KLİNİK ÇALIŞMA / CLINICAL TRIAL
Ege Klin Tıp Derg 2022;60 (3):247-252

Predictive Value Of Systemic Inflammatory Indices In Bronchopulmonary Dysplasia

Bronkopulmoner Displazi Tanısında Sistemik İnflamatuar Belirteçlerin Rolü

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Geliş Tarihi: 15/09/2022
Kabul Tarihi: 30/10/2022

Abstract

Objective: We aimed to determine the predictive role of systemic inflammatory biomarkers for bronchopulmonary dysplasia (BPD).

Methods: We examined infants who were born at gestational age below 32 weeks and followed in a neonatal intensive care unit (NICU) of a tertiary center between January 2017 and August 2022. The neutrophil lymphocyte ratio (NLR), systemic immune-inflammation (SII) index, systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV) were calculated from peripheral whole blood cell counts at birth and 72 hours for infants with BPD and without BPD.

Results The study comprised a total of 118 infants, including 55 with BPD and, 63 without BPD. The monocyte count at 72 h was significantly lower and SII at the 72 h was significantly higher in the BPD group.

Conclusion: Systemic inflammatory indices are practical, affordable, and easily available tools derived from serum whole blood cell counts that could be used for BPD early diagnosis and prevention.

Keywords: Bronchopulmonary dysplasia, inflammation, monocyte, systemic immune-inflammation index

Öz

Amaç: Bu çalışmada bronkopulmoner displazi erken tanısında sistemik inflamatuar biyobelirteçlerin tanımlayıcı rolünü belirlemeyi amaçladık.

Yöntem: Ocak 2017-Ağustos 2022 tarihleri arasında üçüncü basamak yenidoğan yoğun bakım ünitesinde takip edilen ve 32 haftanın altında doğan bebekleri inceledik. Hastalar BPD olan ve BPD olmayan bebekler olarak 2 gruba ayrıldı. Tam kan hücresi sayımlarından; nötrofil lenfosit oranı (NLR), sistemik immün inflamasyon (SII) indeksi, sistemik inflamasyon yanıt indeksi (SIRI) ve pan-immün inflamasyon değeri (PIV), doğum ve 72. saat değerleri hesaplandı.

Bulgular: Çalışmaya BPD'si olan 55 ve BPD'si olmayan 63 bebek olmak üzere toplam 118 bebek dahil edildi. BPD grubunda 72. saatte monosit sayısı istatistiksel anlamlı düşük ve 72. saatte SII istatistiksel anlamlı yüksek bulundu.

Sonuç: Sistemik inflamatuar indeksler, BPD'nin erken teşhisi ve önlenmesi için kullanılabilecek serum tam kan hücresi sayımlarından elde edilen pratik, uygun fiyatlı ve kolay erişilebilir araçlardır.

Anahtar Kelimeler: Bronkopulmoner displazi, inflamasyon, monosit, sistemik immün-inflamasyon indeksi

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease with a significant cause of morbidity and mortality in preterm infants (1). Advancements in perinatal and neonatal care have increased the survival rate of extremely preterm newborns, but unfortunately, BPD and BPD-related morbidities remained unchanged (2,3). The pathogenesis of BPD is multifactorial, including immature lung tissue, excessive inflammatory damage, oxygen toxicity, and genetics (4). Survivors with BPD may have lifelong respiratory sequela because of their impaired lung development (5). Prevention and early diagnosis are critical for preventing disease progression.

Systemic inflammatory indices, calculated with the ratio of whole blood cell counts, have been studied in various adult diseases lately. Hematological inflammatory markers and ratios including neutrophil-to-lymphocyte ratio (NLR), the systemic immune inflammation index (SII), and the systemic inflammation response index (SIRI) have been used to predict outcomes in sepsis, lung diseases, cancer, and finally COVID-19 (6-9).

We hypothesized we could show the potential mechanism of early inflammation with increasing peripheral hematologic inflammatory markers. As lung inflammation plays an important role in pathogenesis, we aimed to determine the predictive role of systemic inflammatory biomarkers for BPD.

Methods

This retrospective medical chart review included infants born at a gestational age below 32 weeks and followed in a tertiary care center's neonatal intensive care unit (NICU) between January 2017 and August 2022. We excluded infants with congenital heart disease, chromosomal/congenital abnormalities, incomplete information, or who died. We did not include infants who had early onset sepsis proven with blood culture. The study has been approved by the local ethical committee (0158/2022)

The research team obtained variables such as gestational age, birth weight, sex, maternal age and health status, antenatal steroid administration, presence of premature rupture of membranes (PROM), diagnosis of respiratory distress syndrome (RDS), mechanical ventilation, exogenous surfactant therapy, oxygen therapy, and duration of NICU stay from the medical records.

Using the consensus definition of the National Institute of Child Health and Human Development, our team made the BPD diagnosis for infants born at gestational age (GA) <32 weeks, as a minimum of 28 days long oxygen support requirement followed up by an evaluation at 36 weeks postmenstrual age (10).

The patients were categorized as BPD group and the non-BPD group. The systemic inflammatory markers were calculated from peripheral complete blood cell counts at birth and 72 hours after birth. NLR was calculated by dividing the absolute peripheral neutrophil count (N) count by the absolute lymphocyte (L) count using the formula: NLR= N/L (11).

The systemic immune-inflammation (SII) index, calculated as SII = platelet count × N/L, is a newly introduced inflammation-related index based on peripheral L, N, and platelet counts (12). The systemic inflammation response index (SIRI), calculated using the following formula: SIRI = N x M/L (13), is based on peripheral N, monocyte (M), and L blood counts. The recently proposed pan-immune-inflammation value (PIV), calculated using the following formula: PIV = Platelet x N x M/L, is a scoring system that includes all immune-inflammatory cells in the peripheral blood count (14).

Statistical Analysis

For discrete and continuous variables, descriptive statistics (mean, standard deviation, median, minimum value, maximum value, and percentile) were given. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was checked through Levene's test. The assumption of normality was tested via the Shapiro-Wilk test. To compare the differences between the two groups, the Student's t-test was used when the parametric test prerequisites were fulfilled, and the Mann Whitney–U test was used when such prerequisites were not fulfilled. BPD cut-off values in superovulation responses were evaluated by ROC analysis. Also, AUC Value, Sensitivity, and Selectivity values were calculated. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ were accepted.

Results

This study comprised a total of 118 infants, including 55 with BPD and 63 without BPD. All patients severity classified as mild BPD with FiO2=21%. The main characteristics of the infants are presented in Table 1. The mean gestational week of the infants diagnosed with BPD was 27.36±2.14 weeks, and their mean birth weight was 985.55±314.12 g. The mean gestational week of the infants without BPD was 30.24±1.42 weeks, and their mean birth weight was 1392.30±315.35 g. The mean gestational age and birth weight values in the BPD group were significantly lower than those of infants in the non-BPD group. The BPD group had significantly longer therapy durations for therapies, such as continuous positive airway pressure (CPAP), synchronized intermittent mandatory ventilation (SIMV), and oxygen therapy. The BPD group experienced also a significantly prolonged period of intravenous nutrition and NICU stay (Table 1).

Table 1: Descriptive characteristics

	BPD **n= 55**	**Non-BPD** **n =63**	*p*
Sex (Female)	27 (49.1)[a]	16 (25.4)[b]	**0.008**
Gestational age (weeks) *M* (*IQR*)	27.0 (3.0)	30.0 (1.0)	**<0.001**
BirthWeight (grams) x ± *sd*	985.5±314.1	1392.30±315.3	**<0.001**
Antenatal steroid, *n* (%)	15 (27.3)	27 (42.9)	0.078
Maternal age (years) x± *sd*	28.20±7.13	29.07±7.39	0.514
Gestational hypertension, *n* (%)	12 (21.8)	13 (20.6)	0.875
Gestational diabetes mellitus, *n* (%)	4 (7.3)	4 (6.3)	0.842
Multiple pregnancy	8 (14.5)	14 (22.2)	0.285
Caeserean birth *n* (%)	49 (89.1)	55 (87.3)	0.764
PROM, *n* (%)	10 (18.2)	9 (14.3)	0.566
RDS *n* (%)	41 (74.5)[a]	19 (30.2)[b]	**<0.001**
Surfactant therapy, *n* (%)	40 (72.7)[a]	19 (30.2)[b]	**<0.001**
CPAP *M* (*IQR*)	26.0 (14.0)	4.0 (5.0)	**<0.001**
SIMV *M* (*IQR*)	9.0 (22.0)	0.0 (2.0)	**<0.001**
Oxygen *M* (*IQR*)	10.0 (21.0)	0.0 (0.0)	**<0.001**
Total Oxygen *M* (*IQR*)	48.0 (39.0)	6.0 (7.0)	**<0,001**
Postnatal corticosteroid, *n* (%)	32 (58.2)[a]	0 (0.0)[b]	**<0.001**
TPN *M* (*IQR*)	25.0 (22.0)	10.0 (10.0)	**<0.001**
Duration of NICU stay*M* (*IQR*)	81.0 (50.0)	38.0 (20.0)	**<0.001**

$\bar{x}$: mean, *sd*: Standart Deviation, *M*: Median, *IQR*: Inter Quartile Range. Abbrevations: PROM,premature rupture of membranes; RDS,respiratory distress syndrome; CPAP,continuous positive airway pressure; SIMV,synchronized intermittent mandatory ventilation; NICU, neonatal intensive care unit.Total oxygen:with SIMV,CPAP, and incubator

In the comparison of two groups regarding the blood count and systemic inflammatory indices at birth and 72nd hour, the monocyte count at the 72nd hour was significantly lower, and SII at the 72nd hour was significantly higher in the BPD group (Table 2).

Table 2 : The hematological indices at birth and 72nd hour between BPD and non-BPD groups

	BPD **n= 55**	**Non-BPD** **n =63**	*p*
At birth			
N 10^9/L *M* (*IQR*)	3,4 (5,7)	4,0 (3,5)	0,658
L *M* (*IQR*)	3,6 (1,8)	3,0 (2,5)	0,312
NLR *M* (*IQR*)	1,3 (2,0)	1,4 (1,2)	0,620
P x ± *sd*	229,81±70,58	212,61±61,23	0,159
M *M* (*IQR*)	0,6 (0,8)	0,7 (0,9)	0,831
SII *M* (*IQR*)	327,7 (464,3)	314,7 (310,6)	0,802
SIRI *M* (*IQR*)	0,6 (1,8)	0,9 (1,7)	0,523
PIV *M* (*IQR*)	160,7 (458,7)	190,2 (373,1)	0,688
At 72 h			
N *M* (*IQR*)	3,8 (6,0)	2,4 (2,1)	0,079
L *M* (*IQR*)	3,0 (2,7)	2,8 (1,6)	0,738
NLR *M* (*IQR*)	1,3 (2,1)	0,9 (1,1)	0,9 (1,1)
P x ± *sd*	205,0 (128,0)	192,0 (105,0)	0,381
M *M* (*IQR*)	0,5 (0,9)	1,1 (0,9)	**0,008**
SII *M* (*IQR*)	262,5 (629,2)	178,0 (296,2)	**0,044**
SIRI *M* (*IQR*)	0,7 (2,7)	1,1 (1,6)	0,627
PIV *M* (*IQR*)	128,8 (471,2)	187,5 (284,7)	0,916

$\bar{x}$: mean, *sd*: Standart Deviation, *M*: Median, *IQR*: Inter Quartile Range, *t*: Independet Sample t test, *z*: Mann Whitney U test Abbreviations: N, neutrophil; L, lymphocyte; M, monocyte; P, platelet; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value

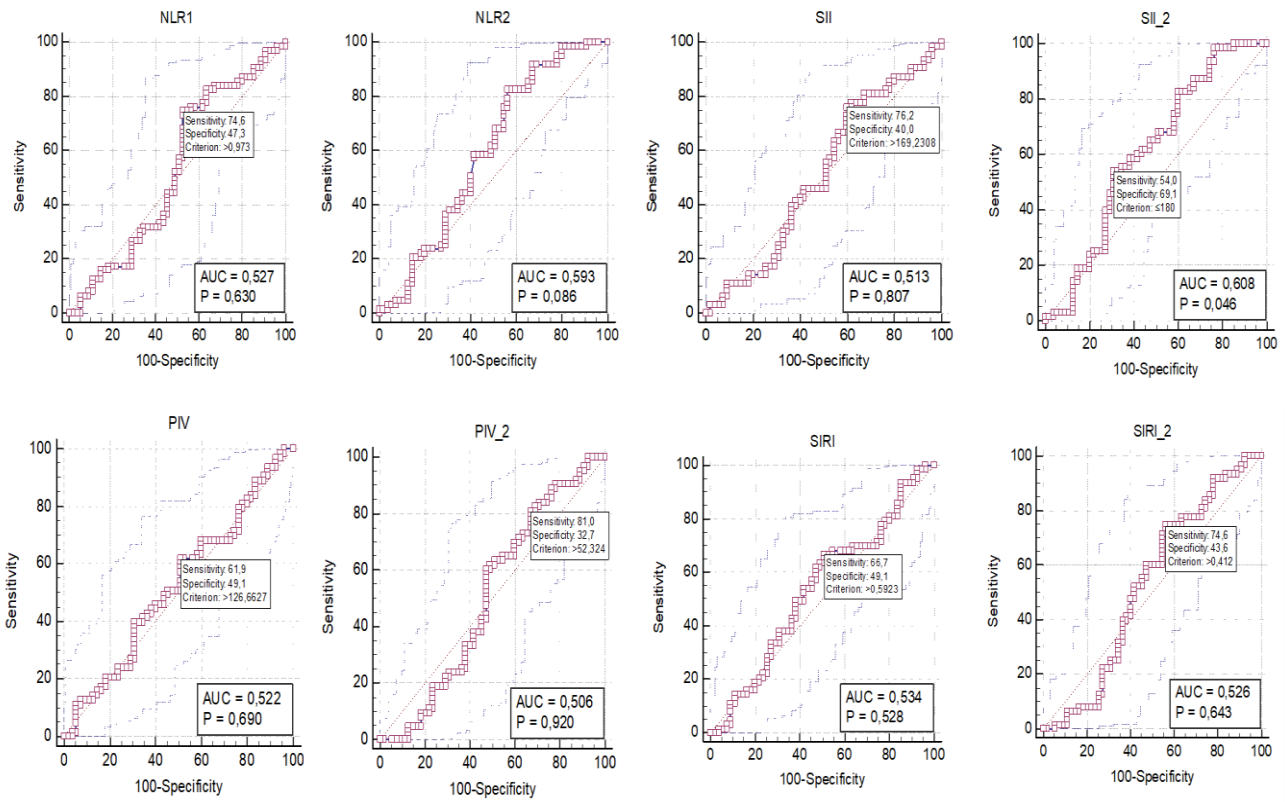
Regarding the ROC analysis, the AUCs for the SII at 72nd h was 0.608 with a sensitivity of 53.97% and specificity of 69.09%, and the cut-off value in predicting BPD was lower than 180 (Table 3, Fig. 1).

Table 3: Sensitivity, specificity, and AUC of NLR, SII, SIRI, and PIV in infants with BPD

	AUC	*p*	95% CI		Sensitivity	Specifity	Cutoff value
			Lower	Upper			
NLR1	0,527	0,629	0,433	0,619	74,60	47,27	>0,973
NLR2	0,593	0,086	0,499	0,683	82,54	43,64	≤1,8
SII	0,533	0,806	0,420	0,606	76,19	40,00	>169,23
SII2	0,608	**0,045**	0,513	0,696	53,97	69,09	≤180
SIRI	0,534	0,527	0,440	0,627	66,67	49,09	>0,59
SIRI2	0,526	0,643	0,432	0,618	74,60	43,64	>0,41
PIV	0,522	0,690	0,428	0,614	61,90	49,09	>126,66
PIV2	0,506	0,919	0,412	0,599	80,95	32,73	>52,32

Abbreviations: AUC, area under curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value. 1; at birth, 2; at 72h

Figure 1. Sensitivity, specificity, and AUC of NLR, SII, SIRI, and PIV in infants with BPD



Abbreviations: AUC, area under curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; SII,systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value. 1; at birth, 2; at 72h

Discussion

In this study, we found SII at the 72nd hour to be an early indicator of BPD in preterm infants. Additionally, we found that the BPD group's monocyte count at the 72nd hour was significantly lower. This is the first study in the literature in which systemic inflammatory indices were used to predict BPD in preterm infants.

Bronchopulmonary dysplasia remains the most important chronic lung disease of the preterm infant, and inflammation plays an important role in pathogenesis. Early pulmonary inflammation is known as the key factor in BPD pathogenesis (15,16). Thus, the association between inflammatory cells and BPD has been investigated in recent studies (17,18). It has been shown that polymorphonuclear cells, macrophages, platelets, and proinflammatory cytokines indicate early inflammation after high oxygen exposition with initial lung injury. Due to the long-term effects of BPD, many biomarkers, scoring systems, and even the latest artificial intelligence have been used so far for early diagnosis and development of preventive strategies (19,20). However, these tests are not included in routine examinations and are not easily accessible.

There is still a need for early biomarkers for preventive strategies.

In adult studies, the absolute counts of white blood cells, neutrophils, lymphocytes, and their ratios have been shown to reflect chronic inflammatory diseases. Especially, NLR seems to be the most used systemic inflammatory marker. In a recent study, serum NLR values were found significantly lower in the BPD group of infants when compared to the non-BPD at birth. They have found NLR as an independent risk factor for BPD (21). Sun et al. studied serum NLR values of preterm infants at birth and 72nd hour to examine the association with BPD. They have claimed that an increase in serum NLR at the 72nd hour could be a predictor of BPD (22). We calculated serum NLR values at birth and 72nd hour, and we found NLR at the 72nd hour significant at borderline (p= 0.086) but we found no statistically significant difference in NLR values between BPD and non-BPD infants.

In our study, we only found the N count higher at the 72nd hour in the BPD group, but it was not significant. In a recent study, serum neutrophil count ≥4,141/µL at birth had an AUC of 0.83, a sensitivity of 56 %, and a specificity of 90% for predicting BPD in infants. Sun et al. have found the N count in the BPD group significantly increased at birth and the 72nd hour (22).

Monocytes are subtypes of leukocytes and are an essential part of the innate immune system. They play an important role in the inflammatory response, and MLR values have been studied as inflammation markers. Some studies have shown a decrease in monocytes in COVID-19 patients. Similarly, we found the monocyte count was significantly lower in the BPD group.

The systemic immune-inflammation index is a novel parameter that reflects the immune and inflammatory status which is a combination of platelets, neutrophils, and lymphocytes. It is associated with clinical outcomes and prediction of the prognosis of several solid tumors (23). Based on its role in inflammation-related events, studies about SII's role in COVID-19 or hypoxic-ischemic encephalopathy have been carried out (24,25). We found that the AUCs for the SII at the 72n^{d} hour was 0.608 with 53.97% sensitivity and 69.09% specificity, and the SII at the 72nd hour could predict BPD.

The study results must be interpreted within its limitations. First, the study was a single-center, retrospective, observational study. Therefore, the potential for residue confounding could not be ruled out. The results must be confirmed by multicenter studies. Second, we did not evaluate the other conventional inflammatory markers, such as CRP or procalcitonin, nor examine the correlations of these parameters with N count and the NLR. And finally, it can be said that preterm birth is a stress factor in itself triggering inflammation but we have also the control group with similar characteristics without BPD.

Anything that can be used for the early diagnosis will help identify high-risk patients early and determine treatment options for them. Based on the precursor role of inflammation in the development of BPD, we inquired whether there is a diagnostic or prognostic effect of systemic inflammatory indices. To summarize, systemic inflammatory indices are practical, affordable, and easily available tools derived from serum complete blood cell counts that could be used for BPD early diagnosis and prevention.

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