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ORIGINAL ARTICLE

# Association of white blood cell count after operative vaginal delivery with maternal adverse outcome: A retrospective cohort study

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## ABSTRACT

### BACKGROUND

The white blood cell count is often used to assess the maternal condition after an operative vaginal delivery. However, it remains unknown whether the maternal white blood cell count on the day after delivery is associated with sequential maternal adverse outcomes, especially infectious complications. The aim of this study was to investigate the association between maternal white blood cell count on the day after operative vaginal delivery and sequential maternal adverse events.

### METHODS

The study was a retrospective cohort study using the Medical Data Vision claims database containing administrative claims data, discharge abstracts, and laboratory values in Japan. We identified all patients who underwent operative vaginal delivery with data on maternal white blood cell count from December 2011 to November 2020. The main composite outcome was maternal adverse outcomes, comprising additional treatment for maternal injuries, postpartum intravenous antibiotic use, and intensive care unit use during hospitalization. We conducted a restricted cubic spline analysis to investigate the nonlinear association between white blood cell count and the primary outcome.

### RESULTS

There were 485 eligible patients including 73 patients with occurrence of the primary outcome. The median (interquartile range) white blood cell count on the day after delivery in all eligible women was 15,170 (12,610–18,300)/mL. In the restricted cubic spline analysis, there was no significant association of white blood cell count with the primary outcome.

### CONCLUSION

White blood cell count on the day after operative vaginal delivery was not significantly associated with maternal adverse outcomes during hospitalization.


KEY WORDS

forceps, instrumental delivery, maternal morbidity, vacuum, white blood cell count

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## INTRODUCTION

Operative vaginal delivery using forceps or vacuum is performed to improve maternal or neonatal outcomes under several situations including maternal medical indications, prolonged second stage of labor, and suspicion of immediate or potential fetal compromise [1]. A global survey from The World Health Organization found that the overall proportion of operative vaginal delivery in Asia was 3.2% [2]. In the United States, 3.1% of all deliveries were accomplished via an operative vaginal approach [3].

Although operative vaginal delivery is useful for specific situations, maternal complications can occur even when instruments are correctly applied and used. Maternal complications associated with operative vaginal delivery include lower genital tract laceration, vulvar and vaginal hematoma, and anal sphincter injury [4]. There is also a risk of secondary infection after a maternal injury has occurred. Maternal infection is the leading cause of death in the pregnant and postpartum population worldwide [5].

The white blood cell (WBC) count is broadly used in various medical practices to assess the severity of diseases and determine the effectiveness of treatments. In the obstetrics field, several studies have examined the association between maternal WBC count and maternal or neonatal adverse outcomes [6–8]. However, it remains unknown whether the WBC count as part of a complete blood count after operative vaginal delivery is associated with sequential maternal adverse outcomes, especially infectious complications. In Japan, women with vaginal delivery are usually hospitalized for 4 to 5 days, and the maternal condition is assessed by physicians using laboratory tests including the WBC count if an operative vaginal delivery is performed. Therefore, the association between maternal WBC count and sequential maternal adverse events related to birth injuries and infection after delivery can be evaluated.

In this study, we investigated the association between maternal WBC count on the day after operative vaginal delivery and sequential maternal adverse events during hospitalization. We conducted a restricted cubic spline (RCS) analysis to assess the potential nonlinear association between maternal WBC count and the outcomes, because this type of analysis can avoid loss of information by categorization of the WBC count [9].

## METHODS

### DATA SOURCE

This was a retrospective cohort study using the Medical Data Vision claims database (Medical Data Vision Co. Ltd., Tokyo, Japan), a commercially available database containing routinely collected data. The database contains Diagnosis Procedure Combination (DPC) data from over 370 Japanese acute-care hospitals, covering more than 25 million patients as of April 2020 [10, 11]. The DPC database includes administrative claims and discharge abstract data. A previous study showed that the validity of the diagnostic records in the DPC database is generally high and that the sensitivity and specificity of the primary diagnoses are 50%–80% and 96%, respectively. The specificity and sensitivity of the procedures have been found to exceed 90% [12]. In addition, validation studies on the DPC data reported a reliability of registered information [13, 14]. Anonymized information on patient demographic characteristics, medical procedures, resource use, childbirth status, and disease diagnoses are available. Laboratory data are provided by approximately 10% of the participating hospitals that agreed to provide the data. Diagnoses, comorbidities, and complications are recorded using *International Classification of Diseases, Tenth Revision* (ICD-10) codes and text data in Japanese. Several published reports have used the Medical Data Vision claims database for clinical studies [15, 16].

### PATIENT SELECTION

The present study used data from December 2011 to November 2020. We identified all patients who underwent operative vaginal delivery and had data on the maternal WBC count measured the day after delivery in the participating hospitals. For this cohort, operative vaginal delivery was defined as delivery using forceps or vacuum. Patients who underwent cesarean section after an operative vaginal delivery trial, had no information on pregnancy period at delivery, and had no data on maternal WBC count on the day after delivery were excluded.

### PATIENT CHARACTERISTICS

We categorized maternal age as ≤19, 20–34, and ≥35 years; body mass index (BMI) as ≤18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m$^2$; and gestational age at delivery as ≤36/6, 37/0–40/0, and ≥40/1 weeks. Admission year was categorized as 2011–2017 and 2018–2020 to approximately halve the eligible patients. Hospital size was categorized as <200, 200–499, and ≥500 beds. The following

comorbidities were also identified: diabetes mellitus (ICD-10 codes, E10, E11, E14), gestational diabetes mellitus (O244), intrauterine infection including chorioamnionitis (O235, O411), inadequate uterine contractions (O620–O622), prolonged labor (O630, O631, O639, O755), and multiple pregnancy (O300–O309, O430, O632, O661, O840, O842, O849). These comorbidities which were recorded during pregnancy were considered eligible. Third- and fourth-degree lacerations were identified by procedure codes. Administration of any type of intravenous antibiotic on the day of delivery was regarded as a single variable for antibiotics administration. We identified the comorbidities based on the inpatient or outpatient ICD-10 codes in all categories, including main disease, sub-disease, and any complications at admission recorded on the delivery day or at any previous time point during pregnancy. Because of the structure of these data, previous outpatient visits of hospitalized patients could only be identified if they visited the same hospital where they had been hospitalized for childbirth.

Regarding clinical practice for operative vaginal delivery, the Japanese perinatal guidelines state that an episiotomy should be performed selectively and do not recommend administration of preventive antibiotics during or after operative vaginal delivery [17]. No major changes in the Japanese perinatal guidelines for operative vaginal delivery have been made in the past 11 years [18, 19].

#### OUTCOME

Assessed outcomes included additional treatment for maternal injuries (re-suturing and/or debridement), postpartum intravenous antibiotic use, and intensive care unit admission during hospitalization. Wound infections often lead to wound dehiscence, which requires re-suturing and/or debridement. When infectious complications including intrauterine infection and urinary tract infection occur, intravenous antibiotic treatment is usually required. These outcomes were identified by procedure codes, and only records of these outcomes registered from the second day after delivery to discharge were considered eligible. We defined the primary outcome as a composite outcome including any of these three outcomes. Diagnosis of intrauterine infection and urinary tract infection were not directly included as outcomes because it was not possible to determine whether they were continuously records from the onset of delivery in the database. The database did not include information on long-term maternal outcomes after discharge or neonatal outcomes.

#### STATISTICAL ANALYSIS

First, we examined the maternal WBC count distribution in all eligible patients. The median and interquartile range were calculated. We also assessed the incidence of the primary outcome in four groups stratified by the 25th percentile of the maternal WBC count. We assessed differences in the baseline variables between patients with and without occurrence of the primary outcome. The incidence of the primary outcome in the four WBC count groups was compared using Fisher's exact test. In addition, we categorized the WBC count in increments of 1,000 cells/mL and presented the results of the association between the categorical WBC count and the primary outcome.

Second, we conducted an RCS analysis to investigate the nonlinear association between maternal WBC count and the primary outcome. All values were used to estimate the dose–response association between the continuous variable of WBC count and the primary outcome in the RCS analysis, because an ordinal regression analysis with categorization of the continuous WBC count could lose information and statistical power [20, 21]. In the present study, we used five points (9,000, 12,000, 15,000, 18,000, and 21,000/mL) as the knots in the cubic splines to allow for nonlinear effects of the continuous WBC count variable. We calculated the odds ratio and 95% confidence interval for each WBC count with respect to the reference value of the median overall WBC count using a logistic regression model with the following dependent variables: age, BMI, smoking status, hospital size, gestational age at delivery, delivery type (forceps or vacuum), third-/fourth-degree laceration, intravenous antibiotics on the day of delivery, and pre-existing comorbidities (diabetes mellitus, gestational diabetes mellitus, intrauterine infection, inadequate uterine contractions, prolonged labor, multiple pregnancy). Some missing patient information was found for BMI, and because it represented about 1% of the total, patients with missing data were excluded from the regression analysis.

Third, we reanalyzed the data by excluding intensive care unit admission from the composite outcome as a sensitivity analysis because intensive care unit admission would not necessarily be related to maternal infectious events. Similarly, RCS analysis was performed for the sensitivity analysis.

Fourth, we performed an RCS analysis by WBC counts in increments of 1,000 cells/mL as a sensitivity analysis because the wide range of exposure values (WBC count range of 9,000–25,000/mL) may not have addressed the high variability of estimated coefficients, especially in datasets with small sample sizes.

All statistical analyses were performed using Stata Version 16.0 software (StataCorp LP, College Station, TX, USA). All tests were two-sided, and values of $P < 0.05$ were considered statistically significant. The spline curve was constructed using the "xbrcspline" and "mkspline" commands in Stata.

### ETHICS

The study was performed in accordance with relevant guidelines and regulations and was approved by the Institutional Review Board of The University of Tokyo (2020310NI). The Institutional Review Board of The University of Tokyo waived the need for informed consent because of the anonymous nature of the data.

## RESULTS

**Fig. 1** shows a flow diagram for the stratification and selection of patients in the present study. During the study period, there were 485 eligible hospitalized patients who had maternal WBC count records on the day after delivery among 23,932 patients who underwent operative vaginal delivery. **Table 1** shows the baseline characteristics of the 485 eligible patients. Ninety-three percent of the patients had delivery in a hospital with >200 beds, and women aged ≥35 years accounted for 32% of all patients. Of the total patients, 3% had preterm delivery and 94% had vacuum delivery. Among the eligible patients, 73 patients (15.1%) had occurrence of the primary outcome, with 50 patients requiring additional treatment for maternal injuries (re-suturing and/or debridement), 25 patients requiring postpartum intravenous antibiotic use, and 2 patients being admitted to the intensive care unit. Patients with the primary outcome were more likely to be hospitalized in 2011–2017 and receive intravenous antibiotics on the day of delivery. On the day after delivery, the median (interquartile range) WBC count was 15,170 (12,610–18,300)/mL. The minimum and maximum WBC counts were 7,300 and 29,360/mL, respectively.

**Table 2** shows the incidence of the primary outcome in four groups stratified by the 25th percentile of the maternal WBC count. Women with the highest incidence of the outcome (16.7%) were in the third quartile of the WBC count group, and women with the lowest incidence (13.1%) were in the fourth quartile of the WBC count group. There was no significant difference among the four groups. The association between each WBC count increment of 1,000 cells/mL and the primary outcome is shown in **Supplementary Table 1**. The patients with the highest frequency of the primary outcome occurrence were those with a WBC count of 24,000 to 24,999/mL.

**Fig. 2** shows the adjusted association between maternal WBC count and the primary outcome in the RCS analysis. For maternal WBC counts between 9,000 and 25,000/mL, the odds ratio tended to increase for WBC counts above 21,000/mL, but there was no significant association of WBC count with the primary outcome.

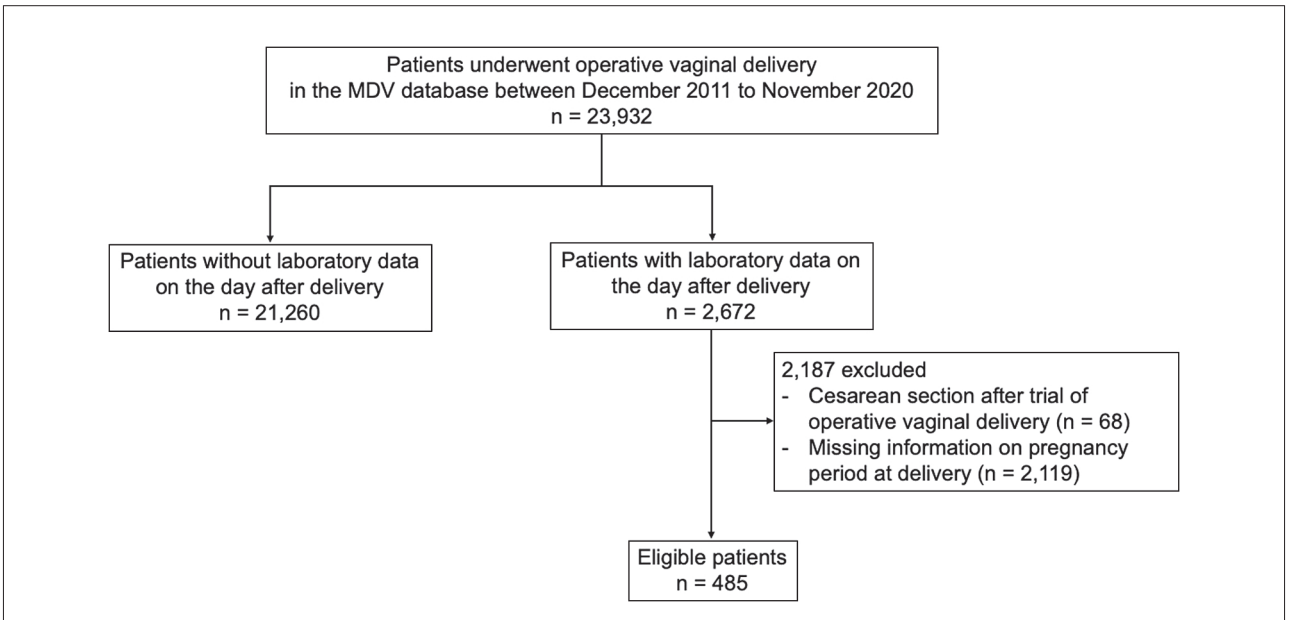


**Fig. 1** Flow diagram for the stratification and selection of the study patients

**Table 1** Baseline characteristics of patients who underwent operative vaginal delivery with and without the primary outcome

| Characteristics | All patients (n = 485) | Patients without the primary outcome (n = 412) | Patients with the primary outcome (n = 73) | P-value |
|---|---|---|---|---|
| Age, years | | | | 0.087 |
| <20 | 2 (0.4) | 2 (0.5) | 0 | |
| 20–34 | 328 (67.6) | 286 (69.4) | 42 (57.5) | |
| ≥35 | 155 (32.0) | 124 (30.1) | 31 (42.5) | |
| Year of admission | | | | 0.001 |
| 2011–2017 | 195 (40.2) | 152 (36.9) | 43 (58.9) | |
| 2018–2020 | 290 (59.8) | 260 (63.1) | 30 (41.1) | |
| Hospital size by number of beds | | | | 0.055 |
| <200 | 35 (7.2) | 34 (8.3) | 1 (1.4) | |
| 200–499 | 343 (70.7) | 285 (69.2) | 58 (79.5) | |
| ≥500 | 107 (22.1) | 93 (22.6) | 14 (19.2) | |
| Body mass index on admission, kg/m$^2$ | | | | 0.137 |
| <18.5 | 9 (1.9) | 8 (1.9) | 1 (1.4) | |
| 18.5–24.9 | 225 (46.4) | 200 (48.5) | 25 (34.3) | |
| 25.0–29.9 | 197 (40.6) | 160 (38.8) | 37 (50.7) | |
| ≥30.0 | 49 (10.1) | 39 (9.5) | 10 (13.7) | |
| Missing | 5 (1.0) | 5 (1.2) | 0 | |
| Gestational age at delivery, weeks | | | | 0.075 |
| <37 | 16 (3.3) | 16 (3.9) | 0 | |
| 37–40 | 410 (84.5) | 350 (85.0) | 60 (82.2) | |
| ≥41 | 59 (12.2) | 46 (11.2) | 13 (17.8) | |
| Delivery mode | | | | 0.798 |
| Vacuum | 454 (93.6) | 386 (93.7) | 68 (93.2) | |
| Forceps | 31 (6.4) | 26 (6.3) | 5 (6.9) | |
| Perineal laceration | | | | 0.109 |
| Third or fourth degree | 21 (4.3) | 15 (3.6) | 6 (8.2) | |
| Smoking | 30 (6.6) | 27 (6.7) | 3 (4.4) | 0.599 |
| Comorbidities on admission | | | | |
| Multiple pregnancy | 0 | 0 | 0 | |
| Diabetes mellitus | 0 | 0 | 0 | |
| Gestational diabetes mellitus | 35 (7.2) | 28 (6.8) | 7 (9.6) | 0.459 |
| Intrauterine infection | 13 (2.7) | 10 (2.4) | 3 (4.1) | 0.426 |
| Prolonged labor | 15 (3.1) | 15 (3.6) | 0 | 0.143 |
| Inadequate uterine contractions | 57 (11.8) | 48 (11.7) | 9 (12.3) | 0.845 |
| Use of intravenous antibiotics on the day of delivery | 106 (21.9) | 76 (18.5) | 30 (41.1) | <0.001 |

Data are presented as n (%).

**Table 2** Incidence of the primary outcome by four groups stratified by the 25th percentile of the maternal WBC count

| | Maternal WBC count on the day after delivery | | | | |
|---|---|---|---|---|---|
| | First quartile (<12,600/mL) | Second quartile (12,600–15,200/mL) | Third quartile (15,201–18,300/mL) | Fourth quartile (>18,300/mL) | P-value |
| Composite outcome[a] | 19/119 (16.0) | 18/124 (14.5) | 20/120 (16.7) | 16/122 (13.1) | 0.872 |
| Additional treatment for maternal injuries[b] | 15 (12.6) | 11 (8.9) | 12 (10.9) | 12 (9.8) | 0.808 |
| Postpartum intravenous antibiotic use | 5 (4.2) | 7 (5.7) | 9 (7.5) | 4 (3.3) | 0.492 |
| Intensive care unit use | 1 (0.8) | 1 (0.8) | 0 | 0 | 0.744 |

Data are presented as n (%).
[a] The number of patients who had composite outcome include patients with more than one outcome.
[b] Including procedures of re-suturing and debridement
WBC, white blood cell

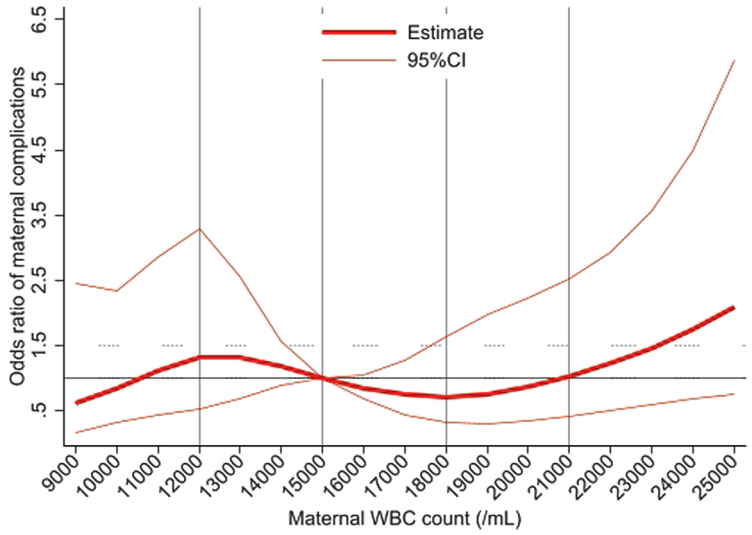


**Fig. 2** Adjusted association between maternal WBC count and the primary outcome

Multivariable logistic regression was performed using a restricted cubic spline analysis with five knots (9,000, 12,000, 15,000, 18,000, and 21,000/mL). The Y-axis represents the odds ratio for maternal complications, comparing women with WBC count of 15,000/mL and women with any other WBC counts. Estimates are shown with 95% confidence intervals. The points of intersection of the lines on the X-axis and the restricted cubic spline represent the five knots.
CI: confidence interval; WBC: white blood cell.

The sensitivity analysis using a composite outcome comprising limited outcomes (re-suturing, debridement, and postpartum intravenous antibiotic use) did not significantly change the results, with only one fewer patient having the composite outcome. The other sensitivity analysis using RCS by WBC count increments of 1,000 cells/mL did not significantly change the results (**Supplementary Figure 1**).

## DISCUSSION

In the present retrospective cohort study, patients who underwent operative vaginal delivery were assessed to examine the association between maternal WBC count on the day after delivery and maternal adverse outcomes during hospitalization. The incidence of the primary outcome was 15.1% in all eligible women. The median WBC count was 15,170/mL, which was higher than the value in

the general population. However, there was no significant association of WBC count with incidence of the primary outcome. The incidence of the primary outcome in the present study was similar to the reported incidences (3.5% to 16%) of postpartum infection or endometritis [22].

To date, no clear criteria have been established for the distribution of the maternal WBC count or abnormal values on the day after operative vaginal delivery. In a 2016 retrospective study on the postpartum WBC count in women with no pre-existing chronic diseases such as hypertension and diabetes, the mean WBC count ± standard deviation at 12 to 24 hours after operative vaginal delivery was 15,730 ± 4,400/mL [23]. Considering the previous report and clinical perspectives, the median (interquartile range) WBC count of 15,170 (12,610–18,300)/mL in the present study can be clinically relevant. The results may be used as a reference for assessment of the WBC count in women after operative vaginal delivery, even in populations that include women with comorbidities.

In the current study, the proportions of women who received intravenous antibiotics on the day of delivery among patients with and without the primary outcome were significantly different (41.1% vs 18.5%). Although it was not possible to determine from the data whether the reason for intravenous antibiotics administration on the day of delivery was prophylactic or therapeutic, women who received intravenous antibiotics on the day of delivery could be more likely to receive intravenous antibiotics during their subsequent hospitalization. In general, women with a healthy postpartum status do not receive continuous antimicrobial therapy, suggesting that intravenous antibiotic administration on the day of delivery may indicate the presence of adverse events after operative vaginal delivery.

Previous studies on the prediction of maternal morbidity after vaginal delivery mainly assessed maternal physical and social factors including age, race, BMI, comorbidity, delivery time, and induction of labor, or pre-delivery laboratory test results [24–26]. However, WBC count on the day after delivery was often excluded from the analyses. The present study showed no significant association between WBC count on the day after delivery with the primary outcome using RCS analysis among women who underwent operative vaginal delivery. These results suggest that physicians cannot easily predict the occurrence of short-term complications by the WBC count on the day after delivery.

In this study, we investigated the association between maternal WBC count on the day after operative vaginal delivery and sequential maternal adverse events during hospitalization. However, other maternal adverse events including endometritis and sepsis could not be evaluated because we were unable to identify these complications with high accuracy from the database. Therefore, future studies to analyze more kinds of complications associated with instrumental deliveries are warranted.

We conducted RCS analysis to assess the potential nonlinear association between maternal WBC count and the outcomes to avoid loss of information by categorization of the WBC count. However, due to the small number of patients with very high WBC count, the current study was not able to provide sufficient statistical examination of some of the WBC count. Validation in a future study including WBC count ≥25,000/mL with a large sample size is warranted.

The strength of the present study is the nonlinear description on the association between the WBC count distribution on the day after operative vaginal delivery and maternal adverse outcomes using RCS analysis. Despite this strength, several limitations of the study should be acknowledged. First, our results do not represent WBC counts and complications among all women who underwent operative vaginal delivery in Japan. In addition, because the present results were obtained in a Japanese setting, they may not be generalizable to other regions or countries. Second, the database used in the study did not contain detailed data on socioeconomic status including education level and economic situation, parity, and birthweight of neonates, although these factors could influence maternal adverse outcomes after operative vaginal delivery [24–26]. Third, adverse outcomes that occurred after hospital discharge could not be detected in the database. However, because a wound in the birth canal is generally rechecked before discharge, it would be rare for wound problems to occur after discharge in Japan. Fourth, the database did not include information on follow-up visits and diagnoses in other institutions before hospitalization. Finally, the database used in this study may have had limited representativeness because it contained only approximately 10% of the total patient data with laboratory values.

## CONCLUSIONS

There was no significant association of WBC count on the day after operative vaginal delivery with maternal adverse outcomes in the current study. Therefore, physicians cannot estimate the prognosis based on the WBC

count alone, and need make a comprehensive judgment by including other clinical findings after operative vaginal delivery.

## CONFLICTS OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.


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