Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1159549

J Med Palliat Care 2022; 3(3): 221-227

Should we have any predictive marker for estimating the severity of community-acquired pneumonia at admission?

Başvuru sırasında toplum kökenli pnömoninin ciddiyetini tahmin etmek için herhangi bir prediktif belirtecimiz olmalı mı?

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Cite this article as/Bu makaleye atıf için: Hangül M, Köse M, Pür H, et al. Should we have any predictive marker for estimating the severity of community-acquired pneumonia at admission?. J Med Palliat Care 2022; 3(3): 221-227.

ABSTRACT

Aim: Community-acquired pneumonia (CAP) is a disease that affects children. One hundred fifty-five million children under five years are diagnosed with pneumonia yearly, 20 million are hospitalized, and 2 million die. Early diagnosis and severity assessment reduce mortality and morbidity. This study aimed to determine the effect of basic hemogram parameters, neutrophil-lymphocyte ratio (NLR), immature (IG) granulocyte, immature granulocyte percentage (IG%), C-reactive protein (CRP), and oxygen saturation.

Material and Method: This case-control study was conducted between November 2018 and May 2019 at Erciyes University School of Medicine in the Department of Paediatric Pulmonology. Sixty-nine patients diagnosed with CAP had enrolled in the study by clinical and radiological findings. The patients were classified into two subgroups: mild-to-moderate pneumonia and severe pneumonia. The CAP severity of the disease was determined using the criteria indicated for children by the British Thoracic Society. Univariate analysis was used to identify independent factors that affect the severity of pneumonia.

Results: Pneumonia was mild-moderate in 46.3% (n=32/69) patients. Pneumonia was severe in 63% (n=37/69) of patients. Leukocytes, neutrophils, IGn, IG%, and saturations of these two groups were compared. There was a statistically significant difference between the two groups (p 0.05). However, there was no statistically significant difference in lymphocyte count, NLR, or CRP (p>0.05). Leukocytes, neutrophils, IGn, IG%, and saturation significantly predicted pneumonia severity (p<0.05).

Conclusion: Our studies show that increased IGn, IG%, and decreased oxygen saturation are related to severe outcomes in children with pneumonia. They may be effective parameters in determining the severity of pneumonia.

Keywords: Community-acquired pneumonia, children, immature granulocyte, oxygen saturation, disease severity

ÖZ

Amaç: Toplum kökenli pnömoni (TKP), çocukları etkileyen önemli bir hastalıktır. Her yıl beş yaş altı yüz elli beş milyon çocuğa zatürre teşhisi konmakta, 20 milyonu hastaneye kaldırılmakta ve 2 milyonu ölmektedir. Erken tanı ve şiddet değerlendirmesi mortalite ve morbiditeyi azaltır. Bu çalışmada temel hemogram parametreleri, nötrofil-lenfosit oranı, immatür granülosit, immatür granülosit yüzdesi, CRP ve oksijen satürasyonunun hastalık şiddetine etkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu vaka-kontrol çalışması, Kasım 2018-Mayıs 2019 tarihleri arasında Erciyes Üniversitesi Tıp Fakültesi Çocuk Göğüs Hastalıkları Anabilim Dalı'nda yürütülmüştür. Klinik ve radyolojik bulgulara göre TKP tanısı konan altmış dokuz hasta çalışmaya dahil edildi. Hastalar hafif-orta pnömoni ve şiddetli pnömoni olmak üzere iki alt gruba ayrıldı.

Bulgular: Hafif-orta pnömonisi (%32/46,3) ve şiddetli pnömonisi (%37/53,6) olan hastaların lökosit, nötrofil, IGn, IG% ve satürasyonu karşılaştırıldı. İki grup arasında istatistiksel olarak anlamlı fark vardı (p 0,05). Ancak lenfosit sayısı, nötrofil lenfosit oranı (NLO) veya CRP'de istatistiksel olarak anlamlı bir fark yoktu (p>0,05). Pnömoninin şiddetini etkileyen bağımsız faktörleri belirlemek için tek değişkenli analiz kullanıldı. Lökositler, nötrofiller, immatür granülosit, immatür granülosit yüzdesi ve saturasyon, pnömoninin şiddetini öngörmede önemli bir etkiye sahipti (p<0,05).

Sonuç: Çalışmamız, artan immatür granülosit, immatür granülosit yüzdesi % ve azalmış oksijen satürasyonunun pnömonili çocuklarda ciddi sonuçlarla ilişkili olduğunu göstermektedir. Pnömoninin şiddetini belirlemede hastaneye başvuruda bu parametreler etkili olabilirler.

Anahtar Kelimeler: Toplum kökenli pnömoni, çocuklar, immatür granülosit, oksijen satürasyonu, hastalık şiddeti

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Received/Geliş: 08.08.2022 **Accepted/Kabul:** 11.09.2022

INTRODUCTION

A clinical diagnosis of community-acquired pneumonia (CAP) in a previously healthy child is described as pneumonia caused by an infection obtained outside the hospital (1). CAP is a disease that affects children all over the world and has a high mortality and morbidity rate (2). World Health Organization estimates that 155 million children under the age of five are diagnosed with pneumonia each year. Over 20 million are hospitalised, and more than 2 million children die from pneumonia (3). As a result, it is critical to detect the disease early and identify the severity of the condition so that mortality and morbidity can be decreased.

Many research has been conducted to investigate the predictive usefulness of serum inflammatory biomarkers such as white blood cells (WBC) and their subtypes, C-reactive protein (CRP), procalcitonin (PCT), interleukin-8, interferon-alpha, tumor necrosis factor, and kallsitatin, endocan, Mid-regional proadrenomedullin (MR-proADM), and kopeptin in CAP patients. Additionally, since some of these indicators are very costly and difficult to get, there is still a need for simple, specific, generally accessible, and affordable biomarkers in pneumonia patients (4-9).

Nowadays, in blood samples taken from peripheral blood, next-generation analyzers can automatically and extremely correctly count and assess the genuine immature granulocyte number (IGn) and percentage (IG%) (10-12). The immature granulocyte comprises promyelocytic, intermediate, and late granulocytes, all precursor cells for mature white blood cells. They have been used to diagnose several different infections (13). Immature granulocytes are not usually found in the peripheral blood of healthy people. However, severe clinical infections can deplete many neutrophils, and the body compensates by releasing immature granulocytes from the bone marrow into the peripheral bloodstream (13) The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the total neutrophil count by the absolute lymphocyte count. Several studies have used the neutrophil-to-lymphocyte ratio to indicate the body's systemic inflammatory response and immune status. NLR measurement is a useful marker for determining the severity of pneumonia patients and predicting their prognosis (14). These markers can be determined with a simple hemogram result, easy to calculate without extra payment. However, no research evaluating the percentage of immature granulocytes and the number of immature granulocytes in childhood community-acquired pneumonia was reported in the literature. To the best of our knowledge, this is the first study to investigate the relationship between the severity of pediatric community-acquired pneumonia and the number of immature granulocytes in the peripheral blood.

This study aimed to determine the effect of basic hemogram parameters such as leukocyte, neutrophil, lymphocyte, neutrophil-lymphocyte ratio, immature granulocyte, and immature granulocyte percentage on the severity of community-acquired pneumonia in children. Additionally, we evaluated the effects of another inflammatory marker, CRP, and a clinical finding, oxygen saturation.

MATERIAL AND METHOD

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 09.05.2018, Decision No: 2018/237). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective case-control study was conducted between November 2018 and May 2019 at Erciyes University School of Medicine in the Department of Pediatric Pulmonology.

Sixty-nine patients diagnosed with CAP by clinical and radiological findings were included in the study who had not been treated previously and were aged between 3 months and 18 years. The association of clinical symptoms is defined as CAP (i.e., fever>38.0C, coughing, dyspnea, tachypnea, and pleuritic chest pain), physical examination findings (i.e., crackles, retractions, and rhonchus), and chest X-ray findings (i.e., air bronchogram, consolidation, opacities, and pleural effusion) and diagnosed by a pediatrician. If there were suspicious radiological findings, patients underwent a consultation with a pediatric radiologist. If the patients had the above mentioned features, they were enrolled in the study (15).

The following conditions were excluded from the study:<3 months, >18 years, cystic fibrosis, bronchiectasis, tuberculosis, immotile cilia syndrome, sickle cell anemia, Down syndrome, cerebral palsy, acute/chronic renal insufficiency, acute/chronic liver failure, congenital heart disease, chemical pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia, patients who had previously been treated at other centers, patients receiving multiple antiepileptic and immunosuppressive treatments.

The patients were classified into two subgroups: mild-to-moderate pneumonia and severe pneumonia. The CAP severity of the disease was determined using the criteria indicated for children by the British Thoracic Society (BTS) (1). The following features in an infant were evaluated as a sign of severe illness: cyanosis;

respiratory rate >70 breaths/min; significant tachycardia for the fever level; prolonged central capillary refill time >2 s; difficulty breathing; intermittent apnea; grunting; and inability to feed. Severe disease in an older child manifested in the following ways: cyanosis; respiratory rate >50 breaths/min; substantial tachycardia at any level; prolonged central capillary refill time >2 s; difficulty breathing; apnea, grunting; and signs of dehydration. A blood sample was obtained from all the patients included in the research during the first 24 hours of admission.

Recent generations of automated cell analysers provide many parameters, including cellular hemoglobin levels, large platelet counts, nucleated red blood cells, and basic hemograms. Detection of specimens was accomplished using the USES in-1000 automatic hematological analyzer (Japan Sysmex Company), and reagents were obtained from the original package of supporting reagents. Sheath flow technology, electrical impedance technology, and nucleic acid fluorescence staining were used to detect IG. This new-generation device can measure the number and percentage of immature granulocytes (16).

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Science Studies) version 22.0 for Windows. Firstly, descriptive statistics were performed with the data obtained. Then, the Shapiro-Wilk test was used to test whether the variables were normally distributed. Characteristic data are presented as n (%) for categorical variables and as mean±SD or median (interquartile range [IQR1-IQR3] for continuous variables, where appropriate.

Two-group comparisons were performed using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve assessed the leukocyte, neutrophil, lymphocyte, NLR, IGn, IG%, CRP, and oxygen saturation for pneumonia severity. The area under the curve (AUC) was used to calculate the predictive value of the markers. Logistic regression was used to efficiently determine the ability of laboratory values and oxygen saturation to predict the severity of pneumonia. Logistic regression identified associated factors and calculated odds ratios and 95% confidence intervals. Additionally, we generated predicted probability graphs to show how altering immature granulocyte number and oxygen saturation levels affect pneumonia severity's estimated probabilities. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant in all cases.

RESULTS

Demographic characteristics of the study groups are given in **Table 1**. The median age of patients with mild to moderate pneumonia was 7 (IQR1:5-IQR3: 10), and the median age of patients with severe pneumonia was 5 (IQR1:1.5-IQR3:5). When the two groups' ages were compared, a statistically significant difference in their ages was discovered (p=0.03) (**Table 1**).

Table 1. Demographic and hematological markers, CRP and oxygen saturation findings of patients.

	Mild-moderate pneumonia (n:32/46.3%.)	Severe pneumonia (n:37/53.6%)	P value
Age	7 (5-10)	2 (1.5-7)	p:0.03
Sex M(44)/F(25)	22(50%)/10(40%)	22(50%)/ 15(60%)	
Leukocyte	9225 (6500-11790)	12020 (8520-18340	p:0.006
Neutrophil	4600 (3242-8137)	7330 (4879-12220)	p:0.009
Lymphocyte	2465 (1557-3682)	2930 (1880-3860)	p:0.370
NLR	2.27 (1.2-3.3)	2.8 (1.1-6.1)	p:0.208
IGn	30 (20-47.5)	60 (40-125)	p:0.001
IG%	0.3(0.2-0.4)	0.5 (0.4-1)	p:0.001
CRP	26 (11-71)	36(19.5-143)	p:0.112
Oxygen saturation	95 (94-87)	88 (82-92)	p:0.001

Median:(IQR1- IQR3); NLR: Neutrophil/ Lymphocyte ratio; IGn: immature granulocyte number; IG%: immature granulocyte percentage; CRP: C-reactive protein M: male; Female: F

Patients with mild-moderate pneumonia (32/46.3%) and those with severe pneumonia (37/53.6%) had their leukocyte, neutrophil, IGn, IG%, and oxygen saturation compared. There was a statistically significant difference between the two groups (p<0.05). However, there was no statistically significant difference in lymphocyte count, NLR, or CRP (p>0.05) (**Table 1**).

Univariate analysis was used to identify independent factors that affect the severity of pneumonia. Leukocytes, neutrophils, IGn, IG%, and oxygen saturation significantly predicted pneumonia severity (p<0.05). They were positively correlated with the severity of the disease (OR>1), but oxygen saturation was negatively correlated (OR<1) (**Table 2**). The positive predictive value (PPV) of these parameters, respectively, was 56%, 61%, 59%, 51%, and 83%. Negative predictive value (NPV): 65%, 62%, 90%, 81%, and 83%, respectively (**Table 2**). Lymphocyte, NLR, and CRP had no significant effect in predicting the severity of pneumonia (p>0.05) (**Table 2**). As a result of the univariate analysis, multivariate logistic regression analysis (forward LR) was performed for the statistically significant parameters. Step 1: Oxygen saturation (odds ratio [OR] 0.535, 95% confidence interval [CI] 0.384-0.744, p 0.0001; PPV: 81, NPV: 83) and step 2: Oxygen saturation and IGn together (OR 1.008, 95% CI: 1.000-1016 p< 0.045, PPV: 86, NPV: 93) showed sufficient statistical power to discriminate between the two patient groups (**Table 2**). Oxygen saturation and IGn had a significant predictive value for disease severity. For these values, a probability curve was formed (**Figure 1,2**).

Table 2. Logistic regression analysis of hematological markers, CRP, and oxygen saturation

	Univariate logistic regression analysis						βMultivariate logistic regression analysis					
	OR	95% CI	P-value	PPV%	NPV%	OAP%	OR	95%CI	P-value	PPV%	NPV%	OAP%
Leukocyte	1.00	1.000-1.000	0.016	56	65	60						
Neutrophil	1.00	1.000-1.000	0.029	62	62	62						
Lymphocyte	1.00	1.000-1.000	0.216	40	62	52						
NLR	1.138	0.975-1.326	0.102	54	50	52						
IGn	1.008	1.000-1.016	0.05	59	90	74	+1.008	1.000-1016	0.045	86	93	90
IG%	10.792	1.614-72.137	0.014	51	81	65						
CRP	1.006	0.998-1.1013	0.149	52	56	53						
Saturation	0.570	0.428-0.759	0.0001	83	81	82	*0.53	0.384-0.744	0.0001	83	81	82

β: Forward LR; *Step1; +: Strep 2, OR: odds ratio, CI:confidence interval , PPV:positive predictive value, NPV: Negative predictive value; OAP:overall percentage; CRP: C-reactive protein; IGn: Immature granulocyte number IG%:Immature granulocyte percent; NLR: neutrophil/lymphocyte ratio

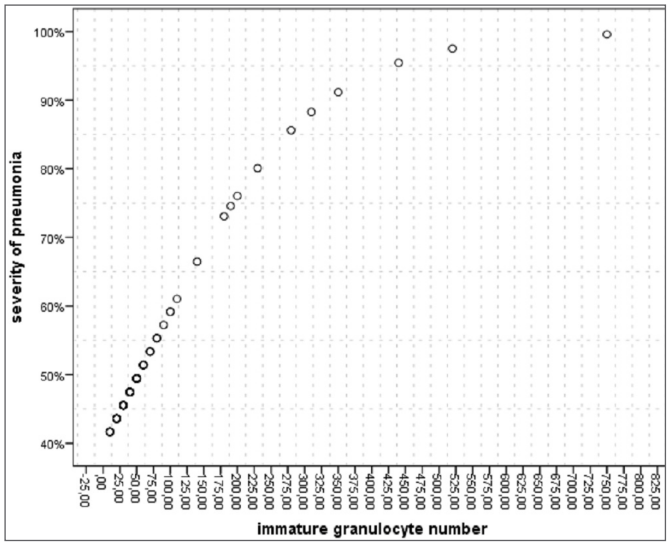

Figure 1. Predicted probability of mild-moderate or severe severe pneumonia by immature granulocyte numbers. IGn was modeled by scatter/dot. For example, if the IGn value is 325, around 90% of patients may be suffering from severe pneumonia.

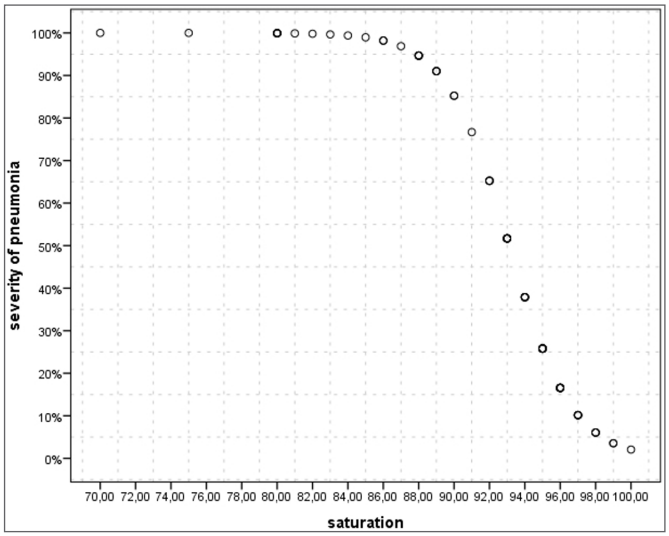

Figure 2. Predicted probability of mild-moderate or severe severe pneumonia by oxygen saturation. IGn was modeled by scatter/dot. For example, if the oxygen saturation value is 90%, around 89% of patients may be suffering from severe pneumonia

The receiver operating characteristic (ROC) curve analysis was performed to assess the ability of leukocytes, neutrophils, lymphocytes, NLR, IGn, IG%, CRP, and oxygen saturation. ROC analysis of pneumonia severity AUC (95% CI) was, leukocytes: 0.694 (0.569-0.818), p=0.006; neutrophils: 0.685 (0.559-0.810), p=0.009; lymphocytes: 0.563 (0.426-0.700), p=0.370; NLR: 0.588 (0.453-0.724), p=0.209; IGn: 0.746 (0.627-0.864), p=0.0001; IG%: 0.775 (0.664-0.887), p=0.0001; CRP: 0.611 (0.478-0.745), p=0.112, oxygen saturation: 0.89 (0.824-0.978), p=0.001 (**Table 3**, **Figure 3**).

Table 3. ROC curve analysis of blood parameters, CRP and, oxygen saturation in the prediction of CAP

Pneumonia severity			
	AUC	CI 95%	P
Leukocyte	0.694	0.569-0.818	0.006
Neutrophil	0.685	0.559-0.810	0.009
Lymphocyte	0.563	0.426-0.700	0.370
NLR	0.588	0.453-0.724	0.209
IG%	0.746	0.627-0.864	0.0001
IGn	0.775	0.664-0.887	0.0001
CRP	0.611	0.478-0.745	0.112
Oxygen saturation	0.891	0,824-0.978	0.001

AUC:Area under the curve; CI: confidence interval; CRP: C-reactive protein; IGn: Immature granulocyte number; IG%:Immaturegranulocyte percent; NLR: neutrophil/ lymphocyte ratio

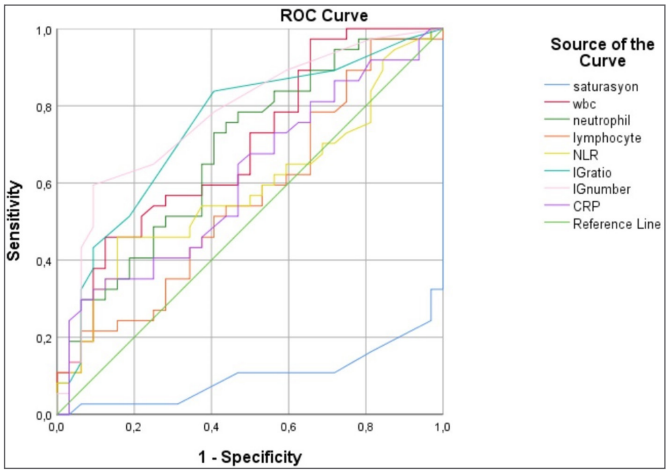

Figure 3. Receiver operating curves for immature granulocyte number (IGn), immature granulocyte number (IG%) percentage, white blood count (WBC), Neutrophil, lymphocyte, Neutrophil/ lymphocyte ratio (NLR), C-reactive protein (CRP), oxygen saturation.

DISCUSSION

Pneumonia is a disease with high mortality and morbidity in children. Many markers have been investigated to determine the severity of pneumonia. However, as a result of the research, a marker with high reliability has not been determined yet. BTS and

many classifications determine disease severity based on clinical findings rather than biological markers (1,17). However, clinical findings can be misleading, as examining children can sometimes be challenging. As a result, objective data on the severity of pneumonia are required. To establish the severity of the disease, we investigated hemogram results and oxygen saturation, both of which are objective data that are easily accessible and cost-effective.

The complete blood count is the most frequent and simple laboratory test, providing a wealth of data on an individual's health state. Due to technological advancements in automated hematological analyzers, the percentage and number of IG and IG% are now detectable. IG and IG% are immature cells that have just been released into the bloodstream. They are seen as signs of bone marrow activity and regeneration. CBC parameters and neutrophil/lymphocyte (NLR), IG, and IG%, which are considered biomarkers of systemic infections and inflammations, have been reported many times in sepsis, bronchiolitis, rheumatological diseases, cardiovascular disease, and various cancers (18-20).

Our study found that IGn, IG%, and oxygen saturation are useful markers to predict community-acquired pneumonia severity. It adds information to the conventional markers WBC, absolute neutrophil count (ANC), NLR, and CRP for the early identification of pediatric patients with CAP. Specifically, when IG number and oxygen saturation (OAP 90%) are used together, it is possible to evaluate the severity of pneumonia more accurately. The NPVa value of IGn (90a%/59b%) and IG (81a%/51b%) percent is greater than the PPVb value when estimating the severity of pneumonia. As a result, lower IGn and IG% levels are more likely to indicate mild-moderate pneumonia than severe pneumonia.

CRP is a blood test widely used to assess inflammation and bacterial infections. It has been related to the severity of the disease in children with bacterial infections (21). However, studies have shown no significant relationship between CRP and the severity of CAP. Elevated CRP was not linked with hypoxemia, dyspnea, or tachycardia in single-center cross-sectional research (22,23). CRP was not as significant in predicting pneumonia severity in our investigation as in previous studies. In determining the severity of pneumonia, IGn and IG% were more effective than CRP.

Florin et al. (7) evaluated proadrenomedulin (ProADM) levels to determine pneumonia severity in children admitted to the emergency room. In their study, ProADM had an AUC of 64% in those with suspected CAP and an AUC of 77% in those with radiographic CAP. Similarly, the prediction value of IGn was 77% in our study. Esposito et al. (8) assessed the relationships between the Soluble Triggering Receptor Expressed on Myeloid Cells (AUC 57%), the Mid regional Proatrial Natriuretic Peptide (AUC 65%), and the Mid regional pro adrenomedullin (AUC 55%) and the severity of pneumonia in children. In our study, IGn (AUC 77%) and IG% (AUC 74%) were more highly predictive of pneumonia severity than the markers used in this study. Esposito et al. (8) also evaluated the levels of WBC (AUC 59%), neutrophils (AUC 59%), and CRP (AUC 58%) to determine the severity of pneumonia. The values of these parameters were relatively similar to the results of our study. IGn and IG% are better options for determining pneumonia's severity than ProADM; Triggering Receptor Expressed on Myeloid Cells, Mid-regional Proatrial Natriuretic Peptide, and Mid-regional ProADM since it is more easily available and less costly.

Gungor et al. (24) evaluated the accuracy of the IG% in predicting severe bacterial infections (SBI). In this study, patients with SBI had a higher IG%, and the IG% had a better sensitivity and specificity for predicting SBI when compared to other biomarkers (WBC, neutrophil, CRP). Pimental et al. (25) assessed the role of immature neutrophils in peripheral blood smears to predict bacteremia in children. There was a significant difference between the number of immature neutrophils in this study when people with community-acquired infections were compared with or without bacterial blood infections. Furthermore, when this study evaluated only children with lower respiratory tract infections, the absolute number of immature granulocytes differed between patients with and without bacteremia. They demonstrated that a high IGn level predicted bacteremia in 82 (AUC) percent of severity pneumonia. In our study, patients with high IGn values have a risk of severe pneumonia. Bacteremia may accompany severe pneumonia in children. It may have the potential to increase the severity of pneumonia. From these study results, it is possible to attribute a role in the severity of pneumonia among these patients to the increased absolute number of immature neutrophils.

Dogan et al. (19) examined the relation between IG% and acute bronchiolitis severity. They found that IG values gradually increased from the mild to the severe group, but their study had no statistically significant difference. The IG value was valuable in determining the pneumonia severity in our study, in contrast to this study. The reason is that viruses are the most prevalent cause of acute bronchitis, but bacteria are the most common cause of pneumonia.

Huang et al. (26) examined the relation between IG% and acute respiratory distress syndrome (ARDS) in patients with acute pancreatitis. This study mentioned an increasing trend in ARDS in patients with acute pancreatitis with increasing IG%, and IG% could discriminate between acute pancreatitis patients with

and without risk for ARDS. Our study determined that IG% is one of the most effective markers for distinguishing mild-moderate from severe pneumonia.

When IGn and oxygen saturation values are evaluated together, they predict pneumonia severity by 90%. Together, these two indicators have more significant prediction power than the severity of pneumonia alone. IGn and oxygen saturation were our investigation's most valuable indicators for determining pneumonia severity. Probability curves that were not available in other studies were generated to show the severity of pneumonia associated with these values. These probability curves demonstrate the ability to estimate disease severity for each value of IGn and oxygen saturation (**Figures 1,2**). For example, if the IGn value is 325, around 90% of patients may suffer from severe pneumonia (figure 1). If the saturation level is 90%, about 89% of patients may suffer from severe pneumonia (**Figure 2**).

In the BTS guidelines, cyanosis is used to determine disease severity. This is not objective data. The cyanotic appearance may not be noticed in some cases because of the lighting, temperature, and other factors (1). Dean et al. (27) report in their study that, even though CAP is a common disease in children, there is no standardised risk classification to guide management. This study aimed to develop expert consensus regarding the parameters associated with varying degrees of disease severity in pediatric CAP. They recommended using oxygen saturation and objective data to determine the severity of pneumonia (24). The study by Awasthi et al. (28) emphasised that hypoxia and pneumonia in children under five years of age increase the mortality rate and may cause severe pneumonia. In their research, Modi et al. (29) emphasised that the sensitivity of the oxygen saturation measurement in evaluating pneumonia is more predictive than other clinical findings in resource-constrained conditions. In our research, oxygen saturation was an efficient parameter in distinguishing between mild-moderate and severe pneumonia, consistent with previous studies. Unlike other studies, we demonstrated the probability of pneumonia severity based on the saturation value on the probability curve. We think using saturation, an objective value, instead of cyanosis, in risk classifications will provide a more accurate assessment.

CONCLUSION

Our studies show that increased IGn, IG%, and decreased oxygen saturation are related to severe outcomes in children with pneumonia. They may be effective parameters in determining the severity of pneumonia. Complete blood count and oxygen saturation measurement are cheap and worldwide available methods. Given pediatric CAP's high incidence and mortality rate in low-income countries, IGn and oxygen saturation measurement give valuable information and may be the most useful method at admission. In addition, our results may contribute to developing more effective management recommendations for pediatric CAP. Additional studies should focus on developing sensitive predictors and a validated scoring system for pediatric pneumonia severity. More research is needed to create clinical-prediction criteria for identifying severe pneumonia in children, including oxygen saturation, IGn, and IG% as predictors of severity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 09.05.2018, Decision No: 2018/237).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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