Amniotic fluid neutrophil gelatinase-associated lipocalin and L-type fatty acid-binding protein in predicting fetal inflammatory response syndrome

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ABSTRACT

Aim: To analyze the effectiveness of amniotic fluid neutrophil gelatinase-associated lipocalin and L-type fatty acid-binding protein as predictive factors for fetal inflammatory response syndrome.

Methods: We classified single pregnancy cases into the fetal inflammatory response syndrome and non-fetal inflammatory response syndrome groups. We collected amniotic fluid at vaginal delivery and cesarean section and compared the patient characteristics, maternal white blood cell count, c-reactive protein level, and amniotic fluid interleukin-6; neutrophil gelatinase-associated lipocalin; and L-type fatty acid-binding protein levels between the groups. We further analyzed the relationship between L-type fatty acid-binding protein levels and neonatal clinical outcomes.

Results: We analyzed 129 pregnancies, of which 36 and 93 (27.9% and 72.1%, respectively) were classified into the fetal inflammatory response syndrome and non-fetal inflammatory response syndrome groups, respectively. We observed significant differences in the maternal white blood cell counts and amniotic fluid interleukin-6 and neutrophil gelatinase-associated lipocalin levels. On the multivariate analysis, the useful predictive factors were maternal white blood cell count and amniotic fluid interleukin-6 and neutrophil gelatinase-associated lipocalin levels. Furthermore, the level of L-type fatty acid-binding protein was significantly higher in the transient tachypnea of the newborn and postnatal respiratory support group than in the control group.

Conclusions: The maternal white blood cell count and amniotic interleukin-6 and neutrophil gelatinase-associated lipocalin levels were effective predictors of fetal inflammatory response syndrome. Amniotic fluid L-type fatty acid-binding protein level was an effective predictor of neonatal respiratory support.

Keywords: amniotic fluid, inflammatory response syndrome, interleukin-6, L-type fatty acid-binding protein, neutrophil gelatinase-associated lipocalin, predictive factor.

1. Introduction

Preterm births are associated with neonatal complications, which often result from an intertwined complex of factors such as cervical vulnerability, uterine inflammation due to chorioamnionitis, and/or funisitis. Predicting and preventing preterm birth is an important clinical issue that requires resolution. Uterine inflammation is one of the main contributors to preterm birth. Chorioamnionitis is a maternal infection, whereas funisitis indicates fetal inflammation, which may be accompanied by a state of progressive intra-amniotic infection.[1] The presence of at least one of the following findings is required for the diagnosis of fetal inflammatory response syndrome (FIRS): fetal plasma interleukin-6 (IL-6) >11 pg/mL or histologic chorioamnionitis and funisitis.[2–3] FIRS is associated with adverse events, such as respiratory distress syndrome, neonatal sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and cerebral palsy.[2, 4] Prenatal FIRS may be suspected in case of fetal deterioration. Although ultrasonographic findings, such as the ratio of early to late diastolic filling (E/A ratio), velocity time integral, Tei index, strain imaging of the heart, thymus volume, splenic vein flow pattern, and adrenal gland volume, have been reported as indicators of FIRS,[5] they have not yet been established. Percutaneous umbilical blood sampling (PUBS) is used for measuring fetal plasma IL-6 levels during pregnancy; however, the procedure is highly invasive. Amniocentesis is more common and less invasive than PUBS. Amniotic fluid neutrophil elastase, lactate dehydrogenase, white blood cell (WBC), glucose,[6] Interleukin 6 (IL-6), and matrix metalloproteinase-9 levels[7] have been reported as amniotic fluid biomarkers for predicting chorioamnionitis or intra-amniotic infection, that may indicate a positive amniotic fluid culture. However, the use of amniotic fluid biomarkers to predict FIRS has not been systematically

reported. Twenty percent of FIRS cases reportedly have no bacteria in the amniotic fluid.[8] Predictive factors that reflect the fetal condition in FIRS are required as their presence may indicate fetal inflammation.

Urinary neutrophil gelatinase-associated lipocalin (NGAL) and L-type fatty acid-binding protein (L-FABP) may be useful in detecting acute kidney injury caused by septic shock.[9] NGAL levels correlate with inflammatory markers such as the WBC count and C-reactive protein (CRP), while L-FABP levels correlate with hypoperfusion or oxidative stress.[9] Elevated amniotic fluid NGAL levels may represent fetal inflammation, and elevated amniotic fluid L-FABP levels may represent fetal tissue hypoperfusion since amniotic fluid contains fetal urine. These biomarkers may be useful factors for predicting FIRS.

We aimed to evaluate the effectiveness of amniotic fluid NGAL and L-FABP levels as predictive factors for FIRS.

2. Methods

2.1 Patients

We included single pregnancies that were managed and delivered at the Department of Obstetrics and Gynecology, Shiga University of Medical Science Hospital, Shiga, Japan, between August 2020 and December 2020. All procedures followed were in accordance with the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of the Shiga University of Medical Science Hospital. Informed consent was obtained from all patients. Pregnancies with chromosomal abnormalities, major structural anomalies, and fetal growth restriction (FGR) were excluded.

2.2 Data measurement

To measure the IL-6, NGAL, and L-FABP levels, amniotic fluid samples were collected transvaginally when the membrane ruptured during vaginal delivery (VD) or by puncturing the membrane using an 18-gauge needle before cesarean section (CS). An umbilical venous blood sample was collected at the time of delivery to measure the IL-6 level. Samples were centrifuged at 3000 revolutions per min for 20 min, and plasma from the umbilical venous blood and supernatants from the amniotic fluid were collected and cryopreserved at −80 ℃ until the analysis was performed. We assayed IL-6 levels using the Human IL-6 Quantikine enzyme-linked immunoassay kit (R&D Systems, Bio-Techne, Minneapolis, United States). Qualified pathologists histologically assessed the placenta and umbilical cord for the diagnosis. FIRS was diagnosed when at least one of the following was present: umbilical venous plasma IL-6 level >11 pg/mL

or histologic chorioamnionitis and funisitis. Further, we classified the cases into FIRS and non-FIRS groups.

We collected data on the maternal characteristics and clinical outcomes, including maternal age, parity, body mass index (BMI), gestational age at delivery, maternal white blood cells (WBC) count and c-reactive protein (CRP) values, cardiotocogram before delivery, mode of delivery, birth weight, and umbilical artery pH. We also recorded the neonatal outcomes—hospitalization in the neonatal intensive care unit (NICU), neonatal jaundice, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), the need for respiratory support, such as nasal directional positive airway pressure and conventional mechanical ventilation, chronic lung disease (CLD), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and neonatal death.

2.3 Statistical analyses

We used Fisher's exact probability test and the Mann–Whitney *U* test to compare the data. We calculated receiver operating characteristic (ROC) curves to demonstrate the relationship between the sensitivity and false positive rate (1–specificity) for IL-6, NGAL, and L-FABP. The point corresponding to the highest sensitivity in relation to the highest specificity was considered the optimal cut-off point. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using Easy R (EZR, R Foundation for Statistical Computing, Vienna, Austria) for Windows.[10]

3. Results

In this study, 160 single pregnancies were analyzed. We excluded pregnancies with chromosomal abnormalities (n=3), major structural anomalies (n=16), and fetal growth restriction (FGR; n=12). Overall, 129 single pregnancies were analyzed. Thirty-six (27.9%) pregnancies had FIRS (FIRS group), and 93 (72.1%) did not have FIRS (non-FIRS group). The demographic data, characteristics, and clinical outcomes are shown in Table 1, depicting significant differences in the BMI and prevalence of gestational diabetes mellitus (GDM). There were no cases of CLD, PVL, NEC, or neonatal death.

We performed univariate analyses between the FIRS and the non-FIRS group for maternal WBC, CRP levels, and amniotic fluid IL-6, NGAL, and L-FABP levels. No significant differences were observed in the CRP and L-FABP levels. However, significant differences were observed in the WBC count, IL-6, and NGAL levels (Table 2). The area under the concentration-time curve (AUC) and optimal cut-off values for the maternal WBC levels and amniotic fluid IL-6 levels were 0.654 and 9600/μL (sensitivity: 48.5%; specificity: 77.1%; positive predictive value [PPV]: 67.9%; negative predictive value [NPV]: 60.0%; odds ratio [OR]: 3.171 [95% confidence interval (CI): 2.615–3.844]), and 0.766 and 6944 pg/mL (sensitivity: 74.2%; specificity: 71.1%; PPV: 72.0%; NPV: 73.4%; OR: 7.705 [95% CI: 5.811–8.614]), respectively.

For 67 and 62 (51.9% and 48.1%, respectively) pregnancies, amniotic fluid was collected at VD and CS, respectively. Blood contamination, amniotic fluid collection after labor onset, and turbidity were observed in 48, 68, and 9 (37.2%, 52.7%, and 7.0%, respectively) pregnancies, respectively. We performed univariate analysis for the amniotic-fluid collection method, presence or absence of blood contamination, labor

onset, and turbidity to investigate the factors influencing IL-6, NGAL, and L-FABP levels. The amniotic fluid collection method influenced NGAL levels ($p=0.002$), whereas turbidity affected L-FABP levels ($p<0.001$).

Therefore, the NGAL levels were classified according to the values collected at VD and CS and analyzed. In both VD and CS cases, NGAL levels were significantly higher in the FIRS group than in the non-FIRS group (Table 2). We calculated a ROC curve for NGAL's ability to predict FIRS. The AUC and optimal cut-off values for NGAL at VD and CS were 0.761 and 1150 ng/mL (sensitivity: 57.9%; specificity: 95.7%; PPV: 93.1%; NPV: 69.4%; OR: 30.60 [95% CI: 22.02–42.53]), and 0.726 and 120 ng/mL (sensitivity: 94.1%; specificity: 47.7%; PPV: 64.3%; NPV: 89.0%; OR: 14.54 [95% CI: 10.88–19.44]), respectively.

We performed multivariate analyses using a logistic regression model for maternal WBC and amniotic fluid IL-6 and NGAL levels. For multivariate analysis, we calculated ROC curves to assess these variables' ability to predict FIRS. The AUC was 0.869. We evaluated the cut-off values for maternal WBC and amniotic fluid IL-6 and NGAL levels. The significant predictive factors were maternal WBC count and amniotic fluid IL-6 and NGAL levels (Table 3).

We compared and analyzed amniotic fluid L-FABP levels and neonatal clinical outcomes for all patients, except for nine cases with turbidity. Pearson's correlation coefficient for amniotic fluid L-FABP and umbilical artery pH inspection was $r = –0.238$ ($p=0.006$), and a weak negative correlation was observed. The value of L-FABP level was significantly higher in the TTN and respiratory support group than in the control group. It also tended to be higher in the neonates with NICU admission, neonatal jaundice, and RDS than in the control group; no significant between-group

differences were observed in the frequency of CS, IVH, and ROP (Table 4). We also calculated the ROC curve of L-FABP for predicting neonatal respiratory support. The AUC and optimal cut-off values of L-FABP were 0.753 and 2.94 ng/mL, respectively (sensitivity: 70.6%; specificity: 81.6%; PPV: 79.3%; NPV: 73.5%; OR: 10.65 [95% CI: 8.633–13.13]).

Forty-seven (36.4%) pregnancies had spontaneous labor onset, 82 (63.6%) had labor induction and selective CS (control group). We compared and analyzed maternal WBC and CRP levels and amniotic fluid IL-6, NGAL, and L-FABP levels between spontaneous labor onset and control groups. IL-6 and NGAL levels, especially NGAL levels at CS, were significantly higher in the spontaneous labor onset group than in the control group (Table 5).

4. Discussion

FIRS is associated with preterm birth and postnatal morbidity,[1, 2, 4] and its early diagnosis is critical. However, the prenatal diagnosis of FIRS using amniotic fluid biomarkers has not yet been established. Here, we established the maternal WBC count and amniotic fluid IL-6 and NGAL levels as useful predictive factors of FIRS and amniotic fluid L-FABP levels as useful predictive factors of neonatal respiratory support.

NGAL, expressed by the granules of human neutrophils in several tissues, such as the lung, liver, and kidney, has nephro- and immunoprotective effects.[9, 11, 12] Renal disorders upregulate NGAL expression in the renal tubular epithelial cells, releasing it into the urine and plasma.[13] Systemic inflammation stimulates NGAL synthesis in renal and nonrenal tissues and reduces its tubular reabsorption, causing an increase in urinary NGAL.[14] Our study suggested that the amniotic fluid NGAL level is a predictive factor for intrauterine infection, and its predictive ability is equivalent to that of the amniotic fluid IL-6 level. An elevated amniotic fluid IL-6 level has been reported as the most useful predictor for intrauterine infection and is associated with PVL and cerebral palsy.[15] Furthermore, this study suggested that amniotic fluid IL-6 and NGAL levels could predict FIRS. Although we determined that an amniotic fluid IL-6 concentration of 2500 pg/mL was the best cut-off value for the identification of intrauterine infection,[16] the best cut-off values for the identification of FIRS were the amniotic fluid IL-6 concentration of 6944 pg/mL and NGAL concentrations of 1150 ng/mL on the vaginal collection and 120 ng/mL on abdominal collection, respectively. Although the amniotic fluid NGAL level was not influenced by blood contamination, labor onset, and turbidity, we must consider that the cut-off values may differ depending on the

collection method. There was a higher NGAL level in the vaginally collected sample than in the sample collected via the abdomen, which may have been due to more inflammatory cells present in the cervix and vagina.

L-FABP, expressed in the liver and proximal epithelial tubules,[9, 17] reflects hypoxia induced by organ hypoperfusion. It serves as a target for highly cytotoxic aldehydes that are inevitably generated from lipid peroxidation reactions during reperfusion, thereby, reducing lipid peroxidative stress.[17, 18] Although we suspected that amniotic fluid L-FABP level increases in FIRS since tissue hypoperfusion is frequently observed in severe sepsis,[18] in this study, there was no significant difference in the amniotic fluid L-FABP levels between the FIRS and the non-FIRS group. However, there was also no significant difference in the clinical outcomes between the groups, and none of the cases fulfilled the diagnostic criteria for clinical chorioamnionitis.[19] We suspected that amniotic fluid L-FABP levels may not have increased because our FIRS cases were within the mild category of FIRS. Elevated urinary L-FABP levels are observed in neonates with NEC.[20] In addition, in our study, elevated amniotic fluid L-FABP levels were associated with TTN and neonatal respiratory support and tended to be associated with NICU admission, neonatal jaundice, and RDS. The best cut-off value for the identification of neonatal respiratory support was an amniotic fluid L-FABP concentration of 2.94 ng/mL. Therefore, amniotic fluid L-FABP levels might reflect neonatal morbidity. If an intrauterine infection progresses to severe FIRS with fetal tissue hypoperfusion, amniotic fluid L-FABP levels might increase. This could be the subject of future studies. Although the L-FABP levels were not influenced by the amniotic fluid collection method, blood contamination, and labor onset, turbidity may influence its value. Among the nine cases with turbidity, all, except one case of

abruption, had a normal pH for the umbilical cord blood and a good clinical course and were not associated with fetal hypoxia. The precise etiology of amniotic fluid turbidity is unclear and potentially multifactorial.[21] The reason why the turbidity influences the L-FABP level is unclear.

Maternal WBC and CRP levels increase depending on the degree of infection. Although CRP is the most reliable indicator of intrauterine infection and rises earlier than the WBC count,[22] in this study, the WBC count was a more useful predictive factor for FIRS. However, amniotic fluid IL-6 and NGAL levels were more accurate than WBCs. There was also a significantly higher BMI and incidence of GDM in the FIRS group than in the non-FIRS group. The risk of GDM was positively associated with the pre-pregnancy BMI,[23] and GDM led to an increase in the risk of intrauterine infection.[24]

Uterine inflammation is associated with preterm births and spontaneous labor onset.[8, 25] Here, elevated amniotic fluid IL-6 and NGAL levels were associated with spontaneous labor onset; thus, suggesting a relationship between inflammation and labor onset. However, there was also no significant difference in the prevalence of spontaneous labor onset between the FIRS group and the non-FIRS group. The possible cause could be that the FIRS severity, in the present cases, was of mild degree. In addition, there was no significant difference in the NGAL levels at VD between the spontaneous labor onset and control groups. This might have been due to the influence of inflammation induced by labor induction as the NGAL levels at VD in the control group were measured using amniotic fluid samples collected at the rupture of the membrane during labor induction. However, these factors need further consideration.

This study had several limitations. First, we did not include severe FIRS cases, causing adverse neonatal effects. Therefore, further studies are needed to evaluate

amniotic fluid NGAL and L-FABP levels as predictive factors for severe FIRS. Since, severe FIRS with fetal tissue hypoperfusion may indicate a severely compromised fetal condition which could lead to neonatal adverse events, a method for early-stage detection should be devised to prevent deterioration that may develop into such a fatal condition. In this study, FIRS may have been detected at the early stage; therefore, amniotic fluid NGAL and IL-6 may prove to be useful markers in determining the timing of delivery in FIRS cases. Second, the NGAL and L-FABP values during the pregnancy were not systematically examined. Further prospective studies are needed to clarify the clinical applicability of NGAL and L-FABP levels as predictive factors for FIRS and neonatal morbidity.

In conclusion, we cannot suggest that the amniotic fluid NGAL and L-FABP levels are more effective than IL-6 as predictive factors for FIRS. However, this is the first study on the usefulness of amniotic fluid NGAL and L-FABP levels in FIRS. We propose that infants with FIRS must be delivered before fetal tissue hypoperfusion occurs due to fetal inflammation, and amniotic fluid IL-6 and NGAL may be useful markers in determining the timing of delivery in such cases. Moreover, amniotic fluid L-FABP level might be a useful parameter to predict neonatal morbidity. Prediction of FIRS and neonatal respiratory support enables clinicians to manage maternal and fetal conditions effectively during pregnancy and at the time of delivery; besides, it will prepare the clinicians to manage the neonate better. It is necessary to comprehensively evaluate these amniotic fluid biomarkers, as well as the maternal and fetal conditions and gestational age. In these cases, careful judgment, with consideration of the gestational age, is required for the delivery as premature delivery may increase the incidence of neonatal morbidity.

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Author contributions:

DK conceived and designed the study, collected data, performed the analysis and wrote the manuscript. ST, KH, ST, RZ, TH, AN, FK, and NK collected data. AN also contributed to the analysis. TM discussed the results and contributed to the final manuscript.

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Tables

Table 1. Patient characteristics and clinical outcomes of the FIRS and non-FIRS groups

Characteristics	FIRS	Non-FIRS	p-value
Patients	36	93	N/A
Age (years)[a]	33 (22–45)	34 (18–47)	0.654
Primipara (%)[b]	22.5 (20/36)	44.1 (41/93)	0.326
IVF (%)[b]	54.7 (11/36)	17.2 (16/93)	0.146
BMI (kg/m^2)[a]	22.8 (16.4–43.9)	20.9 (15.2–38.6)	0.047
GDM (%)[b]	22.2 (8/36)	6.5 (6/93)	0.022
HDP (%)[b]	16.7 (6/36)	10.8 (10/93)	0.38
Maternal fever (%)[b]	0 (0/36)	1.1 (1/93)	1
Fetal tachycardia (%)[b]	2.8 (1/36)	1.1 (1/93)	0.482
Spontaneous labor onset (%)[b]	36.1 (13/36)	34.4 (32/93)	0.84
CS (%)[b]	61.1 (22/36)	47.3 (44/93)	0.175

GA at delivery (weeks)[a]	38.4 (28.7–40.7)	38.3 (30.4–41.4)	0.282
Birth weight (g)[a]	3006 (1360–3768)	2854 (1324–3594)	0.343
Umbilical artery pH[a]	7.302 (7.016–7.386)	7.302 (7.109–7.412)	0.795
NICU admission (%)[b]	27.8 (10/36)	26.9 (25/93)	1
Neonatal jaundice (%)[b]	13.9 (5/36)	9.7 (9/93)	0.533
TTN (%)[b]	8.3 (3/36)	11.8 (11/93)	0.756
RDS (%)[b]	2.8 (1/36)	1.1 (1/93)	0.482
Respiratory support (%)[b]	16.7 (6/36)	12.9 (12/93)	0.58
IVH (%)[b]	2.3 (1/36)	0 (0/93)	0.279
ROP (%)[b]	2.3 (1/36)	0 (0/93)	0.279

[a]The Mann–Whitney U-test was used for between-group comparisons, which are presented as median (range).

[b]Fisher's exact test was used for between-group comparisons.[†]

[†] FIRS, fetal inflammatory response syndrome; BMI, body mass index; GDM, gestational diabetes mellitus; IVF, in vitro fertilization; CS, cesarean section; GA, gestational age; NICU, neonatal intensive care unit; TTN, transient tachypnea of the newborn; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

Table 2. Maternal WBC and CRP levels and amniotic fluid IL-6, NGAL and L-FABP levels in the FIRS and non-FIRS groups on univariate analysis

Data comparison		FIRS (n=36)	Non-FIRS (n=93)	p-value
WBC (/μL)[a]		9600 (5200-22900)	7950 (4600-19000)	0.008
CRP (mg/dL)[a]		0.22 (0.04–7.27)	0.23 (0.05–3.21)	0.773
IL-6 (pg/mL)		22022 (900.5–225145)	2282 (627.3–77969)	<0.001
NGAL (ng/mL)[a]	Total	581.5 (113–14700)	244.5 (65.0–3090)	0.001
	VD	1180 (230–14700)	529.0 (170–3090)	<0.001
	CS	156.0 (113–5610)	123.5 (65.0–330)	0.006
L-FABP (ng/ml)[a]		2.58 (0.79–91.6)	2.05 (0.42–20.8)	0.232

[a]The Mann–Whitney *U* test was used to compare the data between the groups, presented as median (range).[‡]

[‡] WBC, white blood cell; CRP, C-reactive protein; IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin; L-FABP, L-type fatty acid-binding protein; FIRS, fetal inflammatory response syndrome; VD, vaginal delivery; CS, cesarean section.

Table 3. Maternal WBC level and amniotic fluid IL-6 and NGAL levels on multivariate logistic regression analysis[§]

Data comparison	OR (95% CI)	p-value
WBC	4.02 (1.33–12.1)	0.013
IL-6	10.9 (3.41–35.0)	<0.001
NGAL	9.33 (2.86–30.4)	<0.001

§ WBC, white blood cell; IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin; OR, odds ratio; CI, confidence interval.

Table 4. The relationship between amniotic fluid L-FABP levels and neonatal clinical outcomes

Data comparison		L-FABP	control	p-value
CS (%)[a]	50.8 (61/120)	2.13 (0.42-24.7)	1.96 (0.57-17.3)	0.258
NICU admission (%)[a]	28.3 (34/120)	2.05 (0.90-24.7)	1.98 (0.42-9.17)	0.07
Neonatal jaundice (%)[a]	10.8 (13/120)	2.69 (1.06-17.3)	1.97 (0.42-24.7)	0.09
TTN (%)[a]	11.6 (14/120)	3.18 (1.06-24.7)	1.95 (0.42-13.9)	0.018
RDS (%)[a]	1.6 (2/120)	5.19 (4.07-6.31)	1.97 (0.42-24.7)	0.066
Respiratory support (%)[a]	14.1 (17/120)	4.57 (0.90-24.7)	1.94 (0.42-9.17)	<0.001
IVH (%)[a]	0.8 (1/120)	4.57 (4.57-4.57)	1.98 (0.42-24.7)	0.237
ROP (%)[a]	0.8 (1/120)	4.96 (4.96-4.96)	1.98 (0.42-24.7)	0.194

[a]The Mann–Whitney U-test was used for between-group comparisons, which are presented as median (range).¶

¶ L-FABP, L-type fatty acid-binding protein; CS, cesarean section; NICU, neonatal intensive care unit; TTN, transient tachypnea of the newborn; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

Table 5. Maternal WBC and CRP levels and amniotic fluid IL-6, NGAL and L-FABP levels in the spontaneous labor onset and control groups on univariate analysis

Data comparison		Spontaneous labor onset (n=47)	Control (n=82)	p-value
WBC (/μL)[a]		8700 (5400-22900)	7800 (4600-21700)	0.209
CRP (mg/dL)[a]		0.26 (0.05–3.21)	0.22 (0.04–7.27)	0.846
IL-6 (pg/mL)[a]		8738.4 (737.4–225145)	2096.9 (627.3–199347)	0.002
NGAL (ng/mL)[a]	Total	565 (142–14700)	172.5 (65.0–5610)	<0.001
	VD	618 (170–14700)	477 (188–5610)	0.411
	CS	218 (142–3010)	139 (65.0–5610)	0.013
L-FABP (ng/ml)[a]		1.97 (0.79–17.3)	2.34 (0.42–91.6)	0.512

[a]The Mann–Whitney U-test was used for between-group comparisons, which are presented as median (range).[i]

[i] WBC, white blood cell; CRP, C-reactive protein; IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin; L-FABP, L-type fatty acid-binding protein; FIRS, fetal inflammatory response syndrome; VD, vaginal delivery; CS, cesarean section.