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Nötrofil/Lenfosit Oranı, RDW, RPR, MPV ve MPR Hemogram İndekslerinin Febril Nöbet Tanısına Katkısı

Contribution of Neutrophil/Lymphocyte Ratio, RDW, RPR, MPV and MPR Indexes to Febrile Seizure Diagnosis

Turgay Çokyaman (0000-0002-7108-6839)[1], Tolga Kasap (0000-0002-1046-7638)[2]

[1]Çanakkale Onsekiz Mart Universitesi, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Çocuk Nöroloji Bilim Dalı, Çanakkale

[2]Çanakkale Onsekiz Mart Universitesi, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Çanakkale

Sorumlu yazar yazışma adresi:

Turgay ÇOKYAMAN: Çanakkale Onsekiz Mart Universitesi, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Çocuk Nöroloji Bilim Dalı, Çanakkale, Türkiye

E-mail: drturgay@comu.edu.tr

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ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada nötrofil/lenfosit oranı (NLR), kırmızı kan hücresi dağılım genişliği (RDW), RPR, MPR, ortalama trombosit hacmi (MPV), trombosit sayısı (PLT) gibi hemogram indekslerinin febril nöbet (FS) tanısına katkısının ayrıntılı olarak araştırılması amaçlandı.

YÖNTEM ve GEREÇLER: Çalışmaya 91 FS, 116 ateşli hastalık ve 100 sağlıklı kontrol olgusu dahil edildi. Yerine göre uygun istatistiksel analizlerle ikili ve üçlü grup karşılaştırmaları sonucu FS lehine anlamlı hemogram indeksleri tespit edildi ve ROC eğrisi analizine göre FS tanısı için tanı koydurucu sınır değerleri, duyarlılık ve özgüllükleri hesaplandı.

BULGULAR: NLR indeks FK grubunda anlamlı düzeyde yüksekti. FK grubunda median 2,6, ateşli hastalık ve sağlıklı kontrol grubunda sırasıyla 1,6 ve 0,7 bulundu (p<0,001). ROC eğrisi analizinde FK tanısı için NLR indeksinin sınır değerleri, duyarlılık ve özgüllükleri belirlendi. 1/RPR indeksi FK vakalarında istatistiksel olarak anlamlı düzeyde düşük bulundu. FK grubunda 20,5, ateşli hastalık ve sağlıklı kontrol gruplarında sırasıyla 23,3 ve 23,2 bulundu (p=0,003). NLR'ye benzer şekilde RPR indeks içinde ROC eğrisi analizinde FK tanısı için sınır değerleri, duyarlılık ve özgüllükleri hesaplandı.

TARTIŞMA ve SONUÇ: NLR ve 1/RPR indeksleri, FS tanısına katkıda bulunabilecek ucuz ve kolay erişilebilir hemogram parametreleridir. Acil servislerde ve ayaktan tedavi kliniklerinde pratisyen hekim ve pedyiatristler tarafından kolayca kullanılabilirler.

Anahtar Kelimeler: febril nöbet, hemogram, indeks, çocuk

ABSTRACT

INTRODUCTION: In this study, it was aimed to investigate in detail the contribution of hemogram indices such as neutrophil/lymphocyteratio (NLR), red blood cell distribution width (RDW), RPR, MPR, mean platelet volume (MPV), and platelet count (PLT) to the diagnosis of febrile seizure (FS).

MATERIALS and METHODS: 91 FS, 116 febrile disease and 100 healthy control cases were included in the study. Significant hemogram indices in favor of FS were determined as a result of double and triple group comparisons with appropriate statistical analyzes, and diagnostic cut-off values, sensitivity and specificity were calculated for FS diagnosis according to receiever operating characteristic (ROC) curve analysis.

RESULTS: NLR index was significantly higher in the FS group. The median was 2.6 in the FS group, 1.6 and 0.7 in the febrile disease and healthy control groups, respectively ($p<0.001$). In the ROC curve analysis, thecut-off values, sensitivity and specificities of the NLR index for FS diagnosis were determined. The 1/RPR index was found to be statistically significantly lower in FS group. It was found to be 20.5 in the FS group, 23.3 and 23.2 in the febrile disease and healthy control groups, respectively ($p=0.003$). Similar to the NLR, cut-off values, sensitivity and specificities were calculated for FS diagnosis in the ROC curve analysis within the 1/RPR index.

CONCLUSIONS: NLR and 1/RPR indexes are cheap and easily accessible hemogram parameters that can contribute to the diagnosis of FS. They can be used simply by practitioners and pediatricians in emergency rooms and out patient clinics

Key words: febrile seizure, hemogram, index, children

INTRODUCTION

Febrile seizure (FS) is defined by the International League Against Epilepsy as convulsions observed during febrile disease with no central nervous system infection or any other pathological condition (electrolyte imbalance, metabolic derangement, intoxication or trauma) in children between 1 months to 5 years with no history of previous afebrile convulsion [1]. FS is the most common type of convulsion observed in children, generally has a benign course and heals without sequelae in cognitive or motor functions [2].

Inflammatory mechanisms, especially proinflammatory cytokines such as IL-1β, IL-6 and TNF-α have been emphasized in the FS pathophysiology [3]. Blood cell proportions and functional properties change under the influence of these cytokine levels increasing in peripheral blood. Erythrocyte, neutrophil and platelet counts rise and their cellular volumes change to enhance their functional capacity [4]. In this context, leukocyte count, neutrophil-lymphocyte count ratio (NLR), platelet count (PLT), mean platelet volume (MPV) and red blood cell distribution width (RDW) in peripheral blood are certain hemogram indexes that can be used as inflammation indicators [5,6]. NLR increases as an indicator of systemic inflammatory response, especially in heart disease, hepatic fibrosis, diabetes mellitus and some malignancies [7]. Similarly, RDW increases in sepsis, chronic liver disease, cerebrovascular diseases and some cancers, in conjunction with inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [8]. In addition to these parameters, thrombocyte count also rises in infectious and non-infectious inflammatory cases. MPV is the index of platelet function and reflects thrombocyte production rate in bone marrow. MPV was shown to decrease (inversely proportional to inflammation) in systemic inflammatory diseases like inflammatory bowel diseases, rheumatoid arthritis and ankylosing spondylitis [9].

The majority of FS's happen at home or en route to the hospital and diagnosis essentially depends on the anamnesis obtained from the parents. However, FS causes serious anxiety and fear in parents, which results in weakening of anamnesis trustworthiness and contribution to diagnosis [10]. The number of cases suspected in the diagnosis of FS is not low in the presence of information with low reliability from anamnesis. Events such as hyporesponsive state, cutis marmorata, febrile reaction, breath holding spell and perioral cyanosis can be seen during fever in children and can be conveyed to the physician as seizure [11]. This naturally leads to physicians ordering unnecessary blood and other laboratory tests.

Hemogram, which is cheap and easily accessible, is the foremost test used in FS. On the hemogram, parameters such as leukocyte, PLT and RDW are evaluated as markers of the inflammatory response. Indexes like NLR, RDW/PLT ratio (RPR) and MPV/PLT ratio (MPR) are frequently overlooked. There is limited literature about these indexes that are usually disregarded in FS. In this context, the aim of this study is to evaluate the contribution of these rarely-used indexes to the diagnosis of FS.

MATERIALS and METHODS:

Patient selection: This study was conducted in the pediatric neurology outpatient clinic of a tertiary university hospital. Digital medical files of patients between 5 months< - >72 months of age were evaluated retrospectively. Cases who applied between 01 January 2018 and 31 December 2019 and with routine hemogram examination performed within the first 24 hours were included in the study. Design of working groups were those diagnosed with 1; FS, 2; febrile disease but not FS (FD) and 3; healthy controls (HC). Children with no previous history of afebrile seizures and who had generalized seizures within the first 3 days after the onset of febrile illness were accepted as simple FS and were included in the study. Focal, seizures lasting more than 15 minutes and repeated more than once in 24 hours were defined as complex FS and these cases were also included in the study.Cases with symptoms such as fever, sore throat, nasal obstruction, tonsillitis and pharyngitis, only those diagnosed with viral upper respiratory tract infection, were included in the PD group.

While simple and complex FS cases were included in this study, febrile status epilepticus cases were not included. Patients with neurological problems such as cerebral palsy, epilepsy, global developmentaldelayorintellectualdisabilityand those with a central nervous system infection and suspicion of bacterial infection (high CRP and ESR) were not included in the FS group. Bacterial otitis, urinary tract infection and vaccine-related FS cases were also excluded.

High clinical suspicion of bacterial infection (together with high CRP and ESR) or those with central nervous system, lower respiratory system, gastrointestinal system and urinary tract infections were excluded in the FD group.

Patients with a history of afebrile seizure, head trauma, haematological disease, those using antiepileptic drugs and neurologic developmental delay and sepsis were also excluded.

Recording hemograms and calculating indexes: Hemograms extracted into an EDTA tube within the first 24 hours of FS or FD were included in the study and the cases were coded according to the order of application to the clinic and recorded. Total white blood cell count (WBC), red blood cell count (RBC), haemoglobin (HB), haematocrit (HCT), mean corpuscular volume (MCV), RDW, PLT, MPV, neutrophil and lymphocyte count data were recorded. In addition, CRP levels viewed simultaneously with the hemogram were recorded. NLR index was calculated by dividing absolute neutrophil count by absolute lymphocyte count.

The RPR index was calculated by dividing RDW by PLT. Since RPR index takes very small values such as 0.00 in normal calculations, RPR^{-1} (1/RPR) is presented for easy understanding.

The MPR index was calculated by dividing MPV by PLT. Since MPR index takes very small values such as 0.00 in normal calculations, MPR^{-1} (1/MPR) is presented for easy understanding.

Statistical analysis: Statistical analysis was performed by using the SPSS Statistics 19.0 for Windows (SPSS Inc., Chicago, IL, USA) program. The categorical data were expressed as numbers and

percentages; the numerical data were expressed as mean ± standard deviation and median according to the appropriate place. When appropriate, χ^2-test was used for the comparison of categorical data. If the numerical data fit to normal distribution, they were evaluated with the independent samples *t*-test. The Mann-Whitney U-test was used for evaluation of numerical data without normal distribution. One-way ANOVA or Kruskal Wallis-test was used according to the suitability of numerical data for triple group comparisons.

Receiver operating characteristic (ROC) curve analysis was used to calculate the optimal cut-off values, sensitivity, and specificity of NLR and RPR^{-1}. Significant associations were defined as *P value*< 0.05.

Ethical approval: Informed consent was obtained from the parents of children included in this study. Ethical approval was also obtained from the local ethics committee of the university (Ethical approval was received on 26.08.2020 with file number E.1900184278).

RESULTS:

Demographic characteristics of study groups: During the study period, digital medical files of 307 cases were analyzed retrospectively. Of these cases, 91 were FS, 116 were FD and 100 were HC. Mean ages were 3.2±1.0, 3.2±1.0 and 3.4±0.5 respectively (p=0.099). Male/female ratios were also 47/44 (1.06), 74/42 (1.76) and 50/50 (1.0) respectively (p=0.082). There were no significant differences between the groups regarding age and gender. Demographic data of FS, FD and HC groups are presented in Table-1.

Table-1: Demographiccharacteristics of thestudypopulation. Valuesareexpressed as mean ± standarddeviationormedian (range) depending on suitability.

Variables	**FS**	**FD**	**HC**	***P value***
Age (years)	3,2±1,0	3,2±1,0	3,4±0,5	KWT 0,099
Male/femaleratio	47/44 (1.06)	74/42 (1.76)	50/50 (1.0)	PCS 0,082

FS: febrileseizure, FD: febriledisease, HC: healthycontrol, PCS: Pearsonchi-square test, KWT: Kruskal-Wallis test.

Hemogram results and correlations of NLR, RPR^{-1} and MPR^{-1} indexes with FS: The mean ±SD and median (maximum-minimum) values of the hemogram indexes in the study groups are presented in Table-2. According to this table, the highest WBC was found in the FD group ($14.1x10^3/mm^3$ ±7.3) and the lowest in the HC group ($8.3x10^3/mm^3$ ±1.8) (p<0.001). WBC was $12.6x10^3/mm^3$ ±5.1 in the FS group, and this value was lower than the FD group (p=0.274) but higher than the HC group (p<0.001). RBC, HB and HCT values were consistently high in the HC group, but were not different between MCV groups. RDW was found as 15.0% ±2.1 and 14.9% ±2.0 in FS and FD groups, respectively, and there was no statistical difference (p=0.601).

Tablo-2: Hemogram results of the groups and NLR, RPR^{-1} and MPR^{-1}index rates.

Hemogram parameters	**FS (n=91), simple FS 82%, complex FS 18%**	**FD (n=116)**	**HC (n=100)**	***P value***
WBC (x103 mm3)	12.6±5.1	14.1±7.3	8.3±1.8	KWT p<0.001
				FS-FD p=0.274, FS-HC p<0.001, FD-HC p<0.001 MWU
RBC (x106 /mL)	4.4±0.3	4.4±0.4	4.6±0.3	ANOVA p=0.002
				FS-FD p=0.636, FS-HC p=0.001, FD-HC p=0.003 post hoc LSD
HB (g/dL)	11.3±1.0	11.2±1.1	12.3±0.7	ANOVA p<0.001
				FS-FD p=0.666, FS-HC p<0.001, FD-HC p<0.001 post hoc LSD
HCT (%)	33.7±2.7	33.9±3.2	35.9±2.1	ANOVA p<0.001
				FS-FD p=0.564, FS-HC p<0.001, FD-HC p<0.001 post hoc LSD
MCV (fL)	75.3±5.0	75.7±6.6	77.0±4.2	KWT p=0.063
RDW (%)	15.0±2.1	14.9±2.0	13.9±0.9	KWT p<0.001
				FS-FD p=0.601, FS-HC p<0.001, FD-HC p=0.001 MWU
PLT ($x10^6$/mL)	305±108	334±114	323±70	KWT p=0.044
				FS-FD p=0.028, FS-HC p=0.036, FD-HC p=0.501 MWU
MPV (fL)	7.4±0.8	7.4±0.8	7.6±0.7	KWT p=0.381
Neutrophil count (/mm^3)	8036±4916	8004±6337	3265±1191	KWT p<0.001
				FS-FD p=0.405, FS-HC p<0.001, FD-HC p<0.001 MWU
Lymphocyte count (/mm^3)	3309±2084	4275±2271	4136±1258	KWT p<0.001
				FS-FD p=0.001, FS-HC p<0.001, FD-HC p=0.721 MWU
NLR	Median 2.6 (max 21.5-min 0.09) Mean 4.0	Median 1.6 (max 18.7-min 0.1) Mean 2.6	Median 0.7 (max 2.8-min 0.2) Mean 0.8	KWT **p<0.001**
				FS-FD p=0.006, FS-HC p<0.001, FD-HC p<0.001 MWU
RPR^{-1}	20.5±7.4	23.3±9.5	23.2±5.3	KWT **p=0.003**
				FS-FD p=0.016, FS-HC p<0.001, FD-HC p<0.542 MWU
MPR^{-1}	42.2±18.1	45.6±17.6	43.3±12.6	KWT p=0.157
CRP	Median 0.8 (max 15-min 0.1)	Median 1.9 (max 34-min 0.1)	Median 0.1 (max 0.5-min 0.1)	KWT p<0.001
				FS-FD p<0.001, FS-HC p<0.001, FD-HC p<0.001 MWU

WBC: White blood cel lcount, RBC: red blood cell count, HB: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, RDW: red blood cell distribution width, PLT: platelet count, MPV: mean platelet volume, NLR: neutrophil/lymphocyte count ratio, RPR^{-1}(converted from RPR, 1/RPR): RDW/PLT, MPR (converted from MPR, 1/MPR): MPV/PLT, CRP: c-reactive protein, KWT: Kruskal-Wallis test, MWU: Mann Whitney U test.

However, RDW of 13.9% ±0.9 was found in the HC group and the difference with other groups was significant (FS-HC; p<0.001 and FD-HC; p=0.001). The PLT count was slightly lower in the FS group than in the other groups ($305x10^6$/mL ±108), and this difference was significant compared to the FD and HC groups (respectively p=0.028 and p=0.036). MPV index was not different between the groups (p=0.381). Neutrophil counts were detected to be highest in the FS group (8036/mm^3 ±4916) and it was 8004/mm^3 ±6337 in the FD group which was not different from FS (FS-FD; p=0.405). The lowest neutrophil counts were detected in the HC group and were significantly lower than FS and FD (FS-HC; p<0.001, FD-HC; p<0.001). Lymphocyte counts were highest in the FD group (4136/mm^3 ±1258) and lowest in the FS group (3309/mm^3 ±2084). The low lymphocyte count in the FS group was different from the other groups (FS-FD; p=0.001, FS-HC; p<0.001, FD-HC; p=0.721). It was observed that the NLR index tended to increase in FS and the highest rate was in the FS group (median 2.6, range 21.5-0.09). It had a lower rate in the FD group (median 1.6, range 18.7-0.1) and in the HC group (median 0.7, range 2.8-0.2). NLR index differences between the groups were significant (FS-FD; p=0.006, FS-HC; p<0.001, FD-HC; p<0.001). It was observed that the RPR^{-1} index tended to decrease in the FS group and was 20.5±7.4 in FS, 23.3±9.5 in FD and 23.2±5.3 in HC groups. Low RPR^{-1} index in FS group was different than FD and HC groups (FS-FD; p=0.016, FS-HC; p<0.001, FD-HC; p=0.542). The MPR^{-1} index was not different between groups (p=0.157).

ROC curve analysis and sensitivity and specificity of NLR and RPR^{-1} for FS: According to ROC curve analysis to differentiate between FS and FD (Table-3, Figure-1), the optimal cut-off value for NLR was found to be 2.0 (58% sensitivity, 58% specificity, AUC: 0.611). An optimal NLR cut off value of 1.1 was found to differentiate between FS and HC (76% sensitivity, 82% specificity, AUC: 0.801).

According to ROC curve analysis for differentiation between FS and FD (Table-3, Figure-1), the optimal cut-off value for RPR^{-1} was 21.0 (59% sensitivity, 59% specificity, AUC: 0.597). An optimal RPR^{-1} cut off value of 21.1 was found for FS and HC (59% sensitivity, 59% specificity, AUC: 0.648).

Table-3: Receiver operating curve analysis results of NLR and $RPR^{-1}$to distinguish between FS and FD-HC.

Compared groups	**Index**	**AUC (%95)**	**Cut-off**	**Sensitivity**	**Specificity**	***P value***
FS-FD	NLR	0.611 (0.532-0.689)	1.82	62%	53%	0.006
FS-HC	NLR	0.801 (0.730-0.872)	1.37	76%	82%	<0.001
FS-FD	RPR^{-1}	0.597 (0.520-0.675)	21.37	60%	58%	0.016
FS-HC	RPR^{-1}	0.648 (0.569-0.727)	21.59	63%	55%	<0.001

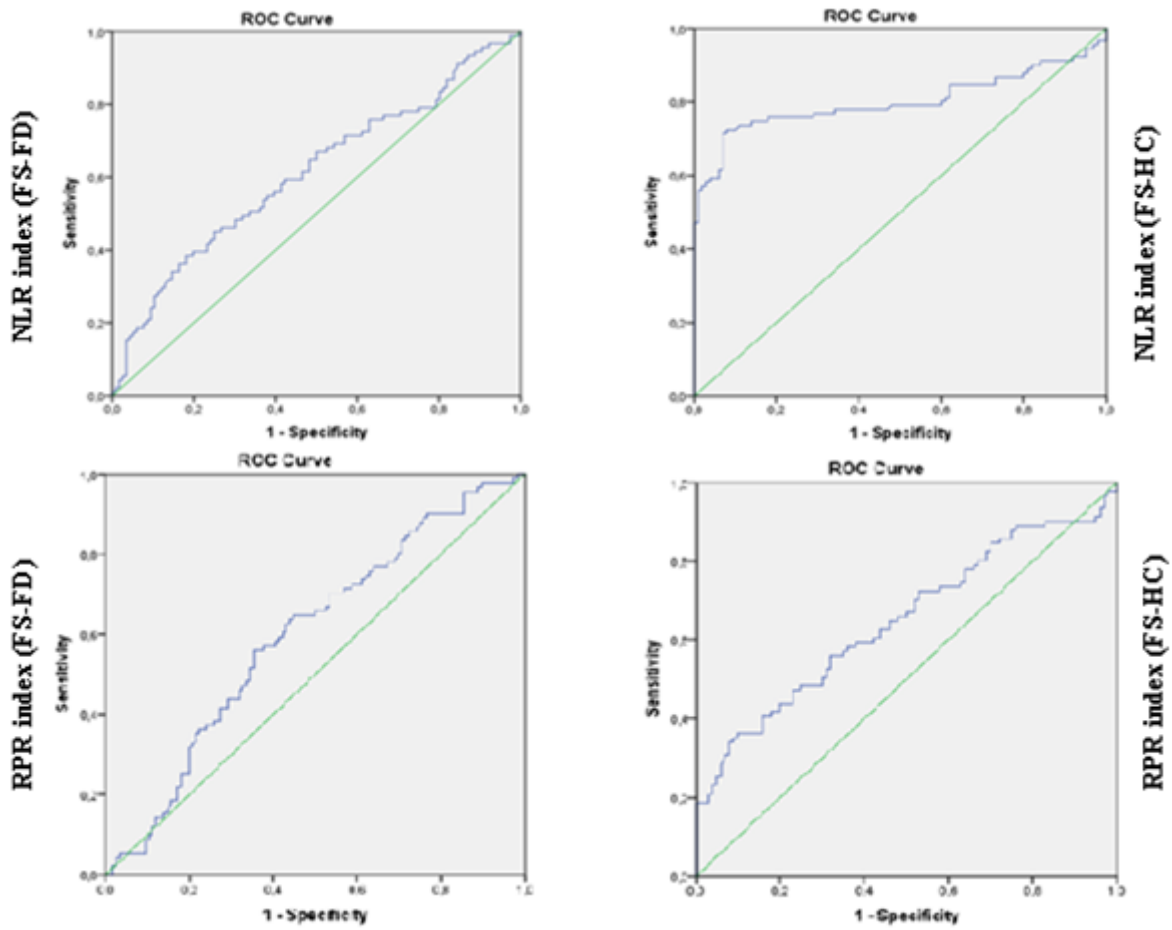

Figure-1: ROC curve analysis results of NLR and $RPR^{-1}$to distinguish between FS and FD-HC.

DISCUSSION

Our main purpose in this study was to define the peripheral blood markers of FS and determine the importance of objective hemogram indexes such as NLR, RPR^{-1} and MPR^{-1} in order to achieve diagnosis of FS more precisely. As a result of this study, we determined that NLR and RPR^{-1} indexes can be used by paediatricians and paediatric neurologists to differentiate FS, but we found that MPR^{-1} cannot be used for this distinction.

NLR is a measure of the ratio of peripheral blood neutrophils and lymphocytes and may be used as an emerging new hemogram index that reflects various inflammatory diseases. When we look at the pathophysiology of FS, neutrophilia in peripheral blood is linked to increased proinflammatory cytokine, adrenaline and cortisol during a seizure. These mediators that emerge from the resulting excessive sympathetic activity increase neutrophil diapedesis from bone marrow [12,13]. In our study, the NLR index was found statistically significantly higher in FS (NLR 2.6 for FS, Table-2). According to ROC

analysis, a cut-off value of 2.0 was found for FS-FD distinction, and a cut-off value of 1.1 was found for FS-HC (Table-3, Figure-1). In some previously reported studies, NLR was found to be close to the rate in our study. Goksugur et al. (2014) found NLR was 2.18 for simple FS, 3.89 for complex FS, while Yigit et al. (2017) found values of 2.38 in simple FS and 3.42 in complex FS [14,15]. In both of these studies, NLR was evaluated for the simple and complex FS distinction. However, no comparison was made according to those with febrile disease without FS or healthy control cases, and in fact this is a severe limitation for these studies. In practice FS is often confused with other clinical conditions with or without fever. Moreover, due to the design of these studies, the simple and complex FS ratios seem to be high (Goksugur et al. found simple/complex FS ratio 60%/40% and Yigit et al. 64%/36%). However, according to our current information, 70-75% of FS cases are simple and 25-30% of them are complex [16]. Therefore, the simple/complex FS ratio in these two studies overshadowed the randomization of case selection. From this aspect, it is clear that NLR, which we found in our study, will provide a more accurate estimate for FS diagnosis because we compared with both febrile illness and healthy control cases.

Liu et al. (2018) found the mean NLR was 3.2 in their studies comparing FS and healthy control cases [17]. In this study, neutrophilia compatible with the literature was observed in FS cases, but the expected moderate increase in leukocyte count was not shown. Therefore, the fact that higher NLR was found compared to our study can be explained by the absence of moderate peripheral leucocytosis in FS cases reported by Liu et al. Romanowska et al. (2017) found that peripheral blood neutrophil counts were high and lymphocyte counts were significantly lower in FS cases compared to febrile patients [18]. Although NLR was not reported in this study, the ratio appears to be high in favour of FS. However, in this study, the absence of healthy control cases is an important handicap because the CRP values of the control group were found to be very high.

RPR index is measured by dividing RDW by PLT; however, we used the RPR^{-1} index to make it more understandable in our study. In our study, unlike the previous ones, the relationship between the RPR^{-1}index and FS was investigated for the first time. RDW describes size variations in red blood cellsand has been widely used in investigating the aetiology of anaemia [19]. There was a close correlation with inflammatory markers such as CRP, ESR, and proinflammatory cytokines in various diseases [20]. Infectious diseases are the most common cause of thrombocytosis in children under 5 years of age [21]. Due to increased pro-inflammatory cytokines, there is reactive thrombocytosis in peripheral blood, but MPV decreases inversely [22]. RDW was found to be higher in complex FS cases compared to simple ones in the study by Goksugur et al., but PLT was not different. Yigit et al. did not show any difference between RDW and PLT in simple and complex FS. Liu et al. did not detect RDW differences between FS and healthy control cases in their study. Interestingly, the same study showed that PLT is lower in FS. In our study, RPR^{-1} index was found to be significantly lower in the FS group. In FS and FD groups accompanied by inflammation, RBC, HB, HCT, and MVC decreases, while RDW was slightly increased. There is a significant correlation between IL-1β, IL-6, TNF-α and impaired oxidative balance and RDW

in chronic inflammatory processes. It is not easy to explain RDW changes in a disease such as FS, in which acute inflammation plays a role in its generation [23]. The high RDW in hypertensive patients was linked to chronic inflammation, the low RPR index in our study is more related to lower PLT than acute inflammation.

Hemogram indexes may be affected by factors such as brand and quality of the devices used in laboratories, measurement methods and the skill of the laboratory workers. It can also be influenced by personal factors such as the time of day the blood sample is taken, hunger-satiety, gender, and body weight. In addition, it is clear that hemogram indexes may also be affected by factors such as cytokines, hormones, and neurotransmitters in chronic or acute inflammation.

As a result, in this study, where features such as age and gender were excluded, it was revealed that NLR and RPR^{-1} are hemogram indexes that can assist with FS diagnosis. In a disease accompanied by acute inflammation such as FS, further randomized studies with larger case numbers where simultaneous proinflammatory cytokines, adrenaline, cortisol and may be oxidative balance are measured are needed to increase the diagnostic reliability of indexes such as RDW, NLR, RPR, and MPR.

Conflict of Interest: We declare that there is no conflict of interest.

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