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Utility of immature granulocyte count in differentiating between pyelonephritis and cystitis in pediatric patients

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ABSTRACT

Aims: Immature granulocyte (IG) is an easily accessible and inexpensive test that can be measured in hemogram parameters without additional analysis. It can be used in differentiation because of its practical applicability. This study aimed to investigate the role of IG count and inflammation-related complete blood count (CBC) parameters in differentiating between cystitis (CYS) and pyelonephritis (PYL) in pediatric patients.

Methods: This retrospective cross-sectional study analyzed data from 79 pediatric patients (40 with PYL and 39 with CYS) who presented at a hospital pediatric outpatient clinic between January 2020 - February 2021. In addition to clinical symptoms and signs, laboratory and urinalysis results were evaluated. Laboratory analyses focused on IG count, IG percentage, and all hemogram parameters.

Results: No significant demographic differences were observed between the PYL and CYS groups ($p>0.05$). IG counts, and C-reactive protein levels significantly differed between the two conditions ($p<0.001$). IG count was identified as an independent factor for distinguishing between PYL and CYS, with a sensitivity of 89.5% and a specificity of 92.6% ($p<0.0001$).

Conclusion: The IG count, an easily accessible and cost-effective test, is valuable in differentiating PYL and CYS ($p<0.001$). This finding holds promising implications for the prompt and accurate diagnosis of these conditions in pediatric patients.

Keywords: Immature granulocyte, C-reactive protein, pyelonephritis, cystitis

INTRODUCTION

Urinary tract infections (UTIs) are among the common diseases in early childhood, even though the findings or symptoms may vary according to demographic conditions.[1] Due to long-term sequelae in children, it is essential to distinguish between upper and lower UTIs.[2,3] In the diagnostic evaluation of infection, when it is limited to the bladder, it may cause pyelonephritis (PYL). If the infection spreads to the kidneys, we encounter the clinic of cystitis (CYS).[4] Although the long-term damage of CYS is limited, the situation may be more troublesome for pyelonephritis.[5] Because it increases the risk of renal scarring, which can lead to proteinuria and chronic kidney disease in the long term.[6,7] Although the clinical diagnosis of acute pyelonephritis is based on symptoms such as fever and pain associated with pyuria, urine culture, and blood tests support the diagnosis.[8,9] Screening 99mTc-dimercaptosuccinic acid (DMSA) is beneficial but has a high cost and radiation exposure.[10]

C-reactive protein (CRP) and procalcitonin are commonly used parameters for laboratory evidence of pyelonephritis.[11] Although it is the cheapest and most accessible method, its specificity and sensitivity are insufficient.[12] Today, immature granulocyte (IGs), especially in the routine evaluation of neonatal sepsis and associated with many inflammatory events, nine can be used in UTI differentiation in correlation with CRP. It can be preferred to CRP because the hemogram device analyzes it without requiring additional analysis, such as CRP.[13] The IG count, calculated by counting the cells in the area above the neutrophil granulocytes, is the combination of promyelocyte, myelocyte, and metamyelocyte cells that mature with myeloid cells. It can be helpful for prompt diagnosis and discrimination of UTIs.[9,14]

Immature granulocyte is an easily accessible and inexpensive test that can be measured in hemogram parameters without additional analysis and can be used

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in differentiation because of its practical applicability. The study investigates the role of the IG count and inflammation-related CBC parameters in CYS and pyelonephritis and whether these parameters are helpful in the differentiation of CYS and PYL.

METHODS

The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/KAEK-143-89). The ethics committee exempted the current research coordinator and participants from the need to get any informed consent due to the retrospective design. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This cross-sectional retrospective research analyzed 79 patients in 2 groups, including 40 PYL and 39 CYS with homogeneous distribution in terms of age and gender, who applied to the hospital pediatric outpatient clinic between January 2020 - February 2021.

Patient Collection

We analyzed the parameters including clinical signs, general laboratory and urinalysis results in PYL (n:40) and CYS (n:39). As seen in the flowchart (Figure 1), according to power analysis (α:0.05 | β:0.10 | Power:0.80), the study needs 72 participants at least. All pediatric patients aged 0-18 were included in the study, and the mean age was 44.1±42.5 for all the participants. Acceptance criteria for the study are: being in the pediatric age group and having PYL or CYS. Exclusion criteria for research are the history of systemic disease (e.g., diabetes, autoimmune), long-term or recent use of drugs, bacterial infection other than UTI, hematological/oncological disease, and lack of hospital record. We confirmed the diagnosis of PYL and CSY at the first admission according to the guidelines: There were symptoms such as fever, dysuria, abdominal pain, and costovertebral/abdominal tenderness during the examination. We evaluated hemogram, urinary culture, radiological evaluation records, and ultrasonography/voiding cystourethrography.

Laboratory Analysis

The laboratory results were obtained using the first sampling data after the admission of all the participants. The IG count, IG percentage (IG count divided by WBC×100), and all the hemogram parameters were analyzed using an XN1000 SYSMEX (Kobe, Japan). The CRP and other routine biochemistry parameters were determined using the DxC 700AU Beckman Coulter Autoanalyzer (Beckman Coulter Co., United States). We analyzed all the variables, including CRP, leukocyte esterase, leukocyte count, IG, neutrophil, platelet, lymphocyte count, and demographic data in both groups.

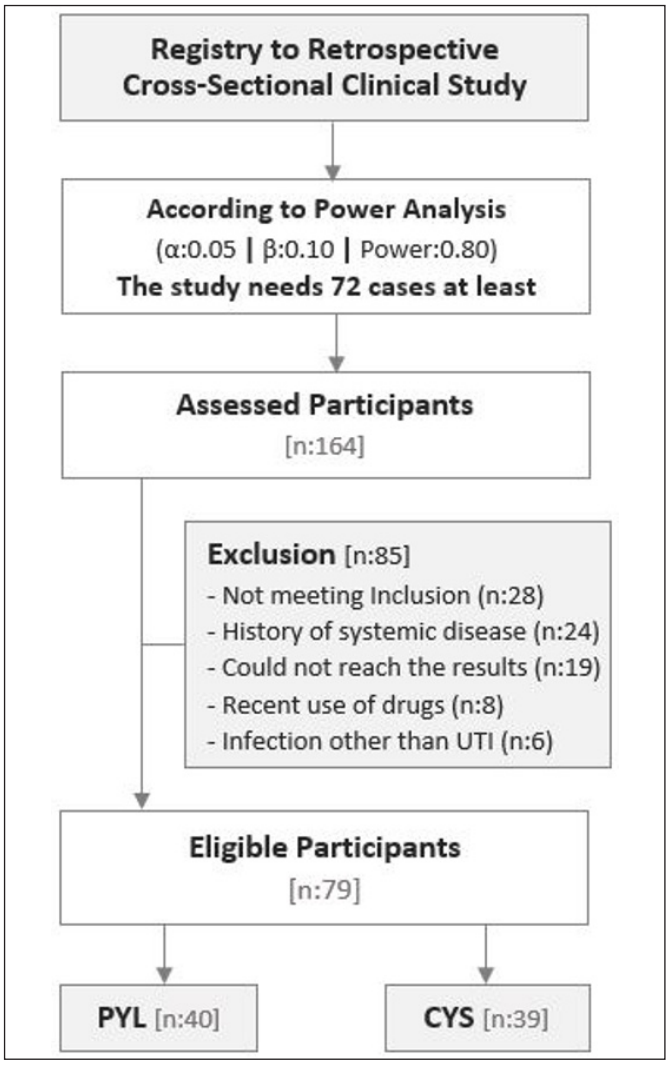

Figure 1. The flowchart presenting the selection of pyelonephritis and cystitis

Statistical Analysis

We used an MS-Windows 64bit-based SPSS program for data evaluation in the study (version 25, USA). The cut-off for significance is a 2-sided-p-value less than 0.05. While Mann-Whitney U was used for continuous data pairwise comparisons, we applied the Chi-square test to compare categorical data. According to the result values, we shared the median and interquartile ranges if the variables are numeric and frequency and percentage if the variables are categorical; In the regular distribution analysis, we used the Kolmogorov-Smirnov test for the suitability of numerical variables. We designed a logistic regression model to determine independent parameters in the differentiation of PYL and CYS. Associations between the IG count and other parameters were assessed using Spearman correlation analysis. Variables were tested using multivariate linear regression analysis to identify the essential independent factors influencing IG count. To evaluate the predictive ability of the PYL from CYS, we used a Receiver operating characteristic (ROC) for IG, CRP, neutrophile, and leukocyte.

RESULTS

All data, including demographic results, were similar in PYL and CYS (p>0.05). The mean age was 43.9 (29.6-58.3 months) and 44.5 (30.6-58.4 months) in PYL and CYS, respectively. Fever was detected in 42% of the patients on examination, while the most common presenting symptoms included dysuria (36.2%), abdominal pain (13.5%), and vomiting (12.1%). There were more urinary leukocytes in PYL than in CYS (p=0.041). No difference was seen in a comparison of PYL and CYS variables in terms of gender (p=0.919), urine bacteria (p=0.156), culture (p=0.513), urine nitrite (p=0.16), and leucocyte esterase (p=0.299). In comparing blood parameters, immature granulocytes, and CRP differed regarding PYL vs. CYS (Table 1).

Table 1. Comparisons of blood parameters according to the groups

Variables	Pyelonephritis	Cystitis	P value
Age, months	43.9±44.8	44.46±40.4	0.959
Leucocyte esterase, U/ml	159±295.2	57±119.3	0.354
C-reactive protein, mg/L	90.2±89.82	4.32±11.9	0.0001
WBC, 10^3/uL	13.6±4.52	8.35±4.37	0.0001
Red blood cell, 10^6/uL	4.57±0.58	4.72±0.49	0.217
Hemoglobin, g/dl	11.7±1.43	12.26±1.85	0.155
Hematocrit, %	35.4±4.34	37.03±5.04	0.154
Neutrophil, 10^3/uL	7.87±3.91	3.27±2.68	0.0001
Lymphocyte, 10^3/uL	4.34±3.07	4.14±2.01	0.743
Monocyte, 10^3/uL	1.22±0.7	0.69±0.54	0.0001
Eosinophil, 10^3/uL	0.16±0.23	0.21±0.14	0.284
Basophil, 10^3/uL	0.049±0.026	0.041±0.025	0.318
IG, 10^3/uL	0.073±0.076	0.021±0.023	0.0001

Abbreviations. IG: Immature granulocyte, WBC: White Blood Cell

There were significant correlations between IGs and the parameters, including eosinophil (r:-0.242; p=0.036), basophil (r:-0.278; p=0.016), WBC (r:0.494;p<0.001), CRP (r:0.705; p<0.001), neutrophil (r:0.459; p<0.001). We designed a logistic regression model to determine the effectiveness of IG in differentiating PYL and CYS. The model Nagelkerke's R square was 51.4%. This model could detect PYL with 92.5%. Moreover, IG was an independent factor in differentiating PYL and CYS (Table 2). Dominant parameters for predicting PYL, IG (p<0.0001), and CRP (p<0.0001). Leucocyte esterase (p=0.331) did not show significance in the ROC analysis (Table 3). The AUC for the CRP, IG, leukocyte, and neutrophil were 0.946 (95% CI: 0.891-0.999), 0.957 (95% CI: 0.9173-0.997), 0.861 (95%CI: 0.772-0.951), and 0.859 (95% CI: 0.768-0.951), respectively. The IG count's cut-off value as a PYL predictor was 0.031, with an 89.5% sensitivity and 92.6% specificity value (Figure 2).

Table 2. Logistic regression for differentiating pyelonephritis and cystitis

Variables	B	Wald	P value	Exp (B)	95% CI	
					Lower	Upper
IG, 10^3/uL	-76.918	16.744	0.0001	0.0001	0.00001	0.0001
Sex, male	0.853	1.027	0.311	2.348	0.450	12.235
Age, months	-0.008	1.126	0.289	0.992	0.976	1.007
Constant	2.623	12.054	0.001	13.774	-	-

Abbreviations. IG: Immature granulocyte, CI: Confidence interval, Exp(B): the odds ratio.

Table 3. The ROC analysis for predicting pyelonephritis against cystitis

Variables	AUC	SE	P value	95% CI	
				Lower	Upper
C-reactive protein, mg/L	0.946	0.027	0.0001	0.892	0.999
Leucocyte esterase, U/ml	0.565	0.067	0.331	0.435	0.696
WBC, 10^3/UL	0.861	0.046	0.0001	0.772	0.951
NEUT, 10^3/UL	0.859	0.046	0.0001	0.768	0.949
IG, 10^3/UL	0.957	0.020	0.0001	0.917	0.997

Abbreviations. IG: Immature granulocyte, WBC: White Blood Cell, NEU: Neutrophile, CI: Confidence interval, AUC: Area Under Curve, SE: Standart error.

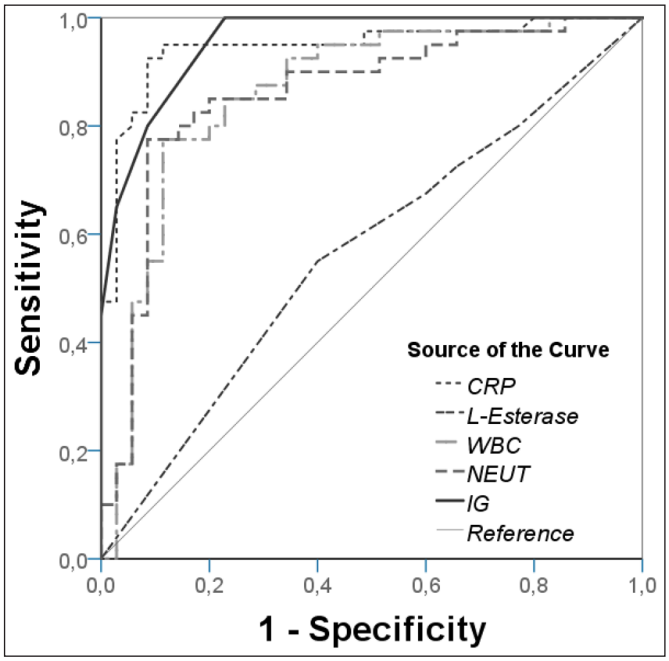

Figure 2. The ROC analysis for discrimination of pyelonephritis from cystitis

DISCUSSION

Knowing the long and short-term clinical importance of the distinction between PYL and CYS and seeking a diagnostic marker out of necessity, we conducted a detailed IG analysis for these two diseases regarding cost and practical applicability. This first study presented that IG count can cost-effectively meet all needs in distinguishing these two diseases.

Today, DMSA screening is considered the gold standard for diagnosing PYL.[10] DMSA is accessible in almost all centers in Turkey, hence using the immature granulocyte

count for a patient's acute management in provincial hospitals is appropriate. In addition, as a costly diagnostic tool, biomarkers such as CRP are also regarded as valuable in determining the presence of PYL.[11] It is noteworthy to remember that the level of CRP can increase in many other conditions, such as viral infection, non-infectious inflammatory diseases, and myocardial infarction.[15] CRP test in UTIs was investigated alone or in combination with other parameters in several studies regarding its predictive value.[16] According to Biggi et al.[17] and Kotolula et al.[18], CRP's specificity and sensitivity in PYL were 63-98% and 5-92%, respectively. Guven et al.[19] examined the diagnostic efficacy of CRP in diagnosing PYL and found that the cut-off of 2, 5, and 10 mg/dl showed a sensitivity of 67%, 68%, and 73%, respectively.

Although CRP and CBC are comprehensive tests in the diagnosis and follow-up of infections, the IG is a newly evaluated marker to potentially detect inflammation or bacterial infection. The appearance of IGs in peripheral blood indicates an early response to infection, and inflammation, especially in inpatients other than the neonate and pregnant population.[20] Detecting IG quickly and reliably provides a new diagnostic opportunity for related diseases. Nierhaus et al.[21] showed the diagnostic power of IGs on discrimination between infected and uninfected patients with systemic inflammatory response syndrome at 89.2% sensitivity and 76.4% specificity. They also found that IG is a more potent predictive marker than CRP and interleukin.[6] In a similar article, Henriot et al.[22] showed that the number of IGs in children with viral or bacterial infections was significantly higher than in healthy children.

Few studies on the relationship between UTI and IG have shown evidence to be very useful in bacterial infections. Incir et al.[23] in a study with 55 patients and 47 controls, presented evidence that IG count is a readily available measure that can be used in conjunction with the CRP value and other indicators in managing UTIs. Yoon et al.[24] investigated the role of the delta neutrophil index, which shows the ratio of IG to total neutrophil count in infants with febrile UTI-associated bacteremia. Significantly higher values were observed compared to infants with UTI and without bacteremia. In the present analysis, IGs, CRP, and hematologic infection markers increased in both groups, consistent with these two studies. However, the increase rate exhibited a positive divergence in the form of a more substantial and tremendous increase in IG values for PYL than CYS.

Incir et al.[23] found 65.45% sensitivity and 65.96% specificity of the IG count to predict a UTI above the 0.03 cut-off value.Lee et al.[25] reported a sensitivity value of <50% for IG as a predictor of UTI and a moderate specificity ranging from 70% to 90%. In contrast, another study by Park et al.[26] examining the number of IGs in patients with UTIs has reported high sensitivity values of 82% to 95%. This highly significant difference in susceptibility may be related to the study populations' adult age or systemic infections such as bacteremia or sepsis in selected patients. In the present study, IG presented an independent factor in differentiating PYL and CYS. IG and CRP were the dominant parameters for prediction in the ROC analysis. The cut-off value of the IG count as a predictor of PYL was 0.031, with an 89.5% sensitivity and 92.6% specificity value.

The strength of the present study is that, to our best knowledge, it is novel research to evaluate the diagnostic value of IG count in the differentiation of PYL and CSY in children. Homogeneous demographic data and detailed analysis of patient data are valuable. The main limitation of the research is that we examined PYL with clinical, laboratory, and ultrasonographic findings. The number of patients was relatively limited to perform the two-group analyses. Sensitivity and specificity values will be more accurate for the number of IGs calculated with a more significant number of patients.

CONCLUSION

Immature granulocyte is an easily accessible and inexpensive test. It helps differentiate PYL from CYS because it has practical applicability instead of Crp and related hemogram parameters. Our results strongly support that IG count can meet all needs cost-effectively in the differentiation of PYL and CSY, and its routine application will provide physicians with much comfort in practice.

Abbrevation: IG: Immature granulocyte, CBC: Complete blood count, CYS: Cystitis, PYL: Pyelonephritis, UTIs: Urinary tract infections, DMSA: 99mTc-dimercaptosuccinic acid, CRP: C-reactive protein, WBC: White Blood Cell, ROC: Receiver operating characteristic, AUC: Area under the curve.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/KAEK-143-89)

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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

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Author Contributions: All 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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