Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(4):1347-1356
DOI: 10.17826/cumj.1366249

RESEARCH

Effect of sex and mode of delivery on systemic inflammatory indices in preterm infants

Prematüre bebeklerde cinsiyet ve doğum şeklinin sistemik inflamatuar indeksler üzerine etkisi

Ufuk Çakır[1], Cüneyt Tayman[1]

[1]Department of Neonatal Intensive Care Unit, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Turkey

Abstract

Purpose: Information on systemic inflammatory indices in the field of neonatology is limited. How sex and mode of delivery affects systemic inflammatory indices is unknown. The aim of our study was to evaluate the effect of mode of delivery and sex on systemic inflammatory indices in preterm infants.

Materials and Methods: Preterm infants <32 weeks of gestation were evaluated retrospectively. Complete blood count parameters, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), pan immune inflammation value (PIV), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), systemic inflammation response index (SIRI), demographic and clinical characteristics were compared in terms of sex and mode of delivery.

Results: In our study, 1322 preterm infants were evaluated. Leukocyte, platelet, neutrophil, monocyte, lymphocyte count, hemoglobin levels, NLR, MLR, PLR, PIV, SII, and SIRI values were found to be similar between genders. Leukocyte, neutrophil, monocyte, lymphocyte count, hemoglobin levels, MLR, PLR, and SIRI values did not differ significantly according to mode of delivery. The values of platelet count (225 10^3 μ/L), NLR (0.30), PIV (42.17) and SII (67.86) in the cesarean section group were higher than those in the vaginal delivery group (platelet count: 248 10^3 μ/L, NLR: 0.44, PIV: 80.88 and SII: 91.63).

Conclusion: Gender had no effect on systemic inflammatory indices and NLR, PIV, and SII were lower in cesarean delivery in preterm infants born <32 weeks of gestation.

Keywords: Infant, pan immune inflammation value, premature, systemic immune-inflammation index

Öz

Amaç: Neonatoloji alanında sistemik inflamatuar indekslere ilişkin bilgiler sınırlıdır. Cinsiyet ve doğum şeklinin sistemik inflamatuar indeksleri nasıl etkilediği bilinmemektedir. Çalışmamızın amacı preterm bebeklerde doğum şeklinin ve cinsiyetin sistemik inflamatuar indekslere etkisini değerlendirmektir.

Gereç ve Yöntem: 32 haftanın altındaki prematüre bebekler retrospektif olarak değerlendirildi. Tam kan sayımı parametreleri, monosit-lenfosit oranı (MLR), nötrofil-lenfosit oranı (NLR), pan immün inflamasyon değeri (PIV), trombosit-lenfosit oranı (PLR), sistemik immün inflamasyon indeksi (SII), sistemik inflamasyon yanıt indeksi (SIRI), demografik ve klinik özellikler cinsiyet ve doğum şekli açısından karşılaştırıldı.

Bulgular: Çalışmamızda 1322 prematüre bebek değerlendirildi. Lökosit, trombosit, nötrofil, monosit, lenfosit sayısı, hemoglobin düzeyleri, NLR, MLR, PLR, PIV, SII ve SIRI değerleri cinsiyetler arasında benzer bulundu. Lökosit, nötrofil, monosit, lenfosit sayısı, hemoglobin düzeyleri, MLR, PLR ve SIRI değerleri doğum şekline göre anlamlı farklılık göstermedi. Sezaryen grubunda trombosit sayısı (225 10^3 μ/L), NLR (0,30), PIV (42,17) ve SII (67,86) değerleri vajinal doğum grubuna (trombosit sayısı: 248 10^3 μ/L, NLR: 0,44, PIV: 80,88 ve SII: 91.63) göre daha düşüktü.

Sonuç: Çalışmamızda cinsiyetin sistemik inflamatuar indeksler üzerine etkisinin olmadığı ve <32 haftadan önce doğan prematüre bebeklerde sezaryen doğumda NLR, PIV ve SII'nin daha düşük olduğu gösterilmiştir.

Anahtar kelimeler: Yenidoğan, pan immün inflamasyon değeri; prematüre; sistemik immün inflamasyon indeksi

Address for Correspondence: Ufuk Çakır, Department of Neonatal Intensive Care Unit, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Turkey E-mail: drufukcakir@hotmail.com
Received: 25.09.2023 Accepted: 12.12.2023

INTRODUCTION

Preterm birth is defined as the birth of a baby before completing 37 weeks of gestation. Preterm birth occurs in 5% to 10% of all pregnancies. The most common cause of many perinatal morbidity and mortality, especially respiratory distress syndrome (RDS), is prematurity. In order to reduce negative clinical outcomes in preterm infants, preventive care services and determination of risk factors are important in terms of providing good health care[1].

The rate of cesarean delivery (CD) has increased in the last 20 years. In terms of the safety of the newborn, the mode of delivery is one of the most important concerns in modern obstetrics. The choice of mode of delivery depends on obstetric indications, the severity of the mother's diseases and the conditions of the hospital facility. Although it is thought that CD may have a possible positive effect on the fetus, it is also considered that it can increase respiratory morbidities[2]. In preterm birth, the choice of delivery method continues to be a matter of debate[1,3]. The mode of delivery may affect the hematological parameters of the term newborn. There are insufficient data on the effect of delivery method of preterm infants on hematological parameters[4].

Another factor affecting preterm morbidity is gender. Male gender is more risky in terms of respiratory morbidity, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP), cerebral palsy, sensorineural hearing loss, adverse long-term neurodevelopmental outcomes, and mortality. Physiological, hormonal and immunological factors are thought to play a role in these negative clinical outcomes[5]. In adult studies, it has been reported that the difference between the sexes in terms of both hematological cell count and inflammatory markers is the reason for the disadvantage of the male gender in terms of clinical outcomes[6-9]. Hematological parameters in umbilical cord blood may differ between genders. The main reason for the variability in morbidity between the sexes may be due to this hematological difference[10,11].

Systemic inflammatory indices are accepted as an indicator of inflammation. It has been stated that these indices can be useful markers of diagnosis and prognosis for different diseases in adult[12,13]. In the field of neonatology, it has been reported that some systemic inflammatory indices may be useful markers in the diagnosis of hypoxic ischemic encephalopathy (HIE), patent ductus arteriosus (PDA), sepsis, ROP, IVH, and necrotizing enterocolitis (NEC)[14-19]. Systemic inflammatory indices, which can be important parameters in the diagnosis and prognosis of adult, pediatric and neonatal diseases, have not been tested before, whether they change in relation to genders and mode of delivery in preterm newborns.

According to the hypothesis of our study, if gender and mode of delivery can affect the results of complete blood count, it may also affect systemic inflammatory indices. To test our hypothesis, we evaluated the changes of neutrophil-to-lymphocyte ratio (NLR), systemic immune–inflammation index (SII), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), pan immune inflammation value (PIV), and systemic inflammation response index (SIRI) values according to gender and mode of delivery in preterm infants.

MATERIALS AND METHODS

Sample

This study was conducted in the neonatal intensive care unit (NICU) between October 2020 and June 2022. Preterm babies born at <32 weeks of gestation were included in the study. Babies born at ≥32 weeks of gestation, babies with major chromosomal anomalies, twin-to-twin transfusion syndrome, and babies with hematological disorders were excluded from the study. The local ethics committee (Zekai Tahir Burak Maternity Training and Research Hospital Clinical Research Ethics Committee) approved the study (date: 11.04.2019 and number: 48/2019).

Study design and data collection

All data were obtained from hospital medical records and evaluated retrospectively. To ensure the reliability of the records and to protect the privacy of the patients, all data were kept confidential and not shared anywhere. All stages of the study were carried out by two specialist physicians. The same treatment protocols were applied to all patients throughout the study period.

Demographic and clinical features such as GA, birth weight (BW), antenatal steroid, sex, mode of delivery, small for gestational age (SGA), Apgar scores at 1st and 5th minutes, duration of mechanical ventilation

(MV) support, early onset sepsis (EOS), late onset sepsis (LOS), RDS, IVH, PDA, NEC, BPD, ROP, NICU stay, mortality, and complete blood count results were recorded for all premature infants.

Preterm morbidities

Infants with positive blood cultures in the first 3 postnatal days were defined as EOS, and infants with positive blood cultures after the 3rd day were defined as LOS[20]. Infants who needed surfactant treatment were registered as RDS[21]. Infants with PDA detected after Doppler echocardiography examination with clinical findings were recorded as hemodimanic significant PDA[22]. Infants with moderate or advanced (stage ≥2) NEC were enrolled[23]. According to the BPD, if <30% oxygen needed at the postmenstrual age of 36th week, and severe BPD if it required positive pressure respiratory support or ≥30% oxygen[24]. Infants who were diagnosed with retinopathy in routine retinal screening examination and received treatment were recorded as ROP[25]. Infants with grade ≥3 IVH in cranial ultrasonography were recorded[26]. SGA was defined as birth weight below 10% according to GA[27].

Complete blood count

Venous blood samples were taken at the 1st hour after delivery. Venous blood samples were transferred to ethylenediaminetetraacetic acid (EDTA) tubes for complete blood count. The Cell-Dyn 3700 automatic hemocytometer (Abbott, Abbott Park, IL, USA) was used for complete blood count analysis. Hemoglobin levels (g/dL), leukocyte count (10^3 μ/L), neutrophil (N) count (10^3 μ/L), monocyte (M) count (10^3 μ/L), lymphocyte (L) count (10^3 μ/L), and platelet (P) count (10^3 μ/L) results were recorded.

Formulation of systemic inflammatory indices

A total of six systemic inflammatory indices, incluiding NLR, PLR, MLR, SII, PIV, and SIRI, were evaluated. The formulations of these six systemic inflammatory indices are as follows. NLR: N/L, PLR: P/L, MLR: M/L, SII: P x N/L, PIV: P x N x M/L, SIRI: N x M/L[14]. The patients included in the study were divided into groups as female/male and vaginal delivery/CD. Groups were compared with each other in terms of demographical and clinical features, complete blood count, and systemic inflammatory indices.

Statistical analysis

Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc, Chicago, IL, USA) program was used for statistical analysis. The distribution of the data was analyzed with the Histogram and Kolmogorov-Smirnov Test. A Pearson's chi-square test was performed for categorical data. Student's t-test was used for continuous data. Normally distributed data were presented as mean ± standard deviation, and abnormally distributed data were presented as median and interquartile range (IQR). Categorical data were expressed as frequency. Multivariate logistic regression analysis was performed to identify the independent risk factors for mode of delivery that included BW and GA. A P value of <0.05 was considered significant. Calculation of the sample size was performed with G-Power Version 3.1.9.6. Statistical power was calculated before data collection based on information from previous studies[4,8]. Considering mode of delivery, it was found that at least 114 patients (57 patients per group) were required, with an effect size of 0.50, type I error of 0.05, and power of 0.80. If gender was taken into account, it was decided to study with at least a total of 98 patients (49 patients and 49 controls) with an effect size of 0.50, type I error of 0.05 and 80% power.

RESULTS

During the study period, 1336 preterm infants born at <32 weeks of gestation were evaluated. A total of 14 babies were excluded from the study; including 8 babies with major congenital anomalies, 4 babies with twin-to-twin transfusion syndrome, and 2 babies with hematological disorders. The remaining 1322 preterm infants were eligible. It was determined that there were 658 infants (49.8%) with female gender and 664 (50.2%) infants with male gender. Of all preterm infants eligible for the study, 200 were born by vaginal delivery (15.1%) and 1122 by CD (84.9%).

There was no statistical difference between the genders in terms of GA, BW, antenatal steroid, SGA, mode of delivery, Apgar scores at 1st and 5th minutes, duration of MV support, EOS, LOS, IVH, PDA, NEC, ROP, NICU stay, and mortality (p>0.05). RDS and BPD were found to be higher in male infants compared to female infants (p=0.004 and p=0.033, respectively) (Table 1). Leukocyte, platelet, neutrophil, monocyte, lymphocyte count, hemoglobin levels, NLR, MLR, PLR, PIV, SII, and SIRI values were found to be similar between genders (p<0.05) (Table 2). There was no difference between CD and vaginal deliveries in terms of GA, antenatal

steroid, sex, 1st and 5th minutes Apgar scores, duration of MV support, EOS, LOS, IVH, PDA, ROP, BPD, ROP, NICU stay, and mortality (p>0.05). BW was found to be lower in those born with CD (p=0.010). The rate of SGA, RDS, and NEC was statistically significantly higher in infants born with CD (p<0.001, p<0.001, and p=0.026, respectively) (Table 3).

Table 1. Demographic characteristics and clinical outcomes according to sex in the preterm newborns

Characteristics	Female, (n=658)	Male, (n=664)	P value
Gestational age, weeks [a]	28.0±1.2	28.1±1.2	0.061
Birth weight, g [a]	1013±221	1053±2160	0.080
Antenatal steroid, n (%)	442 (67.1)	446 (67.1)	0.645
Small for gestational age, n (%)	59 (8.9)	45 (6.7)	0.075
Cesarean delivery, n (%)	556 (84.4)	566 (85.2)	0.707
Apgar 1st min, [b]	5 (2)	5 (2)	0.297
Apgar 5th min, [b]	8 (1)	8 (2)	0.649
Duration of MV, days [b]	1 (3)	1 (5)	0.789
EOS, n (%)	12 (1.8)	16 (2.4)	0.673
LOS, n (%)	163 (24.7)	135 (20.3)	0.145
RDS, n (%)	380 (57.7)	434 (65.3)	0.004*
IVH, n (%)	40 (6.1)	53 (7.9)	0.101
PDA, n (%)	255 (38.7)	231 (34.7)	0.135
NEC, n (%)	13 (1.9)	7 (2.1)	0.877
BPD, n (%)	98 (14.8)	124 (18.6)	0.033*
ROP, n (%)	68 (10.3)	47 (7.0)	0.487
NICU stay, days, [b]	55 (34)	52 (38)	0.077
Mortality, n (%)	96 (14.5)	113 (17.0)	0.227

[a] mean ± standard deviation, [b] median (interquartile range); *P<0.05 was considered statically significant.; BPD, bronchopulmonary dysplasia; EOS, early onset sepsis; IVH, intraventricular hemorrhage; LOS, late onset sepsis; MV, mechanical ventilation; NEC, necrotising enterocolitis; neonatal intensive care unit, NICU; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

Table 2. Systemic inflammatory indices and complete blood count according to sex in the preterm newborns

Parameters	Female (n=658)	Male (n=664)	P value
Leukocyte count (10^3 μ/L) [a]	11.00 (9.47)	11.10 (8.00)	0.109
Hemoglobin, (g/dL) [a]	16.40 (2.80)	16.60 (2.80)	0.054
Platelet count (10^3 μ/L) [a]	227.00 (95.25)	228.00 (116.00)	0.211
Neutrophil count (10^3 μ/L) [a]	2.44 (2.45)	2.27 (2.78)	0.134
Monocyte count (10^3 μ/L) [a]	0.67 (0.69)	0.66 (0.59)	0.138
Lymphocyte count (10^3 μ/L) [a]	7.21 (6.42)	7.21 (5.79)	0.096
NLR [a]	0.31 (0.37)	0.31 (0.39)	0.380
MLR [a]	0.08 (0.06)	0.09 (0.05)	0.553
PLR [a]	32.23 (28.91)	32.89 (32.19)	0.797
PIV [a]	43.41 (82.93)	48.82 (94.57)	0.057
SII [a]	69.56 (70.59)	71.77 (71.45)	0.427
SIRI [a]	0.19 (0.32)	0.20 (0.34)	0.069

[a] median (interquartile range); MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PIV, pan immune inflammation value; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index..

Table 3. Demographic characteristics and clinical outcomes according to mode of delivery in the preterm newborns

Characteristics	Vaginal delivery (n=200)	Cesarean delivery (n=1122)	P value
Gestational age, weeks [a]	28.0±1.2	28.1±1.2	0.086
Birth weight, g [a]	1101±221	1057±224	0.010*
Antenatal steroid, n (%)	140 (70.0)	748 (66.7)	0.768
Small for gestational age, n (%)	6 (3.0)	98 (8.7)	<0.001*
Male, n (%)	98 (49.0)	566 (50.4)	0.707
Apgar 1st min, [b]	6 (1)	5 (2)	0.096
Apgar 5th min, [b]	8 (1)	8 (1)	0.817
Duration of MV, days [b]	1 (2)	1 (4)	0.064
EOS, n (%)	7 (3.5)	21 (1.8)	0.088
LOS, n (%)	43 (21.5)	255 (22.7)	0.053
RDS, n (%)	82 (41.0)	732 (65.2)	<0.001*
IVH, n (%)	14 (7.0)	105 (9.3)	0.187
PDA, n (%)	62 (31.0)	424 (37.8)	0.067
NEC, n (%)	1 (0.5)	18 (1.6)	0.026*
BPD, n (%)	25 (12.5)	197 (17.5)	0.054
ROP, n (%)	18 (9.0)	97 (8.6)	0.641
NICU stay, days, [b]	50 (26)	54 (37)	0.060
Mortality, n (%)	31 (15.5)	178 (15.8)	0.896

[a] mean ± standard deviation, [b] median (interquartile range); *P<0.05 was considered statically significant; . BPD, bronchopulmonary dysplasia; EOS, early onset sepsis; IVH, intraventricular hemorrhage; LOS, late onset sepsis; MV, mechanical ventilation; NEC, necrotising enterocolitis; neonatal intensive care unit, NICU; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity;

Table 4. Systemic inflammatory indices and complete blood count according to mode of delivery in the preterm newborns

Parameters	Vaginal delivery (n=200)	Cesarean delivery (n=1122)	P value
Leukocyte count (10^3 μ/L) [a]	11.30 (9.76)	11.00 (8.76)	0.354
Hemoglobin, (g/dL) [a]	16.60 (2.90)	16.80 (3.30)	0.055
Platelet count (10^3 μ/L) [a]	248.00 (84.50)	225.00 (110.00)	0.032*
Neutrophil count (10^3 μ/L) [a]	2.80 (3.42)	2.16 (2.40)	0.280
Monocyte count (10^3 μ/L) [a]	0.72 (0.82)	0.65 (0.61)	0.960
Lymphocyte count (10^3 μ/L) [a]	7.05 (7.32)	7.21 (6.00)	0.108
NLR [a]	0.44 (0.48)	0.30 (0.34)	0.034*
MLR [a]	0.10 (0.07)	0.08 (0.06)	0.145
PLR [a]	34.59 (26.93)	32.46 (31.18)	0.897
PIV [a]	80.88 (104.77)	42.17 (84.96)	0.014*
SII [a]	91.63 (114.83)	67.86 (84.36)	<0.001*
SIRI [a]	0.25 (0.35)	0.18 (0.31)	0.082

a median (interquartile range); *P <0.05 was considered statically significant; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PIV, pan immune inflammation value; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index

Leukocyte, neutrophil, monocyte, lymphocyte count, hemoglobin levels, MLR, PLR, and SIRI values did not differ significantly according to the mode of delivery (p>0.05). Platelet count was significantly lower in the CD group (p=0.032). NLR, PIV, and SII values were found to be significantly lower in the CD group than in the vaginal delivery group (p=0.034, p=0.014, and p<0.001, respectively) (Table 4).

Multiple logistic regression analysis showed that NLR, PIV and SII were significant parameters associated with mode of delivery (OR 1.213, 95% CI 1.101-1.647, p=0.001, OR 1.488, 95% CI 1.202-2.474, p=0.001, and OR 2.246, 95% CI 1.250-3.708, p=0.001, respectively).

DISCUSSION

In our study, the frequency of RDS, IVH, and BPD in infants born at <32 weeks of gestation was higher in male infants. While BW was lower in preterms born with CD, SGA, RDS, and NEC were higher. Complete blood count, NLR, MLR, PLR, PIV, SII, and SIRI values did not differ significantly between genders. Platelet count, NLR, PIV, and SII were lower in preterm infants born with CD. Leukocyte, neutrophil, monocyte, lymphocyte count, hemoglobin levels, MLR, PLR, and SIRI values did not differ significantly with mode of delivery.

Differences in the inflammatory response between the sexes draw attention in many diseases. It has been reported that inflammation markers are higher in individuals with the same disease, especially in male gender. Due to this increased inflammation, the male gender may be more disadvantageous than the female gender in terms of the prognosis of some diseases[6,7,28]. Fundamental biological differences such as sex chromosomes and hormonal factors are thought to be the possible cause of the difference between the sexes in the immunological system. However, there is no definitively proven literature on this subject[28].

In the neonatal area, there is limited information on the effect of gender on preterm morbidity, especially in preterm infants. A male preterm infant may have an increased risk of respiratory morbidities and mortality such as IVH, ROP, RDS and BPD[29]. In our study, we found that male gender was disadvantaged in terms of the frequency of RDS and BPD. It is thought that RDS may develop as a result of delay in bronchiole budding modulation and surfactant production in the fetal lung, due to higher levels of androgen receptors as a cause of increased RDS in male gender[5,29]. Thus, surfactant production may occur earlier in females than males. Early production of surfactant in girls may contribute to higher airflow and decreased resistance in the respiratory system. As a result, this seems to prevent premature closure of alveoli and small airways in girls[5]. Fleisher et al. have showed that both the 2:1 lecithin/sphingomyelin ratio and phosphatidylglycerol appeared one week earlier in girls than boys[30]. Moreover, male newborns have a lower rate of alveolar sodium transport channels than females, thus preventing gas exchange in the lungs, which may contribute to fluid accumulation and increased respiratory distress[5]. Due to all these reasons, postpartum respiratory outcomes may progress worse in male gender than in female gender[29]. Antenatal steroid reduces the frequency of RDS and BPD. In our study, although antenatal steroids were used at similar rates according to gender, the rate of RDS was found to be higher in males. This result can be explained by the intertwined mechanisms mentioned above[5,29,30]. Similar to our results, Ito et al. have used a 10-year database from the neonatal research network in Japan, they noted that male gender was disadvantageous for BPD in preterm infants[31]. Furthermore, male mice have been reported to have more developmental arrest and more inflammation in alveolization and pulmonary angiogenesis compared to females[32]. The above pathophysiological mechanisms may explain the increased incidence of BPD and RDS in male infants, as in the results of our study.

The reason for the higher lymphocyte, lower neutrophil and monocyte count in the neonatal period compared to adults is due to the development of the incomplete acquired and adaptive immune system, in addition to a feature of neonatal innate immunity[33]. Another feature of newborns is that leukocyte parameters vary in their distribution according to GA. While the lymphocyte ratio is more dominant in infants born at <32 gestational weeks, the neutrophil ratio is lower than in term infants. After the 32nd week of gestation, the lymphocyte ratio decreases until the term, while the neutrophil ratio increases[34]. This is because the hematopoiesis originates from the fetal liver before 30-32 weeks of gestation.

Although there are studies on sex-related hematological parameters in the adult and pediatric patient population, there is not enough data in the neonatal period less than 28 days. Glasser et al. have evaluated the lymphocyte subsets in newborns and stated that lymphocyte subgroups differed between the sexes[35]. It has been previously shown that the number of lymphocytes, neutrophils, monocytes and leukocytes is not affected by gender in term newborns[33,36,37]. In our results, it was shown that leukocyte parameters were similar in both sexes in preterm infants born before the 32nd weeks of

gestation. However, it was not tested whether there was a difference in terms of leukocyte parameters in term and preterm infants.

It has been reported that NLR is higher in adult male patients with chronic obstructive pulmonary disease than in females[38]. Moreover, SII has been shown to be higher in female patients with essential hypertension than in males[39]. They have reported that both NLR and SII elevations are associated with negative clinical outcomes of patients[38,39]. Although some systemic inflammatory indices have been found to be important for the diagnosis in neonatal diseases such as HIE, PDA, ROP, IVH, NEC, and sepsis[14-19]. It is not known whether systemic inflammatory indices vary between genders. Therefore, our study was the first study to show that systemic inflammatory indices were similar between the sexes in infants <32 weeks of gestation. In our study, GA, BW, leukocyte parameters and systemic inflammatory indices were similar in both genders, as well as the frequency of RDS and BPD was higher in males. In a newly published study, it has been shown that high SII values may be a predictor for RDS in preterms ≤32 weeks of gestational age[40]. In another recent study, it has been reported that high SIRI values for both at birth and at the 36th week of postmenstrual age could be a predictor marker for moderate to severe BPD in prematures <32 weeks of gestational age[41]. In both studies examining RDS and BPD, genders were found to be similar between groups[40,41]. These results supported the hypothesis that respiratory morbidities, independent of inflammation, were increased in males and associated with androgen hormone and its receptor[5,29].

Although CD is applied to reduce neonatal morbidities and mortality, its neonatal outcomes are still controversial[3]. As in our results, CD may be associated with increased SGA, RDS and NEC. Our infants, possibly exposed to fetal hypoxia, may have been born with a CD. Although the groups were at the same GA, the lower BW and higher SGA in the CD group seems to be evidence of fetal hypoxia[2]. The frequency of RDS and NEC may have been found to be higher in the CD group due to more fetal hypoxia[42]. Accordingly, the connection between CD and fetal hypoxia is based on a cause-effect relationship[1,5]. The possible reasons for the similar and different aspects of the findings between our results and other studies may be due to the varying rates of antenatal steroid administration, different nutritional and respiratory support strategies, and the evaluation of patients at different GA[1,2,5,42].

Although there are studies evaluating the effect of mode of delivery on hematological parameters in term newborns, there is not enough data on this subject in preterm babies. In this study, which we aimed to address this deficiency, platelet counts were found to be lower in preterm babies born with CD compared to vaginal delivery. There are conflicting results regarding the effect of mode of delivery on platelet count[4,43]. In our study, the possible reason for the lower platelet count in preterm infants in the CD group may be due to the increased frequency of SGA in this group. Because chronic intrauterine hypoxia has been suggested to cause a decrease in megakaryocytic lineage cells in the bone marrow[44]. While evaluating the mode of delivery and platelet relationship in the above studies, SGA data was not shared[4,43]. Therefore, in this study, the effect of SGA on platelet count was evaluated together with mode of delivery. In our study, hemoglobin levels were similar between the groups. In previous studies, higher hemoglobin levels have been reported in those born by vaginal delivery. It is thought that the reason for the higher hemoglobin level in vaginal delivery may be due to a larger amount of blood transfused through the placenta[4]. Lubetzky et al. have suggested that the higher hemoglobin level in babies born by vaginal delivery may be due to the shift of body fluids from the intravascular area to the extravascular area before delivery[43]. Thus, it has been stated that hemoglobin may increase in vaginal deliveries depending on delivery physiology and hemoconcentration[37]. It was shown in our results that these hypotheses, which are valid for term babies, may not be valid for preterms who are more immature in terms of hemodynamic transition and hemoglobin may not vary between genders.

Although it was stated that neonatal leukocyte count increased due to increased catecholamine and cortisol in vaginal delivery, our results did not support this hypothesis in preterm infants. An important factor that will affect the leukocyte count is neonatal sepsis. However, in previous studies, there was no data on the frequency of sepsis between the groups[35,45]. In our study, the frequency of sepsis and leukocyte count were found to be similar. Therefore, according to our results, it can be concluded that mode of delivery does not affect leukocyte, neutrophil, lymphocyte and monocyte counts in preterm infants. Similar to our results, Sheffer-Mimouni et al. have showed that the method of delivery does not affect

leukocyte parameters in newborns[46]. A study by Cairo et al has shown that lymphocyte subgroups can be affected by the delivery method[10]. However, lymphocyte subgroups could not be evaluated in our patients. Additionally, the mentioned studies have evaluated the leukocyte count in term infants. Mode of delivery may not affect leukocyte parameters in preterm infants due to the immaturity of the immune system[10,35,46]. Therefore, the relationship between mode of delivery and leukocyte count should be evaluated based on the GA.

The effect of mode of delivery on systemic inflammatory indices is unknown. From this point of view, in our study, which evaluated systemic inflammatory indices for the first time, MLR, PLR, and SIRI were similar in groups, while NLR, PIV, and SII were significantly lower in the CD group. These indices that differed between groups may have been primarily affected by the mode of delivery, or it could be a secondary consequence of hypoxia in infants born with CD exposed to fetal hypoxia. However, Ceran et al. have previously reported that hypoxic infants with HIE have higher NLR, PIV, and SII compared to the control group[14]. Therefore, in our results, low NLR, PIV, and SII levels in those born with CD are not due to hypoxia, but may possibly be an effect of mode of delivery. According to our results, it was difficult to say definitively whether mode of delivery or fetal hypoxia affected systemic inflammatory indices. However, the association of low NLR, PIV, and SII values with increased RDS and NEC in those born with CD needs to be evaluated in future studies.

Our study had some limitations as it was conducted from a single center and was retrospective. An attempt was made to interpret the results based on a single postnatal measurement. Complete blood count and systemic inflammatory indices values in the following postnatal days could not be examined. Only preterm infants were evaluated and no comparison with term infants could be implemented. Moreover, the effect of the parameters found to be significant on the clinical results could not be evaluated due to being out of our scope of the study.

In conclusion, our study was the first to evaluate the effect of sex and mode of delivery on systemic inflammatory indices in preterm infants born at <32 weeks of gestation. According to our results, while gender had no effect on systemic inflammatory indices, NLR, PIV, and SII values were found to be lower in CD. Future studies are required to obtain information on how these parameters are reflected in clinical results.

Author Contributions: Concept/Design : UC; Data acquisition: UC; Data analysis and interpretation: CT; Drafting manuscript: UC; Critical revision of manuscript: CT; Final approval and accountability: UC, CT; Technical or material support: UC; Supervision: CT; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of the Ministry of Health Zekai Tahir Burak Women's Health Education and Research Hospital with the decision dated 11.04.2019 and numbered 48/2019.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Sangkomkamhang U, Pattanittum P, Laopaiboon M, Lumbiganon P. Mode of delivery and outcomes in preterm births. J Med Assoc Thai. 2011;94:415-20.
2. Gluck O, Tairy D, Bar J, Barda G. The impact of mode of delivery on neonatal outcome in preterm births. J Matern Fetal Neonatal Med. 2021;34:1183-9.
3. Schmidt S, Norman M, Misselwitz B, Piedvache A, Huusom LD, Varendi H et al. Mode of delivery and mortality and morbidity for very preterm singleton infants in a breech position: A European cohort study. Eur J Obstet Gynecol Reprod Biol. 2019;234:96-102.
4. Wu JH, Chou HC, Chen PC, Jeng SF, Chen CY, Tsao PN et al. Impact of delivery mode and gestational age on haematological parameters in Taiwanese preterm infants. J Paediatr Child Healt. 2009;45:332-6.
5. Townsel CD, Emmer SF, Campbell WA, Hussain N. Gender differences in respiratory morbidity and mortality of preterm neonates. Front Pediatr. 2017;5:6.
6. Casimir GJ, Duchateau J. Gender differences in inflammatory processes could explain poorer prognosis for males. J Clin Microbiol. 2011;49:478-9.
7. Lu Y, Zhou S, Dreyer RP, Spatz ES, Geda M, Lorenze NP et al. Sex differences in inflammatory markers and health status among young adults with acute myocardial infarction: results from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) Study. Circ Cardiovasc Qual Outcomes. 2017;10:e003470.
8. Bergens O, Nilsson A, Kadi F. Associations between circulating inflammatory biomarkers and indicators of muscle health in older men and women. J Clin Med. 2021;10:5316.
9. Cartier A, Côté M, Lemieux I, Pérusse L, Tremblay A, Bouchard C et al. Sex differences in inflammatory markers: what is the contribution of visceral adiposity? Am J Clin Nutr. 2009;89:1307-14.
10. Cairo MS, Wagner EL, Fraser J, Cohen G, van de Ven C, Carter SL et al. Characterization of banked umbilical cord blood hematopoietic progenitor cells and lymphocyte subsets and correlation with ethnicity, birth weight, sex, and type of delivery: a Cord Blood

Transplantation (COBLT) Study report. Transfusion. 2005;45:856-66.
11. Aroviita P, Teramo K, Hiilesmaa V, Kekomäki R. Cord blood hematopoietic progenitor cell concentration and infant sex. Transfusion. 2005;45:613-21.
12. Cakir E, Ozkocak Turan I. Which hemogram-derived indices might be useful in predicting the clinical outcomes of sepsis patients in the intensive care unit? Cukurova Med J. 2021;46:532-9.
13. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Rodzki M, Witkowska A, Gąsecka A et al. Neutrophil counts, neutrophil-to-lymphocyte ratio, and systemic inflammatory response index (SIRI) predict mortality after off-pump coronary artery bypass surgery. Cells. 2022;11:1124.
14. Ceran B, Alyamaç Dizdar E, Beşer E, Karaçağlar NB, Sarı FN. Diagnostic role of systemic inflammatory indices in infants with moderate-to-severe hypoxic ischemic encephalopathy. Am J Perinatol. 2021;doi:10.1055/a-1673-1616.
15. Karabulut B, Arcagök BC, Simsek A. Utility of the platelet-to-lymphocyte ratio in diagnosing and predicting treatment success in preterm neonates with patent ductus arteriosus. Fetal Pediatr Pathol. 2021;40:103-12.
16. Can E, Hamilcikan Ş, Can C. The value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for detecting early-onset neonatal sepsis. J Pediatr Hematol Oncol. 2018;40:e229-e232.
17. Kurtul BE, Kabatas EU, Zenciroglu A, Ozer PA, Ertugrul GT, Beken S et al. Serum neutrophil-to-lymphocyte ratio in retinopathy of prematurity. J AAPOS. 2015;19:327-31.
18. Stein AA, Eyerly-Webb S, Solomon R, Tani C, Shachar E, Kimball R et al. Peripheral blood neutrophil-to-lymphocyte ratio in preterm infants with intraventricular hemorrhage. Clin Neurol Neurosurg. 2019;180:52-6.
19. Yang Y, Cao ZL, Zhou XY, Chen XQ, Pan JJ, Cheng R. Does neutrophil/lymphocyte ratio have good diagnostic value in neonatal necrotizing colitis? J Matern Fetal Neonatal Med. 2019;32:3026-33.
20. Cakir U, Tayman C, Buyuktiryaki M. An unknown risk factor for sepsis in very low birth weight preterms: ABO blood groups (BGaPS Study). Am J Perinatol. 2021;38:669-75.
21. Özkan H, Erdeve Ö, Kutman HGK. Turkish Neonatal Society guideline on the management of respiratory distress syndrome and surfactant treatment. Turk Pediatri Ars. 2018;53:45-54.
22. Cakir U, Tayman C, Karacaglar NB, Beser E, Ceran B, Unsal H. Comparison of the effect of continuous and standard intermittent bolus paracetamol infusion on patent ductus arteriosus. Eur J Pediatr. 2021;180:433-40.
23. Cakir U, Tayman C, Yarci E, Halil H, Buyuktiryaki M, Ulu HO et al. Novel useful markers for follow-up of necrotizing enterocolitis: endocan and interleukin-33. J Matern Fetal Neonatal Med. 2020;33:2333-41.
24. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.
25. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128:e51-e68.
26. Volpe JJ. Impaired neurodevelopmental outcome after mild germinal matrix-intraventricular hemorrhage. Pediatrics. 2015;136:1185-7.
27. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.
28. Lin CY, Kwon H, Rangel Rivera GO, Li X, Chung D, Li Z. Sex differences in using systemic inflammatory markers to prognosticate patients with head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2018;27:1176-85.
29. Shim SY, Cho SJ, Kong KA, Park EA. Gestational age-specific sex difference in mortality and morbidities of preterm infants: A nationwide study. Sci Rep. 2017;7:6161.
30. Fleisher B, Kulovich MV, Hallman M, Gluck L. Lung profile: sex differences in normal pregnancy. Obstet Gynecol. 1985;66:327-30.
31. Ito M, Tamura M, Namba F; Neonatal Research Network of Japan. Role of sex in morbidity and mortality of very premature neonates. Pediatr Int. 2017;59:898-905.
32. Lingappan K, Jiang W, Wang L, Moorthy B. Sex-specific differences in neonatal hyperoxic lung injury. Am J Physiol Lung Cell Mol Physiol. 2016;311:L481-93.
33. Zhang X, Zhang Y, Xu Y, Liu J, Fu M, Ding Y et al. Age- and sex-specific reference intervals for complete blood count parameters in capillary blood for Chinese neonates and infants: A prospective study. Clin Chim Acta. 2023;538:104-12.
34. Jung E, Romero R, Yeo L, Diaz-Primera R, Marin-Concha J, Para R et al. The fetal inflammatory response syndrome: the origins of a concept, pathophysiology, diagnosis, and obstetrical implications. Semin Fetal Neonatal Med. 2020;25:101146.
35. Glasser L, Sutton N, Schmeling M, Machan JT. A comprehensive study of umbilical cord blood cell developmental changes and reference ranges by gestation, gender and mode of delivery. J Perinatol. 2015;35:469-75.
36. Zitouni S, Bouatrous E, Laabidi O, Boudrigua I, Chaouachi D, Saidani N et al. Tunisian Newborn's Cord Blood: Reference values of complete blood count and hemoglobin fractions. Am J Perinatol. 2022;39:1241-7.
37. Ronchi F, Porcella A, Porcu PP, Salis S, Locci C, Vacca N et al. Cord blood hematological reference values in term and late preterm infants from the

Mediterranean island of Sardinia: a preliminary study. J Pediatr Neonat Individual Med. 2020;10:e100109.
38. Troianova N, Mariotti B, Micheletti V, Calzetti F, Donini M, Salvagno G et al. Impact of Sex on Circulating Leukocytes Composition in COPD Patients. Int J Chron Obstruct Pulmon Dis. 2021;16:3539-3550.
39. Faraji J, Bettenson D, Babatunde S, Gangur-Powell T, Yong VW, Metz GAS. Thermoregulatory dynamics reveal sex-specific inflammatory responses to experimental autoimmune encephalomyelitis in mice: Implications for multiple sclerosis-induced fatigue in females. Brain Behav Immun Health. 2022;23:100477.
40. Cakir U, Tugcu AU, Tayman C, Yildiz D. Evaluation of the effectiveness of systemic inflammatory indices in the diagnosis of respiratory distress syndrome in preterm with gestational age of ≤32 weeks. Am J Perinatol. 2023;doi:10.1055/a-2051-8544.
41. Cakir U, Tayman C, Tugcu AU, Yildiz D. Role of systemic inflammatory indices in the prediction of moderate to severe bronchopulmonary dysplasia in preterm infants. Arch Bronconeumol. 2023;59:216-22.
42. Werner EF, Han CS, Savitz DA, Goldshore M, Lipkind HS. Health outcomes for vaginal compared with cesarean delivery of appropriately grown preterm neonates. Obstet Gynecol. 2013;121:1195-1200.
43. Lubetzky R, Ben-Shachar S, Mimouni FB, Dollberg S. Mode of delivery and neonatal hematocrit. Am J Perinatol. 2000;17:163-5.
44. Ozyürek E, Cetintaş S, Ceylan T, Oğüş E, Haberal A, Gürakan B et al. Complete blood count parameters for healthy, small-for-gestational-age, full-term newborns. Clin Lab Haematol. 2006;28:97-104.
45. Redźko S, Przepieść J, Zak J, Urban J, Wysocka J. Influence of perinatal factors on hematological variables in umbilical cord blood. J Perinat Med. 2005;33:42-5.
46. Sheffer-Mimouni G, Mimouni FB, Lubetzky R, Kupferminc M, Deutsch V, Dollberg S. Labor does not affect the neonatal absolute nucleated red blood cell count. Am J Perinatol. 2003;20:367-71.