ /L)	9.42 (7.58–10.71)	11.71 (9.75–13.35)	<0.001	2.28 (0.57–4.23) ^a	<0.001
RBC (10 ¹² /L)	3.98 (3.73–4.22)	3.81 (3.52–4.10)	<0.001	–0.17 (–0.40 to 0.11) ^b	<0.001
Hb (g/L)	118.23 (110–126)	113.55 (104–123)	<0.001	–4.68 (–12 to 3) ^c	<0.001
PLT (10 ⁹ /L)	190.41 (153–221)	202.32 (166–234)	<0.001	11.91 (–5 to 30) ^d	<0.001
Neutrophils (10 ⁹ /L)	7.05 (5.20–8.17)	9.19 (7.47–10.66)	<0.001	2.15 (0.52–4.02) ^e	<0.001
Monocytes (10 ⁹ /L)	0.59 (0.45–0.69)	0.61 (0.46–0.73)	<0.001	0.02 (–0.11 to 0.15) ^f	<0.001
Lymphocytes (10 ⁹ /L)	1.71 (1.37–2.01)	1.75 (1.41–2.03)	0.030	0.03 (–0.29 to 0.36) ^g	0.459

Note: *p*' for the comparison of prepartum and postpartum complete blood cell count, and *p*'' for the comparison of complete blood cell count difference (postpartum data minus the corresponding prepartum data) in intrapartum fever and afebrile groups. Superscript a-g means two compared variables for *p*'.

Abbreviations: Hb, hemoglobin; PLT, platelets; RBC, red blood cell; WBC, white blood cell.

fever parturients. As for reduction in the value of RBC and Hb, it might be resulted from intra- or postpartum hemorrhage. All these consequences remind us that we need to pay close attention to the maternal situations after birth process.

In recent years, accumulating researches revealed that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) could be employed as biomarkers, including prognostic markers for tumor therapy,^{35,36} diagnostic markers of cardiovascular disease,^{37,38} predictor of certain disease mortality,³⁹ as well as in fever.⁴⁰ Previous study demonstrated that NLR and MLR could be applied as the diagnostic marker of bacterial infection.⁴⁰ Inspired by this practice, we planned to predict whether the maternity got a fever during labor using NLR, PLR, and MLR. Regrettably, our data showed that these three ratios could not predict maternal intrapartum fever appropriately. This result may be due to that we considered fever and non-fever only, but not other relevant diseases which might lead to the change of the ratio. This is also a question that deserves further detailed research.

Vaginal secretion was cultured in fever subjects and 15.36% positive test rate in this article. There was an article that reported the positive blood and/or placental cultures were occurred in 13.9% women.¹ Though the site of the examination differs, both results declared that intrapartum fever during the labor might not be primarily caused by infection. Combined with the characteristic data, we speculated that nulliparity may be a risk factor for intrapartum fever because of its longer labor time. And the longer labor time resulted in the maternal long-term touching of the external environment and this distracted the puerperae. Along with the fact that

childbirth was likely an inherently stress reaction, women were in a hyp immunity state after long time of labor and then fever came. In addition, more intrapartum hemorrhage, more oxytocin usage rate, and more cloudy amniotic fluid were found in the intrapartum fever group. These findings also implied the fever parturients during labor in a poor state. After vaginal discharge examination, corresponding comparison of the CBC was implemented. And several differences were found among three groups. Then, post hoc analysis indicated the difference mainly existed in bacteria and fungus but not between gram-positive and -negative bacteria. These phenomena gave us a hint that we may develop a new marker to identify whether it is bacteria or fungus and thereby do more fundamental research to exploit the potential mechanism creating this result.

Generally speaking, intrapartum fever was defined as a temperature >38°C during labor.^{3,41} But there were also studies that set the temperature as over 37.4 or 37.5°C.^{4,42} And in our study, we defined the intrapartum fever as more than 37.5°C because fever during labor was associated with neonatal morbidity, sepsis, and even to death and a series of other obstetric complications.^{4,42} Besides, for the most part, fetal heart rate would be faster in pregnant women with temperatures over 37.5°C. Given this, we were looking for better care for parturients and set the temperature of the intrapartum fever as 37.5°C.

Several shortages existed in this study. Firstly, all included parturients received epidural analgesia because of childbirth analgesia rate reached to 90% in our hospital. We had no control group without epidural analgesia, so we could not clarify whether the hematological indicators and converted NLR, PLR, and MLR increased

TABLE 5 Complete blood cell counts of intrapartum fever parturients with positive vaginal secretion culture

Variable	G+ (n = 122)	G- (n = 69)	Fungus (n = 85)	p
Prepartum				
WBC (10 ⁹ /L)	9.43 (7.58–10.74)	9.81 (7.73–11.41)	9.60 (7.89–11.37)	0.465
RBC (10 ¹² /L)	4.12 (3.81–4.31) ^b	4.10 (3.90–4.33) ^c	3.93 (3.70–4.17) ^{b,c}	0.009
Hb (g/L)	121.42 (113–128.75) ^b	122.00 (113–130)	116.04 (108–124) ^b	0.025
PLT (10 ⁹ /L)	184.79 (140.25–215.50) ^b	189.18 (149.50–219.75)	201.86 (169–234) ^b	0.022
Neutrophils (10 ⁹ /L)	6.99 (5.20–8.11)	7.36 (5.53–8.61)	7.10 (5.19–8.85)	0.365
Monocytes (10 ⁹ /L)	0.61 (0.46–0.71)	0.64 (0.49–0.69)	0.61 (0.49–0.71)	0.665
Lymphocytes (10 ⁹ /L)	1.72 (1.43–1.99)	1.64 (1.40–2.00)	1.83 (1.42–2.16)	0.251
Intrapartum				
WBC (10 ⁹ /L)	14.89 (12.74–16.16)	15.21 (12.70–17.50)	14.75 (12.54–16.72)	0.592
RBC (10 ¹² /L)	4.13 (3.91–4.36)	4.20 (3.94–4.36) ^c	3.97 (3.69–4.26) ^c	0.011
Hb (g/L)	123.07 (116–130.75)	125.17 (117–131) ^c	117.17 (108–128) ^c	0.010
PLT (10 ⁹ /L)	176.03 (137–204.75)	184.82 (144.50–216.75)	190.41 (150–232)	0.080
Neutrophils (10 ⁹ /L)	13.01 (10.89–14.32)	13.28 (10.96–15–41)	12.81 (10.89–14.59)	0.659
Monocytes (10 ⁹ /L)	0.73 (0.53–0.91)	0.72 (0.54–0.92)	0.75 (0.58–0.85)	0.959
Lymphocytes (10 ⁹ /L)	1.12 (0.90–1.37)	1.16 (0.89–1.40)	1.17 (0.90–1.36)	0.904
Postpartum				
WBC (10 ⁹ /L)	12.57 (10.73–14.46)	12.75 (10.31–14.10)	12.63 (10.61–14.14)	0.949
RBC (10 ¹² /L)	3.70 (3.40–4.02)	3.70 (3.35–4.05)	3.67 (3.43–3.99)	0.984
Hb (g/L)	111.22 (100.50–123)	110.00 (100–121.75)	108.42 (99–111)	0.071
PLT (10 ⁹ /L)	192.82 (157.25–217) ^a	205.98 (170–232.75) ^a	208.86 (172–245)	0.014
Neutrophils (10 ⁹ /L)	10.27 (8.37–11.84)	10.32 (8.14–11.64)	10.21 (8.22–11.76)	0.995
Monocytes (10 ⁹ /L)	0.61 (0.46–0.74)	0.63 (0.47–0.72)	0.71 (0.50–0.85)	0.222
Lymphocytes (10 ⁹ /L)	1.70 (1.36–1.98)	1.78 (1.45–2.05)	1.80 (1.40–2.14)	0.388

Note: ^a $p < 0.05$, ^b $p < 0.05$, and ^c $p < 0.05$ expressed the post hoc analysis between G+ and G-, G+ and fungus, G- and fungus, respectively.

Abbreviations: Hb, hemoglobin; PLT, platelets; RBC, red blood cell; WBC, white blood cell.

during the delivery in those patients without epidural analgesia or not. Therefore, this research was difficult to reflect the situation of all populations because almost all of the included parturients were Chinese, and especially from Eastern China. And a large multicenter study deserved to be carried out for both maternal and fetal health. Besides, receiving epidural analgesia was a risk factor for intrapartum fever^{7,43,44} and its influence on the followed examination still unknown. Secondly, due to the limitation of conditions, we only designed this retrospective analysis but not randomized controlled study. And further large prospective clinical trials need to be carried out for the purpose of mother and child health. Thirdly, we measured the axillary temperature of maternity, which affected the accuracy of body temperature because of non-core temperature. Lastly, some data were not collected such as times of vaginal exams, internal fetal monitoring, duration of ruptured membranes, instrumental delivery, cesarean section, maternal and fetal umbilical vein serum IL-6 levels, which potentially affected the development of intrapartum fever.

In conclusion, we found differences existed between intrapartum fever and afebrile parturients from Eastern China in prepartum

WBC, RBC, Hb, and monocytes. Meanwhile, the delivery could result in the change of maternity and reflected in the value of CBC and intrapartum fever might aggravate or alleviate this change. In addition, the results of the positive vaginal discharge demonstrated that the intrapartum fever might not be principally caused by infection and the difference between bacteria and fungus could reflect in the CBC and might be other hematological examination. And more prospective studies of all populations were urgently to be done in order to reduce the danger of the maternity and child.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

PL, SF, and XZ designed and supervised the experiments and revised the manuscript. YF, CF, and PM analyzed the data and wrote the first draft of the manuscript. CR and WH were involved in the literature search. TL and ZD were involved in data collection. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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