Original Investigation

The course of infection with the Delta variant of COVID-19 in pregnancy: Analysis of clinical, laboratory, and neonatal outcomes

Göklü et al. Delta variant of COVID-19 and pregnancy

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Abstract
Objective: This study aims to examine the effects of infection with the Delta variant of COVID-19 on the clinical course, laboratory parameters, and neonatal outcomes in pregnant women.
Materials and Methods: A total of 96 pregnant women who tested positive for the Delta variant of COVID-19 were retrospectively examined. The pregnant women were divided into three groups as follows: asymptomatic, non-severe, and severe. Age, obstetric history, symptoms and findings, blood tests, medication and vaccination history, clinical course, and perinatal outcomes of pregnant women were analyzed.
Results: Pregnant women who tested positive for the Delta variant of COVID-19 had an ICU admission rate of 9.4% and a mortality rate of 5.2%. Pregnant women in the severe disease group had significantly higher rates of preterm birth and cesarean section compared with the non-severe and asymptomatic group. Pregnant women in the severe group had high c-reactive protein (CRP) levels at the time of admission. White blood cell (WBC) and procalcitonin levels increased in clinical follow-up in pregnant women in the severe group.
Conclusion: The Delta variant of COVID-19 was found to increase mortality rates in pregnant women compared to pre-Delta variants of COVID-19. In pregnant women infected with the Delta variant of COVID-19, advanced gestational age at diagnosis, high CRP, WBC, and procalcitonin levels were significantly correlated with poor prognosis. Pregnant women infected with the Delta variant of COVID-19 had an increased risk for preterm delivery and cesarean section in the presence of severe disease. Although newborns of women with severe disease were found to have significantly higher rates of ICU admission, there was no significant difference in neonatal mortality rates. We recommend close monitoring of CRP, WBC, and procalcitonin levels in addition to symptoms in pregnant women infected with the Delta variant of COVID-19 in the third trimester.
Keywords: COVID-19, pregnancy, delta variant

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Introduction

Coronavirus 2019 disease (COVID-19) is a highly contagious infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has so far resulted in nearly 300 million cases of COVID-19 and more than 5 million deaths [1,2]. First detected in Wuhan, the capital of China's Hubei province in December 2019, it has since spread rapidly worldwide and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [2]. SARS-CoV-2 is an mRNA virus that acts mainly by binding to the ACE-2 receptor, abundantly found in the respiratory and digestive tract and largely expressed during pregnancy [3,4]. Similar to other RNA viruses, SARS-CoV-2 has genetically mutated over time, resulting in variants with different characteristics [5]. WHO has classified SARS-CoV-2 variants into three groups based on the impact on public health, variation in transmissibility and virulence, and resistance to therapeutics and vaccines: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VOMs). VOCs are the dominant group in the outbreak and comprise Alpha (B.1.1.7), beta (B.1.351), gamma (P.1), Delta (B.1,617.2) variants, and omicron (B.1.1.529) variant, which was added to the list on December 6, 2021. The Delta variant, first isolated in India in October 2020, was classified as a VOI on April 4, 2021, and as a VOC on May 11, 2021, due to its rapid spread worldwide [6]. Data for November 2021 shows that the Delta variant has become the most common VOC, accounting for 99.7% of the variants isolated worldwide over the last 60 days [7]. Pregnancy comprises a unique immunological condition that is regulated since the immune system is affected by signals originated from the placenta [8-12]. Pregnant women are at greater risk for viral infections than the normal population owing to the respiratory, circulatory, endocrine, immunological, and anatomical changes that occur during pregnancy [3,13,14]. Pregnant women reportedly have higher rates of hospital admissions, pneumonia, need for ventilator support, and intensive care unit (ICU) admissions associated with COVID-19 than the non-pregnant population [15]. Studies conducted with different subsets of population to compare the wild type (Wuhan) and the Alpha variant reported that the Delta variant had a higher virulence and was less affected by neutralizing antibodies induced by vaccination than other variants [16-18]. However, few studies in the literature have examined the effect of this variant on the pregnant population. Furthermore, it is crucial to investigate the effects of the Delta variant on pregnant women given that they are more severely affected by COVID-19 compared to the general population and have low vaccination rates worldwide [19]. Therefore, in the present study, we aimed to investigate the effect of the Delta variant of COVID-19 on the clinical course and laboratory parameters as well as neonatal outcomes in pregnant women.

Materials and Methods

In the present study, we retrospectively examined 96 pregnant women admitted to the XX Training and Research Hospital, Department of Obstetrics and Gynecology after testing positive for the Delta variant of COVID-19 following a polymerase chain reaction (PCR) examination between April 2021 and September 2021. The study was approved by the Ethics Committee of the hospital and conducted in accordance with the Helsinki Declaration of

Ethical Principles. Data of the patients included in the study were retrieved from the hospital archiving system and medical records. In PCR tests, the SL452R mutation specific to the Delta variant was detected using SARS-CoV-2 Emerging Plus kits (Bio-Speedy, Istanbul, Tr). COVID-19 diagnosis was established through physical examinations, PCR tests from nasopharyngeal swabs, and X-ray and/or computed tomography (CT) to assess lung involvement in the presence of pneumonia. It was explained that chest CT can be performed safely in pregnant women, and after providing signed consent, symptomatic pregnant women underwent CT examinations [20]. During the CT scan, the lower abdomen and pelvis of the pregnant woman were wrapped in protective aprons.

Among the 96 pregnant women, 49 were asymptomatic and 47 were symptomatic. Asymptomatic pregnant women were admitted with obstetric indications. Symptomatic pregnant women were divided into non-severe, and severe disease groups [21,22]. Pregnant women with mild symptoms (fever, cough, and other upper respiratory symptoms), without abnormalities or with mild changes on chest CT (multiple areas of patch-like involvement and interstitial changes usually found in the outer zone of the lung and beneath the pleura) were included in the non-severe group. The patients were included in the severe group if they had at least one of the following: tachypnea (respiratory rate ≥ 30/min), hypoxia (SpO_2 < 93%), the partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤ 300 mmHg in blood gas analysis, respiratory or organ failure that requires admission to the ICU, or the presence of shock.

There is no agreed and definitive treatment protocol for pregnant women with COVID-19. Low-molecular-weight heparin (LMWH) was used for thromboembolism prophylaxis. Steroids were used for a limited time (3–5 days) in pregnant women who demonstrate the progressive deterioration of oxygen saturation, increased activation of the pro-inflammatory response, and rapid worsening of findings on chest imaging [23]. Betamethasone was given to promote fetal lung maturation at or beyond 24 weeks of gestation who are at risk of preterm birth within 7 days. Antitussive agents and inhaled bronchodilators were used for supportive therapy. Also, patients were started on tocilizumab in the case of cytokine storm syndrome and broad-spectrum antibiotic therapy in the presence of concomitant suspected bacterial pneumonia [21,24].

In the pregnant women, we analyzed age, obstetric history, symptoms and findings, blood tests, medication and vaccination history, clinical course, and perinatal outcomes. Postpartum hemorrhage (PPH) was defined as blood loss of more than 1000 mL following cesarean delivery [25]. We defined IUGR as estimated fetal weight (EFW) <3^{rd} centile based on sonographic measurements of the fetus along with end-diastolic flow loss on Doppler examination [26]. Blood tests were reported at three different time points to better predict the course of the disease; at the time of admission, during the hospital stay, and at discharge. The tests administered during the hospital stay in symptomatic pregnant patients, that is, at the second time point, (excluding 5 pregnant women who died) were taken at the time of clinical worsening (such as the onset of oxygen therapy or the introduction of steroid therapy for pregnant women who were already on oxygen therapy). In asymptomatic pregnant women, tests administered during the hospital stay were used instead. In the newborns, we analyzed weight, Apgar scores, umbilical cord blood gas analysis, neonatal ICU (NICU) admission, and mortality rates.

Statistical Analysis

The SPSS 20.0 software suite was used to evaluate the data collected during the study (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Statistical significance was set at p-value <0.05. Based on the Shapiro–Wilk normality test results, multiple groups of continuous variables were compared with the nonparametric Kruskal–Wallis analysis test, and in case of significant differences, Dunn's multiple comparisons test was used to identify the groups that created the difference. As for descriptive statistics, letter indices were placed on grouped data for the results tabled in median values (minimum-maximum), and the differences between the groups were displayed. The Chi-Square and Fisher's exact test results were used to evaluate the distribution of categorical variables based on groups, and the results were expressed in frequency distributions and percentages. The repeated measures ANOVA model was used to explain the measurements taken at three different time points for the three independent groups, investigating also the main effect groups, and time as well as interaction terms.

Results

A total of 48.9% patients (n= 47) were symptomatic pregnant women, of which 72% (n= 34) were non-severe and 28% (n= 13) were severe patients. There was no significant difference among all three groups in terms of mean age, gestational age, gravidity, parity, and abortus history. A significant majority of the symptomatic group consisted of pregnant women in the third trimester. There was no significant difference between symptomatic pregnant women in the non-severe and severe groups in terms of frequency of fever, cough, shortness of breath, diarrhea, and myalgia. The severe disease group had a significantly higher average heart rate and significantly lower average oxygen saturation than the non-severe disease group. 91.1% of the pregnant women in the non-severe group and 100% of those in the severe group were diagnosed with pneumonia based on physical examination findings, and all of the symptomatic pregnant women underwent a CT scan of the chest. Radiological findings of pneumonia were detected in 50% of those in the non-severe group and 100% of those in the severe group. Steroid and LMWH use was significantly higher in the symptomatic group compared to the asymptomatic group. Furthermore, 19% of the symptomatic pregnant women (n= 9) required ICU admission. Although all non-severe pregnant women were monitored in the clinic, 69% (n= 9) of the pregnant women in the severe group were admitted to the ICU. 55.5% (n= 5) of the pregnant women admitted to the ICU developed acute respiratory distress syndrome (ARDS), and 33.3% (n= 3) developed acute renal failure. A total of 55.5% (n= 5) of the pregnant women in the ICU were intubated and all of the intubated patients died. The mortality rate in pregnant women was calculated at 5.2%. Of all the pregnant women who participated in the study, 46% (n= 44) delivered their babies. The delivery rate in the severe disease group was calculated at 53.8%, and all deliveries were cesarean preterm deliveries owing to maternal conditions. Preterm delivery and cesarean section rates were significantly higher in the severe group compared to the non-severe and asymptomatic group (**Table 1**). The average gestational age and weight at birth, and APGAR scores at minutes 1 and 5 were significantly lower in the newborns of the severe group than those of the non-severe and asymptomatic groups. The neonatal ICU admission rate was calculated at 20.5% for all the groups combined. There was no significant difference in neonatal ICU admission rates between the non-severe and asymptomatic groups; however, this rate was significantly higher in the severe group. There was no significant difference in umbilical cord blood gas pH values of newborns among the three groups. There were no neonatal deaths in our study (**Table 2**). Blood samples collected from each patient at three different time points were evaluated to better predict the clinical course of the disease. There was no significant intergroup difference in the mean levels of white blood cell (WBC), neutrophil, lymphocyte, hemoglobin, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin, and procalcitonin. WBC levels increased over time ($p2 = 0.002$) in the severe group, and the rate of increase in this group was significantly higher than that in the non-severe and asymptomatic groups ($p3 = 0.001$) (**Graphic 1**). Although the mean c-reactive protein (CRP) level was significantly higher in the severe group than in the non-severe and asymptomatic group, there was no significant increase in CRP levels in all three groups in clinical follow-ups (**Graphic 2**). Procalcitonin levels appeared to increase significantly initially in the severe group and remained high in clinical follow-ups (**Graphic 3**) (**Table 3**).

Discussion

Our study revealed that a more advanced gestational age at initial diagnosis was associated with a poorer prognosis of infection with the Delta variant of COVID-19. A total of 19% (n= 9) of all admissions were ICU admissions, of which 55.5% (n= 5) of the patients were intubated, and all intubated patients died. Worsening of the maternal clinical picture was found to cause a significant increase in cesarean delivery, preterm delivery, low birth weight, and NICU admission rates. High CRP values in pregnant women were significantly correlated with severe disease. Increasing WBC and procalcitonin levels during follow-up of pregnant women were significantly associated with poor prognosis. Reportedly, symptomatic disease, severe disease, and ICU admission rates are significantly higher in pregnant women infected with the Delta variant of COVID-19 than in those with pre-Delta variants of COVID-19; however, there was no significant change in maternal mortality rates [27]. Furthermore, 62.3%-84% of pregnant women infected with the Delta variant of COVID-19 were reportedly symptomatic. Also, 48%-79% of symptomatic pregnant women are in the non-severe group and 21%-36% were in the severe disease group. Several studies have reported that 4.9%-29% of pregnant women infected with the Delta variant of COVID-19 are admitted to the ICU, 33.3%-80% of those in the ICU are intubated, and the mortality rate was 0%–2%. Moreover, advanced gestational age at the time of initial diagnosis has been reported to be significantly associated with poor prognosis [27-29]. Our study found that advanced gestational age at the time of initial diagnosis was significantly associated with poor prognosis. ICU admission and intubation rates were similar to those published in the literature. However, our study found a mortality rate of 5.2% in pregnant women infected with the Delta variant of COVID-19. This rate is remarkably high compared to both the literature on pregnant women infected with the Delta variant of COVID-19, and also higher than previous mortality rates found by our clinic in pregnant women infected with the Delta variant of COVID-19 (2.99%, n= 15/501). Our study found that COVID-19-related deaths in pregnant women increased with the Delta variant. A large number of pregnant women with COVID-19-related severe disease are referred to our hospital, which is a tertiary center. This may be another reason why we found increased mortality rates.

There is a paucity of information in the literature on symptomatology in pregnant women infected with the Delta variant of COVID-19. It has been reported that 71% of symptomatic pregnant women infected with the Delta variant of COVID-19 have a cough, 44.7% have a fever, 42% have dyspnea, 37% have myalgia-malaise, and 10.5% have diarrhea [28]. In pregnant women infected with the Delta variant of COVID-19, lymphocytopenia has been reported at a rate of 27.8%, elevated AST at 11.5%, and elevated ALT at 9.8% [28]. No significant difference has been reported among asymptomatic, non-severe, and severe groups of pregnant women infected with the Delta variant of COVID-19 in terms of blood test parameters (lymphocyte, leukocyte, BUN, creatinine, AST, and ALT) at the time of admission [27]. Our study found significantly higher CRP levels in pregnant women in the severe group than the pregnant women in the non-severe and asymptomatic group. Clinical follow-ups showed that increasing WBC and procalcitonin levels were significant predictors of poor prognosis.

The rate of chest CT findings with pneumonia appearance has been reported at 88% in symptomatic pregnant women infected with the Delta variant of COVID-19 [28]. In our study, 64% of the symptomatic pregnant women had findings consistent with pneumonia on their chest CT scans (100% in the severe group, and 50% in the non-severe group).

While Wang et al. reported no significant difference between pregnant women infected with the Delta variant of COVID-19 and those with pre-Delta variants of COVID-19 in terms of preterm delivery rates, fetal weight, and adverse neonatal outcomes (NICU admission, hypoxic-ischemic encephalopathy, sepsis, ventilator support, meconium aspiration, birth trauma, stillbirth, etc.); Seasely et al. have reported an association between infection with the Delta variant of COVID-19 and statistically increased rates of preterm delivery and NICU admission [27,28]. The rate of preterm delivery has been reported at 73% and the rate of NICU admission at 74% in pregnant women infected with the Delta variant of COVID-19 [27]. Comparisons of neonatal outcomes among pregnant women infected with the Delta variant of COVID-19 in asymptomatic, non-severe, and severe groups found no significant difference in terms of preterm delivery and poor neonatal outcomes [28]. Our study found no increase in the incidence of preterm delivery complications such as spontaneous abortion, threatened abortion, and hyperemesis gravidarum in symptomatic pregnant women infected with the Delta variant of COVID-19 [30-33]. However, we found significantly higher cesarean and preterm delivery rates in the severe group compared to the asymptomatic and non-severe groups. We believe that maternal clinical features are the main determinant of preterm delivery and cesarean section rates in symptomatic pregnant women. Our study found that the newborns of mothers in the severe group had significantly lower average gestational age at birth and birth weight, and significantly higher NICU admissions compared to the newborns of mothers in the non-severe and asymptomatic group.

The main limitation of this study is its retrospective design. Despite this, the present study is important due to the scarcity of data in the literature on the effects of the Delta variant on pregnancy outcomes. We think that the current study is original in that it has recorded and analyzed blood parameters at three different time points to better predict the course of the disease.

Conclusion

The Delta variant of COVID-19 was found to result in increased mortality rates in pregnant women compared to pre-Delta variants of COVID-19. In pregnant women infected with the Delta variant of COVID-19, advanced gestational age at diagnosis, elevated CRP, WBC, and procalcitonin levels were found to be significantly correlated with poor prognosis. Pregnant women infected with the Delta variant of COVID-19 were also found to be at increased risk for preterm delivery and cesarean section in the presence of severe disease. Although intensive care admissions were found to be significantly higher in the newborns of pregnant women in the severe disease group, no significant difference was found in neonatal mortality rates. We recommend close monitoring of CRP, WBC, and procalcitonin levels in addition to symptoms, particularly in pregnant women infected with the Delta variant of COVID-19 in the third trimester. We believe that swift decision-making for the delivery of the fetus can improve neonatal outcomes in case of impaired maternal oxygenation.

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Table 1. Age, obstetric history, symptoms and clinical findings, medication, clinical course, and perinatal outcomes					
		Asymptomatic group (n=49)	**Non-Severe group (n=34)**	**Severe group (n=13)**	**p-value**
		n (%) or median (minimum–maximum)	**n (%) or median (minimum–maximum)**	**n (%) or median (minimum–maximum)**	
Age, years		29.0 (18.0–43.0)	29.5 (17.0–40.0)	29.0 (22.0–41.0)	0.708
Trimester	**1st trimester**	14 (28.5)[a]	2 (5.8)[a]	0 (0.0)[a]	**0.025**
	2nd trimester	5 (10.20) [a]	7 (20.5) [b]	2 (15.3) [b]	
	3rd trimester	30 (61.2)	25 (73.5) [b]	11 (84.6) [b]	
Gestational Age, weeks		34.0 (8.0–40.0)	35.0 (7.0–39.0)	31.0 (27.0–36.0)	0.458
Obstetric history	**Gravidity**	2.0 (1.0–7.0)	3.0 (1.0–6.0)	3.0 (1.0–12.0)	0.145
	Parity	1.0 (0.0–5.0)	1.05 (0.0–5.0)	2.0 (0.0–9.0)	0.170
	Previous abortion	0.0 (0.0–3.0)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.888
Symptoms and Clinical Findings					
Body mass index, kg/m^2		25.0 (20.4–29.8)	26.4 (21.2–29.9)	27.2 (22.5–30.4)	0.074
Smoking		7 (14.2)	3 (8.8)	1 (7.6)	0.748*
Systolic blood pressure, mmHg		100.0 (90.0–50.0)	110.0 (90.0–140.0)	100.0 (90.0–160.0)	0.865
Diastolic blood pressure, mmHg		60.0 (60.0–90.0)	60.0 (60.0–90.0)	60.0 (50.0–90.0)	0.812
Pulse, /dk		89.0 (70.0-121.0)[a]	96.0 (75.0–124.0)[b]	108.0 (93.0–125.0)[c]	**<0.001**
Saturation, %		98.0 (90.0-99.0)[a]	97.0 (88.0-99.0)[b]	93.0 (85.0–98.0)[c]	**0.003**
Fever		36.4 (36.1–37.0)	36.4 (36.2–37.1)	36.4 (36.1–36.9)	0.706
Cough		0 (0.0)[a]	32 (94.1)[b]	12 (92.3)[b]	**<0.001**
Shortness of breath		0 (0.0)[a]	28 (82.3)[b]	13 (100.0)[b]	**<0.001**
Diarrhea		0 (0.0)	0 (0.0)	0 (0.0)	NA
Muscle Pain		2 (4.9)[a]	26 (63.4)[b]	13 (31.7)[b]	**<0.001**
Exposed to someone with COVID-19		24 (48.9)[a]	34 (100.0)[b]	13 (100.0)[b]	**<0.001**
COVID-19 findings in chest CT	**Positive**	0 (0.0)	17 (50.0)	13 (100.0)	**<0.001**
	Negative	0 (0.0)	17 (50.0)	0 (0.0)	
	N/A	49 (100.0)	0 (0.0)	0 (0.0)	
Medication and Vaccination					
Vaccination		0 (0.0)	0 (0.0)	0 (0.0)	NA

Antibiotic		26 (53.0)[a]	19 (55.8)[a]	13 (100.0)[b]	**0.007**
Glucocorticoid		2 (4.0)[a]	33 (97.6)[b]	13 (100.0)[b]	**<0.001**
Tocilizumab		0 (0.0)[a]	0 (0.0)[a]	2 (15.3)[b]	**0.016***
Low molecular weight heparin		34 (69.3)[a]	34 (100.0)[b]	13 (100.0)[b]	**<0.001**
Inhaler β2 agonists + antitussive syrup		0 (0.0)[a]	32 (94.1)[b]	13 (100.0)[b]	**<0.001**
Clinical Course					
Viral pneumonia		0 (0.0)[a]	31 (91.1)[b]	13 (100.0)[b]	**<0.001**
Acute respiratory distress syndrome		0 (0.0)[a]	0 (0.0)[a]	5 (38.4)[b]	**<0.001***
Renal Failure		0 (0.0)[a]	0 (0.0)[a]	3 (23.0)[b]	**0.002***
Intensive care unit admission		0 (0.0)[a]	0 (0.0)[a]	9 (69.0)[b]	**<0.001***
Intensive care unit length of stay, days		0.0 (0.0–0.0)[a]	0.0 (0.0–0.0)[a]	3.0 (0.0–15.0)[c]	**<0.001**
Length of hospital stay, days		2.0 (1.0–3.0)[a]	4.0 (2.0–7.0)[b]	7.0 (3.0–22.0)[c]	**<0.001**
Intubation		0 (0.0)[a]	0 (0.0)[a]	5 (38.4)[b]	**<0.001***
Maternal death		0 (0.0)[a]	0 (0.0)[a]	5 (38.4)[b]	**<0.001***
Obstetrical Findings					
Spontaneous abortion		5 (10.2)[a]	0 (0.0)[b]	0 (0.0)[b]	**<0.001***
Threatened abortion		2 (4.0)	0 (0.0)	0 (0.0)	0.375
Hiperemezis gravidarum		9 (18.3)[a]	1 (2.9)[b]	0 (0.0)[b]	**0.035***
Premature rupture of membranes		2 (4.0)	1 (2.9)	0 (0.0)	1.000
Preterm Delivery		6 (12.2)[a]	3 (8.8)[a]	7 (53.8)[b]	**0.002**
Fetal Distress		4 (8.1)	3 (8.8)	1 (7.6)	1.000
Intrauterine fetal demise		2 (4.0)	0 (0.0)	1 (7.6)	0.247*
Fetal growth restriction		0 (0.0)	0 (0.0)	0 (0.0)	NA
Postpartum hemorrhage		0 (0.0)	0 (0.0)	0 (0.0)	NA
Mode of delivery	**Vaginal**	18 (36.7)[a]	4 (11.7)[a]	0 (0.0)[a]	**0.005***
	Cesarean section	7 (14.2) [a]	8 (23.5)[a]	7 (53.8) [b]	
	Not delivered	24 (49.9)[b]	22 (64.7)[a]	6 (46.1)[a,b]	
Indication for cesarean section	**Maternal**	0 (0.0)	0 (0.0)	6 (85.7)	**0.002***
	Fetal	7 (100.0)[a]	8 (100.0)[a]	1 (14.3)[b]	

a,b,c; For medians expressed with indices such as a, b, and c; different indices indicate statistical difference.
*;Fisher's exact p value.
The table prepared for group comparisons above shows p-values found to be significant in bold. For medians expressed by indices such as a, b, and c; statistically different ones have been marked with different letters, and those without statistical difference with the same letters. Likewise, where more than 20% of cells have an expected frequency of less than 5, the symbol "*" has been used for cross-tabulation (contingency tables) Chi-Square analysis, and Fisher's exact test p-value has been given instead of the Chi-Square p-value.

Table 2. Neonatal outcomes

		Asymptomatic group (n = 25)	Non-severe group (n = 12)	Severe group (n = 7)	p-value
		n (%) or median (minimum–maximum)	n (%) or median (minimum–maximum)	n (%) or median (minimum–maximum)	
Gestational age at birth, weeks		37.0 (25.0–40.0)[a]	38.0 (35.0-39.0)[a]	32.0 (29.0–36.0)[b]	**0.035**
Birth weight, g		3000 (690–4200)[a]	3075 (1900–3550)[a]	1900 (1550–2900)[b]	**0.013**
Fetal gender	**Male**	12 (48.0)	9 (75.0)	4 (57.1)	0.367*
	Female	13 (52.0)	3 (25.0)	3 (42.9)	
1-min Apgar score		8.0 (0.0-8.0)[a]	8.0 (4.0-8.0)[a]	7.0 (4.0-8.0)[b]	**0.008**
5-minute Apgar score		9.0 (0.0-9.0)[a]	9.0 (6.0-9.0)[a]	8.0 (7.0-9.0)[b]	**0.011**
Umbilical cord gas analysis	**pH**	7.31 (7.18–7.37)	7.30 (7.12–7.42)	7.31 (7.24–7.37)	0.935
	Base deficit	1.45 (14.3–0.4)	8.9 (12–1.0)	2.4 (4.5–1.0)	0.253
	Lactate, mmol/L	2.70 (2.40–875)	3.3 (1.7–8.0)	2.4 (2.02–4.08)	0.669
Intensive care unit admission		1 (4.0)[a]	3 (25.0) [a]	5 (71.4) [b]	**<0.001***
Intensive care unit length of stay, days		0.0 (0.0-4.0)[a]	0.0 (0.0-8.0)[a]	8.0 (0.0–12.0)[b]	**<0.001**
Neonatal death		0 (0.0)	0 (0.0)	0 (0.0)	NA

a,b,c; For medians expressed with indices such as a, b, and c; different indices indicate statistical difference.
*;Fisher's exact p value.

Table 3. Variation of blood test parameters over time

Variables	Asymptomatic group (n=49)	Non-severe group (n=34)	Severe group (n=13)	p1-value	p2-value	p3-value
WBC 1, mm^3 ×10^3	9.03±3.25	7.77±3.6	6.52±1.86			
WBC 2, mm^3 ×10^3	8.25±2.02	7.94±3.49	9.78±5.16	0.584	**0.002**	**0.001**
WBC 3, mm^3 ×10^3	8.97±3.41	7.82±2.87	10.21±3.98			
Neutrophil 1, ×10^3/uL	7±3.01	6.14±2.58	5.53±1.76			
Neutrophil 2, ×10^3/uL	6.56±1.81	5.91±3.06	7.93±3.18	0.347	**0.028**	**0.001**
Neutrophil 3, ×10^3/uL	6.7±3.32	5.8±2.65	8.01±3.66			

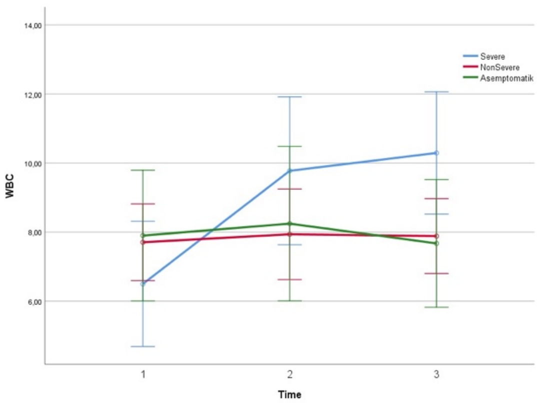
Lymphocyte 1, ×10^3/uL	1.45±0.66	1.09±0.46	0.78±0.19			
Lymphocyte 2, ×10^3/uL	1.41±0.7	1.42±0.44	1.16±0.49	0.283	**<0.001**	0.263
Lymphocyte 3, ×10^3/uL	1.73±0.73	1.61±0.59	1.52±0.69			
Hemoglobin 1, g/dL	11.66±1.82	10.75±2.07	11.3±1.18			
Hemoglobin 2, g/dL	10.78±1.91	10.43±0.9	10.29±1.16	0.453	**0.007**	0.534
Hemoglobin 3, g/dL	11.09±1.7	10.36±1.08	10.46±0.98			
Platelet 1, mm^3 ×10^3	210.33±70.83	197.38±59.16	178.62±46.69			
Platelet 2, mm^3 ×10^3	197.45±78.6	231.47±66.29	273.75±52.02	0.340	**<0.001**	**<0.001**
Platelet 3, mm^3 ×10^3	210.8±72.04	253.15±80.7	284.54±65.72			
AST 1, U/L	34.41±36.02	71.29±204.97	48.15±19.92			
AST 2, U/L	43±15.58	52.52±67.84	38.83±31.96	0.849	0.411	0.849
AST 3, U/L	31.78±15.55	39.68±28.21	35.54±48.1			
ALT 1, U/L	25.22±27.21	53.5±100.45	40.38±25.18			
ALT 2, U/L	36.5±24.96	47±56.05	44.17±36.76	0.771	0.426	0.882
ALT 3, U/L	24±16.48	43±42.12	31.62±20.79			
LDH 1, U/L	267.8±184.4	286.5±153.5	320.3±97.1			
LDH 2, U/L	214.7±162.7	268.0±135.8	366.1±242.3	0.100	0.877	0.400
LDH 3, U/L	267.8±130.0	249.03±97.0	394.2±314.8			
C-reactive protein 1, mg/dL	24.49±32.46	48.46±38.71	74.05±35.03			
C-reactive protein 2, mg/dL	34.71±37.35	33.14±28.94	88.9±75.66	**0.033**	0.804	0.072
C-reactive protein 3, mg/dL	37.89±68.15	27.67±35.93	51.02±67.96			
Ferritin 1, ng/mL	84.9±85.6	93.7±104.4	87.8±63.3			
Ferritin 2, ng/mL	261.8±210.8	88.1±99.5	151.7±199.9	0.108	**0.001**	**0.007**
Ferritin 3, ng/mL	99.7±99.4	80.0±79.9	67.4±64.4			
Procalcitonin 1, ng/mL	0.62±3.41	0.27±0.32	0.25±0.29			

Procalcitonin 2, ng/mL	1.16±2.37	0.22±0.38	5.28±17.24	0.224	0.815	0.109
Procalcitonin 3, ng/mL	0.17±0.22	0.2±0.38	4.82±16.29			

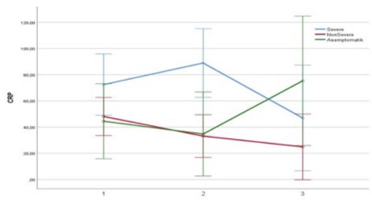
p1: p-value for main effect group, p2: p-value for main effect time, and p3: p-value for interaction term

The repeated measures ANOVA model was used in order to assess the measurements taken at three different time points for the variables of three independent groups.

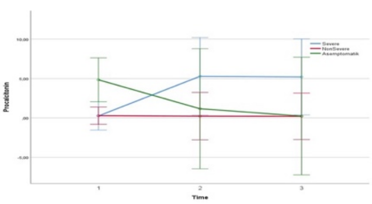
In this analysis, p1-value shows the difference between groups defined as the main effect, p2-value is used to evaluate the effect of time, and p3-value illustrates the effect called interaction term.



Graphic 1. WBC x time relationship



Graphic 2. CRP x time relationship



Graphic 3. Procalcitonin x time relationship