

Are the Hematological Parameters Useful in Differentiating Acute Pyelonephritis from Cystitis in Patients with Chronic Kidney Disease?

Ioana DICU-ANDREESCU^a, Liliana GARNEATA^{a, b}, Otilia-Andreea CIUREA^{a, b}, Irinel-Gabriel DICU-ANDREESCU^a, Elena-Alexandra UNGUREANU^a, Denis-Valentin VLAD^a, Antonia-Constantina VISAN^a, Victor-Gabriel UNGUREANU^a, Violeta-Valentina VLAD^a, Patrick-Christian VASIOIU^a, Elis-Mihaela CIUTACU^b, Mihaela NEICU^b, Mircea PENESCU^{a, b}, Constantin VERZAN^{a, b}, Cristina CAPUSA^{a, b}

^aFaculty of Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

^bNephrology Department, “Dr. Carol Davila” Teaching Hospital of Nephrology, Bucharest, Romania

ABSTRACT

Background and objectives: The importance of hematological parameters has started to be explored with increased interest in many fields lately, with different studies finding an association between those parameters and inflammatory status, atherosclerosis, comorbidities, malnutrition, neoplasia and even a faster progression of chronic kidney disease (CKD). On the other hand, CKD itself presents as an inflammatory condition, in which a lot of pathways are modified and the response to an infectious agent could be less than expected. Regarding the latter aspect, in this study we aim to explore the differences between the hematologic response during a lower versus upper urinary tract infection in patients with CKD.

Materials and methods: We analyzed 70 patients with chronic kidney disease and either cystitis or pyelonephritis considering the hematologic parameters, the classical inflammatory ones as well as the etiology of CKD.

Results: Neutrophils, neutrophils/lymphocytes ratio (NLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen were higher in patients with pyelonephritis (PNA), while albumin was significantly lower. In a binary logistic regression model that explained 80.2% of the variability of PNA diagnosis and correctly predicted it in 92.9% of cases, NLR, CRP and fibrinogen were the independent predictors.

Conclusions: Hematologic parameters can serve not only as an indicator of the inflammatory status, but also as a laboratory biomarker for PNA in patients with CKD.

Keywords: hematological parameters, acute pyelonephritis, cystitis, chronic kidney disease.

Address for correspondence:
Ioana Dicu-Andreescu
Email: ioana.dicu08@yahoo.com

Article received on the 2nd of August and accepted for publication on the 18th of September 2024

INTRODUCTION

Chronic kidney disease (CKD) is defined by the Kidney Disease Improving Global Outcome guidelines (KDIGO) as structural or functional abnormalities of the kidneys that persist for a minimum of three months (1). Also, it is a rather frequent condition which occurs in approximately 10% of the world population, leading to a great individual and social burden because of all involved co-morbidities, among which the most common ones include anemia, dysregulated mineral metabolism that leads to bone disease, the malnutrition-inflammation-atherosclerosis syndrome (MIA), fluid retention and aggravation of hypertension, and last but not least, a greater predisposition to infectious diseases, that can induce a vicious circle, with the aggravation of the CKD and all its complications (2-4). There are multiple mechanisms that allow a greater incidence of infections in CKD patients, including alterations of Toll-like receptors, which predispose especially to urinary tract infections (UTIs), increased apoptosis of T lymphocytes CD4+, and a lower activity of the neutrophils induced by increased levels of fibroblast growth factor 23 (FGF23) and by uremic toxins like p-cresyl sulfate and indoxyl sulfate (5-7). Also, CKD is a state of chronic inflammation besides any superimposed infectious process, so systemic inflammatory markers like C-reactive protein (CRP), tumor necrosis factor alpha (TNF- α) or interleukin 6 (IL6) are often increased in CKD patients (8).

On the other hand, since infectious diseases are also very frequent, numerous parameters have been evaluated and analyzed in order to identify those which best describe the biological response to infection, with the most well-known being the appearance of leukocytosis/leukopenia and increased values of erythrocytes sedimentation rate, C-reactive protein and fibrinogen (9, 10). However, lately, hematological parameters of inflammation like red cell distribution width (RDW), platelet distribution width (PDW), neutrophils/lymphocytes ratio (NLR) or platelets/lymphocytes ratio (PLR) were correlated with overt and subclinical systemic inflammation in various clinical settings, including CKD. For example, a high NLR was associated with poor kidney survival and a greater degree of

malnutrition than expected, while a high RDW was related to all-cause mortality, cardiovascular risk and infections (11, 14).

Because UTIs are very common in the general population (almost 50% of women and 5% of men are supposed to have at least one such episode during their lifetime) and also in CKD, but little is known about the changes in hematological parameters of inflammation in this context, the current study aimed to evaluate the potential role of NLR, PLR, RDW and PDW in differentiating CKD patients with acute pyelonephritis from those with cystitis (6, 8, 15). If confirmed, they could be especially helpful in resource-limited settings, where more costly markers like C-reactive protein might not always be available. $\square$

MATERIALS AND METHODS

This is a retrospective observational study, in which 70 non-dialyzed subjects with CKD stages G3-G5 and UTIs were enrolled. Patients were recruited on a one-year period, between 01.01.2021 and 31.12.2021, using the following criteria: first of all, only patients with an estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m² for at least three months were included, in order to ensure the diagnosis of CKD according to KDIGO guidelines; patients were identified in the informatic system of the hospital using the N18.8 code from the International Classification of the Diseases-10 (ICD-10) – 2 750 patients were initially selected, but only 2 100 of them had an eGFR under 60 mL/min/1.73 m². Secondly, we applied another search criterion to identify patients with UTIs using the codes N30.0, N30.8, N30.9 and N10 and found that 350 patients had such epi-

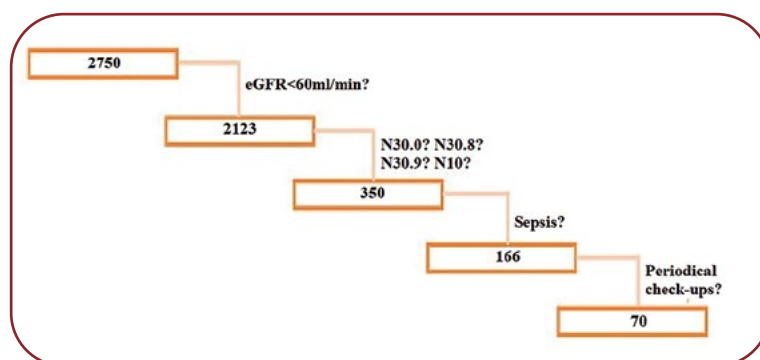


FIGURE 1. Inclusion/exclusion criteria. eGFR=estimated glomerular filtration rate; N30.0, N30.8, N30.9, N10=codes from ICD-10 classification used to identify the presence of a urinary tract infection

sodes. Lastly, we excluded those who did not come to the periodical check-ups (184 patients) as well as those who had a diagnosis of sepsis (96 patients). Therefore, only the remaining 70 patients were further analyzed (Figure 1).

For each subject, past medical history was thoroughly evaluated and the diagnosis of either upper or lower urinary tract infection was verified by the history of the episode described in the documents and by the results of urine cultures. The diagnosis of acute pyelonephritis was made based on the signs and symptoms described in the discharge documents, including fever, low back pain, dysuria, pollakiuria and urgency, and confirmed by the diagnosis mentioned by the clinician who evaluated the patient in the discharge papers and in the informatic system of the hospital. Also, the diagnosis of a simple cystitis was made based on the presence of lower urinary tract symptoms like dysuria, pollakiuria, urgency or a foul smell of the urine and,

again, confirmed by the diagnosis mentioned by the clinician who evaluated the patient. No other parameters were used to differentiate between lower and upper UTIs. Also, for each patient at the moment of the infectious event, the following parameters were registered: demographic data [age, sex, complete blood count, including the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR)], the values of classical inflammatory parameters like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen, serum albumin, serum creatinine in order to estimate the glomerular filtration rate using the CKD-EPI formula (serum creatinine was registered at the time of the first visit in the clinic), the urinary sediment, the results of urine cultures, and last but not least, the etiology of CKD.

The SPSS 26.0 program was used for statistical analysis. The continuous variables are presented as mean or median with confidence in-

	Cystitis (51)	Pyelonephritis (19)	p-value
Age, years, mean (CI)	62 (58.3 to 65.5)	55 (47.7 to 63.4)	0.08
Sex, F, n (%)	38 (74.5)	9 (47.3)	0.03
Hemoglobin, mean (CI)	11.5 (11.09 to 12)	11.6 (10.4 to 12.7)	0.67
WBC, mean (CI)	7541 (6858 to 8223.5)	12657.9 (10.517.2 to 14798.5)	<0.001
Neutrophils, mean (CI)	4933 (4394.8 to 5471.8)	10047 (8002.8 to 12091.9)	<0.001
Lymphocytes, mean (CI)	1986 (1785.2 to 2187.2)	1821 (1401.0 to 2241.1)	0.46
Platelets, mean (CI)	238313 (221236.4 to 255390.9)	235526 (187636.4 to 283416.2)	0.91
NLR, median (CI)	2.38 (2.3 to 3.3)	5.64 (4.7 to 8.6)	<0.001
PLR, median (CI)	124.3 (115.4 to 152.8)	150.2 (114.1 to 186.3)	0.95
RDW, mean (CI)	15 (14.6 to 15.3)	15.5 (15 to 15.9)	0.07
PDW, median (CI)	15.6 (14.6 to 15.3)	15.6 (14.6 to 15.6)	0.95
Albumin, median (CI)	4.4 (4.2 to 4.4)	4.1 (3.7 to 4.3)	0.02
Leukocyturia, median (CI)*	100 (64 to 676.4)	64 (33.4 to 614.4)	0.95
Hematuria, median (CI)*	20 (9.6 to 239.1)	25 (14 to 514)	0.63
ESR, median (CI)	30 (31.1 to 43.6)	67 (48.7 to 85.4)	0.003
CRP, median (CI)	7 (5.7 to 10.4)	67 (46.8 to 128.8)	<0.001
Fibrinogen, mean (CI)	540 (478.9 to 601.2)	735 (569 to 901.2)	0.007
Bacterial cultures, n (%)	1. <i>E. coli</i> : 23 (45) 2. <i>Klebsiella</i> spp: 9 (17) 3. <i>Enterococcus</i> : 6 (12) 4. Others ^{&} : 7 (14) 5. Negative: 6 (12)	1. <i>E. coli</i> : 6 (31) 2. <i>Klebsiella</i> spp: 3 (16) 3. <i>Enterococcus</i> : 2 (11) 4. Others ^{&} : 3 (16) 5. Negative: 5 (26)	0.15
ieGFR, median (CI)	26 (23.6 to 31.3)	35.7 (27.5 to 44)	0.08
Etiology of CKD, n (%)	1. Vascular nephropathy: 13 (25.4) 2. Tubulo-interstitial nephropathy: 13 (25.4) 3. ADPKD: 11 (21.5) 4. Primary glomerulopathy: 3 (5.8) 5. Diabetic nephropathy: 3 (5.8) 6. Mixed nephropathy: 3 (5.8) 7. Obstructive nephropathy: 2 (3.9) 8. Medullary sponge kidney: 2 (3.9) 9. Amyloidosis: 1 (1.9)	1. ADPKD: 10 (52.6) 2. Vascular nephropathy: 4 (21) 3. Tubulo-interstitial nephropathy: 3 (15.7) 4. Diabetic nephropathy: 1 (5.2) 5. Obstructive nephropathy: 1 (5.2)	0.01**

TABLE 1. General characteristics of patients

ADPKD=autosomal dominant polycystic kidney disease; CI=confidence interval; CKD=chronic kidney disease;

CRP=C-reactive protein; ESR=erythrocytes sedimentation rate; n=number of patients;

NLR=neutrophils/lymphocytes ratio; PLR=platelets/lymphocytes ratio; RDW=red cell distribution width;

WBC=white blood cells

*values were obtained from Stansfeld-Webb urinary sediment

**only the ADPKD was significantly different between groups, more frequently in those with pyelonephritis

[&]*Acinetobacter, Candida, Citrobacter, Enterobacter, Pseudomonas, Group B Streptococcus.*

tervals, depending on their distribution, and the nominal variables are presented as percentages. The distribution of variables was determined using the Shapiro-Wilk test and by analyzing their skewness and kurtosis – if the Shapiro-Wilk test was under 0.05, associated with skewness and kurtosis above (+1) or below (-1), an abnormal distribution was assumed. For comparison between episodes of cystitis versus episodes of pyelonephritis we used the Mann-Whitney U test for the continuous variables and Fisher's exact test for the nominal ones; the reason for choosing the two tests was that the majority of the variables had an abnormal distribution. Also, the correlations between variables were assessed with the Spearman rho coefficient and if the p-value was below 0.05, a correlation was established. The multivariate analysis was conducted using binary logistic regression models in which the dependent variable was considered the diagnosis of pyelonephritis and the independent variables were those with a p-value derived from differences between groups below 0.1. $\square$

RESULTS

Patients in the pyelonephritis group were more commonly men, had leukocytosis with neutrophilia, higher NLR value and higher markers of systemic inflammation (ESR, CRP and fibrinogen), lower albumin levels and a greater prevalence of autosomal dominant polycystic kidney disease. The microorganisms involved in the UTIs did not differ in the two groups and were mainly represented by *E. coli*, *Klebsiella* spp. and *Enterococcus*. In addition, trends to higher RDW and lower eGFR were observed (Table 1).

After testing the variables with the Spearman correlation, the following results regarding the relevant variables were obtained: NLR was positively correlated with PLR, RDW, classical inflammatory markers and leukocyturia, and negatively with serum albumin; PLR was correlated with NLR, as already mentioned, and additionally with RDW; and RDW was negatively correlated with the glomerular filtration rate. The PDW did not correlate with any other variable. All remaining parameters were tested and the results are shown in Table 2.

A model of binary logistic regression was built, which included both independent and dependent variables. Thus, independent variables

Variable	Correlations	rs	p-value
NLR	+ PLR	0.465	<0.001
	+ RDW	0.290	0.01
	+ ESR	0.354	0.005
	+ CRP	0.539	<0.001
	+ LU	0.261	0.02
PLR	- SALb	-0.313	0.008
	+ RDW	0.272	0.02
	- eGFR	-0.467	<0.001
	+ HU	0.555	<0.001
	+ NLR	0.261	0.02
RDW	- Ly	-0.256	0.03
	- eGFR	-0.467	<0.001
	+ ESR	0.354	0.005
	+ Fib	0.490	0.002
	+ LU	0.555	<0.001
LU	- SALb	-0.241	0.04
	- Ly	-0.247	0.04
	- eGFR	-0.343	0.004
	- Ly	-0.245	0.04
	- eGFR	-0.370	0.002
HU	+ SALb	0.270	0.02
	+ Neu	0.255	0.03
	+ Ly	0.283	0.01
	- ESR	0.424	0.001
	- ESR	-0.460	<0.001
Serum albumin	- CRP	-0.534	<0.001
	- Fib	-0.462	0.003
	- NLR	-0.313	0.008

TABLE 2. Correlations between the relevant variables

CRP=C-reactive protein; eGFR=estimated glomerular filtration rate; ESR=erythrocyte sedimentation rate; Fib=fibrinogen; HU=hematuria; LU=leukocyturia; Ly=lymphocytes; Neu=neutrophils; NLR=neutrophils/lymphocytes ratio; PLR=platelets/lymphocytes ratio; RDW=red cells distribution width; Salb=serum albumin; +: positively correlated; -: negatively correlated.

comprised those which were significantly higher or lower in the pyelonephritis group, including NLR, serum albumin, ESR, CRP and fibrinogen, RDW (it was also included because it was considered acceptable if a variable had a p-value under 0.1), and urinary leukocytes and erythrocytes, as they were correlated with NLR. The diagnosis of acute pyelonephritis was considered as dependent variable. It returned that the NLR, CRP and fibrinogen were the independent predictors of pyelonephritis diagnosis. The model's goodness-of-fit was assessed using a likelihood ratio test, yielding a significant chi-square statistic of $\chi^2=56.3$, $p<0.001$. Additionally, the model's Nagelkerke R^2 value of 0.876 indicates that almost 88% of the variability in the diagnosis of acute pyelonephritis is accounted for by the model, which is a marked improvement over the null model. Also, it correctly predicts the diagnosis in 92.9% of cases. The values are summarized in Table 3.

TABLE 3.
Independent
predictors of the
diagnosis of
pyelonephritis

Variable	HR	CI	p-value
NLR	1.718	1.048 to 2.814	0.03
CRP	1.158	1.035 to 1.296	0.01
Fibrinogen	1.013	1.003-1.024	0.01

CI=confidence intervals; CRP=C-reactive protein;
HR=hazard ratio; NLR=neutrophil/lymphocyte ratio.
Dependent variable: diagnosis of pyelonephritis;
Chi²=56.07; p<0.001; Nagelkerke R²=0.799.
Variables entered in the first step:
neutrophil/lymphocyte ratio, serum albumin,
erythrocyte sedimentation rate, C-reactive protein,
fibrinogen, urinary leukocytes and erythrocytes.

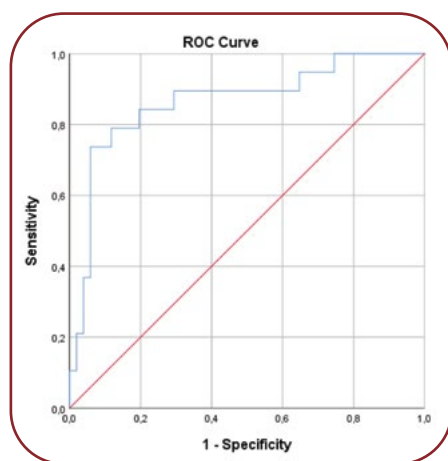


FIGURE 2. Receiver operating characteristic (ROC) curve for neutrophils/lymphocytes ratio (NLR) significance

A receiver operating characteristic (ROC) curve was plotted in order to test the values of NLR and identify a cut-off that could differentiate between an upper versus a lower UTI with a satisfactory sensibility and specificity. The results were very good, with a value of the ROC curve of 0.865, p-value <0.001 and a cut-off value established at 3.53, that provided a rate of true positive diagnostics of pyelonephritis in 84.2% of cases and a rate of false positive diagnostics of pyelonephritis in 19% of cases. □

DISCUSSION

Neutrophils are classically associated with bacterial infections and hospitalization. Moreover, despite the lack of complete function and activation caused by all biochemical changes in CKD, they seemed to respond as expected in UTIs, with significant differences between a lower versus upper UTI, which was confirmed in

our study. Also, they seem to be independent predictors for the diagnosis of pyelonephritis. In addition, an increase in their number seems to be associated with an elevated risk for sepsis in hospitalized patients with pyelonephritis, which can represent a useful marker, as it is very easily obtained using only a basic complete blood count (16, 17).

Neutrophils/lymphocytes ratio is another useful marker which is associated with 90-day mortality and hospital readmission in those with Gram-negative sepsis, and also with AKI in patients with UTIs (17, 18). Also, upper UTIs are often complicated with the development of bacteremia, especially when *Klebsiella* spp. is the involved microorganism, and the patients have also comorbidities like diabetes (19). Interestingly, a recently published study claimed that NLR in association with urinary IL-8 could differentiate between UTIs caused by extended spectrum beta-lactamases *E. coli* (ESBL) and those caused by *Klebsiella pneumoniae* in patients with type 2 diabetes mellitus (20). In addition, it seems that NLR could predict the necessity of nephrectomy in case of emphysematous pyelonephritis, especially when it is associated with AKI (21). Because studies argue that, in CKD patients, the risk for severe infections increases with the decline of eGFR, being two to three times higher in stages G4 and G5 than in stage G2, these facts can become very important as NLR could serve as a marker for both the loss of kidney function and the severity of an infectious event, with the latter being also confirmed by our findings (22, 23). In our study, NLR is confirmed as an independent marker that aids in the diagnosis of pyelonephritis, which is of great importance, especially in resource-limited countries, where more costly markers are lacking.

It should be mentioned that PLR, a very important parameter too, has been found to have increased values in CKD patients, which correlate with all-cause mortality and could even have a better predictive value for diagnosing inflammation in advanced stages of CKD than NLR (24-26). Moreover, it also has a prognostic survival value in patients with acute kidney injury who need intensive care unit (ICU) treatment (27). In infectious diseases, it was especially studied in COVID-19 as a marker of severity and mortality (28). Regarding infectious diseases, PLR was found to be a predictor for 90-day mortality

in hospitalized patients with sepsis (29). Moreover, in association with NLR, it could also predict the occurrence of sepsis after percutaneous nephrolithotomy for kidney stones (30). On the other hand, there are no studies that evaluate its own predictive value in differentiating between UTIs, but nonetheless, it remains a good predictor in CKD patients, both in infections, in association with NLR, and on its own in inflammatory states. In our study, it also did not have significantly different values in those with lower versus upper UTIs.

The red cell distribution width (RDW) is another promising marker evaluated in different affections, with the most important results regarding it as a useful predictor for in-hospital mortality at 30-days for patients in ICU, for comorbidities and pro-inflammatory status, and last but not least, as a marker for mortality caused by infectious diseases, including community acquired pneumonia and Gram negative induced sepsis, especially measured after 72 hours (31-34). In CKD patients, RDW has been demonstrated as a useful prediction tool due to its association with a faster decline in kidney function, a composite cardiovascular outcome when its values are above 14.5% and increased mortality (35-37). It also predicts sepsis-associated acute kidney injury and death in ICU patients (38-40). On the other hand, in more mild infections, RDW has not been studied enough but it can still be a promising marker in UTIs due to its ability to predict a more serious turn of the events and consequently, a more serious infection like pyelonephritis and, eventually, the development of urosepsis. However, in our study, there were no significant differences between patients with cystitis versus pyelonephritis, most probably due to the relatively small number of patients included in research.

The platelet distribution width (PDW) has also been extensively studied as increased values were associated with new-onset cardiovascular events and all-cause mortality both in peritoneal dialysis and hemodialysis patients (41-43). Also, a large prospective study conducted by Zhikai Yu demonstrated that the number of platelets and PDW were associated with cardiovascular events even in pre-dialysis patients (44). Regarding the infectious diseases, a higher PDW (above 18%) in sepsis is correlated with a higher risk of mortality and also seems to have a prognostic value in

patients with COVID-19 infection, but further research is needed (45, 46). Also, in UTIs an increase in the number of platelets is associated with Gram negative strains, while the PDW was found to be lower (47, 48). This fact can be very important: firstly, as the number of platelets and PDW are two markers that indicate the same type of uropathogen, their sensitivity increases; and secondly, they are very easily obtained and can aid the diagnosis before the arrival of the culture results. In our study, there were no significant differences between upper and lower UTIs, which may be explained by the low severity of infections – even in the pyelonephritis group, patients did not progress toward sepsis because the antibiotic treatment was rapidly introduced. Prospective further research is needed in order to identify if the severity of infections correlate with PDW in CKD patients too.

Despite the fact that we mainly focused on the importance of hematologic parameters as laboratory evidence for differentiation between upper and lower UTIs in CKD patients, we also registered the values for the classical markers of inflammation (ESR, CRP and fibrinogen) and, as expected, they were significantly different in the two groups observed by us, with much higher values being seen in those with pyelonephritis. Also, CRP and fibrinogen were independent predictors for the diagnosis of pyelonephritis.

The present study has also some limitations. First of all, it had a retrospective design, with data being acquired from the informatic system of the hospital. However, we only followed a precise group of parameters that were widely available; for that reason, and also because our hospital is a tertiary nephrology center in Romania, there is almost no probability that variables related to the investigated topic to miss. Then, the sample size is relatively small, mainly because of the strict selection criteria. On the other hand, even this relatively small number of subjects seemed enough to generate some significant data and to confirm the importance of some hematological parameters like NLR. It is supposed that other hematological parameters such as RDW or PDW would have been confirmed too, in case of a larger sample, especially because they seem to have an important prognostic value in non-CKD patients. Prospective clinical trials are further required in this matter. Finally, we conducted the study only in our hospital and did

not collaborate with other medical centers; however, as already mentioned, as our hospital is a tertiary center, it has a vast experience with CKD patients, which ensures a high accuracy of the investigations. $\square$

CONCLUSIONS

Although the present study has a retrospective design and included a relatively small number of participants, it draws attention on the importance of hematologic parameters as laboratory markers in differentiation between cystitis and pyelonephritis in CKD patients. The main result of our study was the high diagnostic utility and significance of the neutrophil/lymphocyte ratio in separating the upper urinary tract infections from the lower ones, that could also establish a cut-off value of 3.5. This is a very important finding due to its wide availability and low cost, especially in CKD patients, in whom it has also been reported to be an independent predictor for a faster progression toward ESKD. Further research is needed in order to better explore these parameters, as in many situations they

seem to provide easy and accessible solutions for both prognosis and diagnosis. $\square$

Authors' contributions: conceptualization – C.C.; methodology – I.D.-A., O.-A.C., M.P. and C.V.; software – I.D.-A. and O.-A.C.; validation – C.C., L.G., M.P., M.N. and C.V.; formal analysis – I.D.-A. and O.-A.C.; investigation – I.D.-A., I.-G.D.-A. and E.-M.C.; data acquisition and curation – I.-G.D.-A., E.-M.C., E.-A.U., D.-V.V., A.-C.V., V.-G.U., V.-V.V. and P.-C.V.; writing/original draft preparation – I.D.-A.; writing/review and editing – C.C. and M.P.; supervision – C.C., L.G., M.P., M.N. and C.V. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest: none declared.

Financial support: none declared.

Informed consent: Informed consent was obtained from all subjects involved in the present study.

Data availability: Due to privacy reasons, the data used in the study is not available.

Acknowledgments: The publication of this paper was supported by "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

REFERENCES

1. Stevens PE, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024;105:S117-S314. doi: 10.1016/j.kint.2023.10.018.
2. Zyga S, Christopoulou G, Malliarou M. Malnutrition-inflammation-atherosclerosis syndrome in patients with end-stage renal disease. *J Ren Care* 2011;37:12-15. doi: 10.1111/j.1755-6686.2011.00201.x.
3. Bello AK, et al. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. *Kidney Int Suppl* 2017;7:122-129. doi: 10.1016/j.kisu.2017.07.007.
4. Dicu-Andrescu I, et al. The Impact of Infections on the Progression of Chronic Kidney Disease. *Medicina (B. Aires)* 2023;59:1836. doi: 10.3390/medicina59101836.
5. Godaly G, Ambite I, Svanborg C. Innate immunity and genetic determinants of urinary tract infection susceptibility. *Curr Opin Infect Dis* 2015;28:88-96. doi: 10.1097/QCO.000000000000127.
6. Scherberich JE, Fünfstück R, Naber KG. Urinary tract infections in patients with renal insufficiency and dialysis – epidemiology, pathogenesis, clinical symptoms, diagnosis and treatment. *GMS Infect Dis* 2021;9:Doc07. doi: 10.3205/id000076.
7. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996;49:800-805. doi: 10.1038/ki.1996.111.
8. Kim J, et al. Prognostic role of the neutrophil-to-lymphocyte ratio in patients with chronic kidney disease. *Korean J Intern Med* 2023;38:725-733. doi: 10.3904/kjim.2023.171.
9. Litao MKS, Kamat D. Erythrocyte Sedimentation Rate and C-Reactive Protein: How Best to Use Them in Clinical Practice. *Pediatr Ann* 2014;43:417-420. doi: 10.3928/00904481-20140924-10.
10. Harrison M. Abnormal laboratory results: Erythrocyte sedimentation rate and C-reactive protein. *Aust Prescr* 2015;38:93-94. doi: 10.18773/austprescr.2015.034.
11. Han Q, et al. A high neutrophil to lymphocyte ratio is associated with poor nutritional status in chronic kidney disease patients. *Br J Nutr* 2022;128:1990-1996. doi: 10.1017/S000711452100516X.
12. Yoshitomi R, et al. High neutrophil/lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. *Ren Fail* 2019;41:238-243. doi: 10.1080/0886022X.2019.1595645.
13. Popa O, Popa T, Petre N, et al. Mo293 neutrophil-to-lymphocyte ratio and outcome in crescentic glomerulonephritis. *Nephrol Dial Transplant* 2021;36(Supplement_1):gfab104.0051. doi: 10.1093/ndt/gfab104.0051.
14. Yonemoto S, et al. Red cell distribution width and renal outcome in patients with non-dialysis-dependent chronic kidney disease. *PLoS One* 2018;13:e0198825. doi: 10.1371/journal.pone.0198825.
15. Hooton T, Gupta K. Uptodate – Acute simple cystitis in women. UpToDate 2022. <https://www.uptodate.com/contents/acute-simple-cystitis-in-women/print>.
16. Fukui S, Inui A, Saita M, et al. Clinical prediction rule for bacteremia with pyelonephritis and hospitalization judgment: chi-square automatic interaction detector (CHAID) decision tree analysis model.

- J Int Med Res* 2022;50:030006052110656. doi: 10.1177/0300060521106568.
17. **Kana S, Nachiappa Ganesh R, Surendran D, et al.** Urine microscopy and neutrophil-lymphocyte ratio are early predictors of acute kidney injury in patients with urinary tract infection. *Asian J Urol* 2021;8:220-226. doi: 10.1016/j.ajur.2020.01.002.
18. **Roldgaard M, Benfield T, Tingsgård S.** Blood neutrophil to lymphocyte ratio is associated with 90-day mortality and 60-day readmission in Gram negative bacteremia: a multi-center cohort study. *BMC Infect Dis* 2024;24:255. doi: 10.1186/s12879-024-09127-0.
19. **Dimitrijevic Z, Paunovic G, Tasic D, et al.** Risk factors for urosepsis in chronic kidney disease patients with urinary tract infections. *Sci Rep* 2021;11:14414. doi: 10.1038/s41598-021-93912-3.
20. **Saheb Sharif-Askari F, et al.** Blood Neutrophil-to-Lymphocyte Ratio and Urine IL-8 Levels Predict the Type of Bacterial Urinary Tract Infection in Type 2 Diabetes Mellitus Patients. *Infect. Drug Resist* 2020;13:1961-1970. doi: 10.2147/IDR.S251966.
21. **Punatar C, Jadhav K, Kumar V, et al.** Neutrophil:Lymphocyte Ratio as a Predictive Factor for Success of Nephron-Sparing Procedures in Patients with Emphysematous Pyelonephritis. *Perm J* 2019;23:18-044. doi: 10.7812/TPP/18-044.
22. **Ishigami J, Matsushita K.** Clinical epidemiology of infectious disease among patients with chronic kidney disease. *Clin Exp Nephrol* 2019;23:437-447. doi: 10.1007/s10157-018-1641-8.
23. **Wang HE, Gamboa C, Warnock DG, Muntner P.** Chronic Kidney Disease and Risk of Death from Infection. *Am J Nephrol* 2011;34:330-336. doi: 10.1159/000330673.
24. **Aneez FA, Sharifdeen N, Haleem FA, et al.** Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with proteinuria in different stages of chronic kidney disease. *Egypt J Intern Med* 2024;36(6). doi: 10.1186/s43162-023-00270-9.
25. **Dicu-Andreescu I, Penescu MN, Căpușă C, Verzan C.** Chronic Kidney Disease, Urinary Tract Infections and Antibiotic Nephrotoxicity: Are There Any Relationships? *Medicina (Kaunas)* 2022;59:49. doi: 10.3390/medicina59010049.
24. **Gan W, et al.** The association between platelet-lymphocyte ratio and the risk of all-cause mortality in chronic kidney disease: a systematic review and meta-analysis. *Int Urol Nephrol* 2022;54:2959-2967. doi: 10.1007/s11255-022-03234-0.
25. **Umeres-Francia GE, Rojas-Fernández MV, Herrera-Añazco P, Benites-Zapata VA.** Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as risk factors for mortality in Peruvian adults with chronic kidney disease. *Ren Replace Ther* 2022;8:30. doi: 10.1186/s41100-022-00420-9.
26. **Valga F, Monzón T, Henriquez F, Antón-Pérez G.** Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as biological markers of interest in kidney disease. *Nefrol (English Ed)* 2019;39:243-249. doi: 10.1016/j.nefro.2018.11.013.
27. **Purkayastha A, Kalwar A, Firdaus Z, et al.** Platelet to lymphocyte ratio: can it be an early economical mortality predictor of AKI patients? *Egypt J Intern Med* 2024;36:1. doi: 10.1186/s43162-023-00267-4.
28. **Ravindra R, Ramamurthy P, Aslam SMS, et al.** Platelet Indices and Platelet to Lymphocyte Ratio (PLR) as Markers for Predicting COVID-19 Infection Severity. *Cureus* 2022;14:e28206. doi: 10.7759/cureus.28206.
29. **Spoto S, et al.** Diagnostic Accuracy and Prognostic Value of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Septic Patients outside the Intensive Care Unit. *Medicina (B. Aires)* 2021;57:811. doi: 10.3390/medicina57080811.
30. **Kriplani A, et al.** Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) in predicting systemic inflammatory response syndrome (SIRS) and sepsis after percutaneous nephrolithotomy (PNL). *Urolithiasis* 2022;50:341-348. doi: 10.1007/s00240-022-01319-0.
31. **Owoicho O, Tapela K, Olwal CO, et al.** Red blood cell distribution width as a prognostic biomarker for viral infections: prospects and challenges. *Biomark Med* 2022;16:41-50. doi: 10.2217/bmm-2021-0364.
32. **Lippi G, Targher G, Montagnana M, et al.** Guidi. Relation Between Red Blood Cell Distribution Width and Inflammatory Biomarkers in a Large Cohort of Unselected Outpatients. *Arch Pathol Lab Med* 2009;133:628-632. doi: 10.5858/133.4.628.
33. **Li Z, Yang L, Xu Q, Wu F.** Relation between red blood cell distribution width and 30-day in-hospital mortality of patients with ventilator-associated pneumonia. *BMC Infect Dis* 2023;23:696. doi: 10.1186/s12879-023-08692-0.
34. **Ku NS, et al.** Red Blood Cell Distribution Width Is an Independent Predictor of Mortality in Patients With Gram-Negative Bacteremia. *Shock* 2012;38:123-127. doi: 10.1097/SHK.0b013e31825e2a85.
35. **Deng X, Gao B, Wang F, et al.** Red Blood Cell Distribution Width Is Associated With Adverse Kidney Outcomes in Patients With Chronic Kidney Disease. *Front Med* 2022;9:87220. doi: 10.3389/fmed.2022.877220.
36. **Lu Y-A, et al.** Red cell distribution width associated with adverse cardiovascular outcomes in patients with chronic kidney disease. *BMC Nephrol* 2017;18:361. doi: 10.1186/s12882-017-0766-4.
37. **Yoo KD, et al.** Red blood cell distribution width as a predictor of mortality among patients regularly visiting the nephrology outpatient clinic. *Sci Rep* 2021;11:24310. doi: 10.1038/s41598-021-03530-2.
38. **Ramires MLV, et al.** Relation between red blood cell distribution width and acute kidney injury in patients with sepsis. *Einstein (São Paulo)* 2022;20:eAO6828. doi: 10.31744/einstein_journal/2022AO6828.
39. **Kara AV, et al.** Evaluation of the effect of red cell distribution width on the development of acute renal failure in patients with sepsis. *Dicle Tip Derg* 2017;44:191-191. doi: 10.5798/dicletip.319769.
40. **Moreno-Torres V, et al.** Red blood cell distribution width as prognostic factor in sepsis: A new use for a classical parameter. *J Crit Care* 2022;71:154069. doi: 10.1016/j.jcrc.2022.154069.
41. **N. Su et al.** The relationship between platelet distribution width and new-onset cardiovascular disease events in patients with peritoneal dialysis. *Ren Fail* 2022;44:1641-1649. doi: 10.1080/0886022X.2022.2130802.
42. **Ruiyan W, Bin X, Jianhua D, et al.** Platelet Distribution Width and Mortality in Hemodialysis Patients. *Evidence-Based Complement Altern Med* 2021;2021:1-6. doi: 10.1155/2021/6633845.
43. **Lu C, Cheng S, Fan W, et al.** The relationship of platelet distribution width with all-cause and cardiovascular mortality in peritoneal dialysis patients. *Ren Fail* 2024;46. https://doi.10.1080/0886022X.2023.2300730.
44. **Yu Z, et al.** The association between platelet indices and cardiovascular events in chronic kidney disease patients without dialysis. *Int Urol Nephrol* 2021;53:961-971. doi: 10.1007/s11255-020-02696-4.
45. **Guclu E, Durmaz Y, Karabay O.** Effect of severe sepsis on platelet count and their indices. *Afr Health Sci* 2013;13:333-338. doi: 10.4314/ahs.v13i2.19.
46. **Ligi L, et al.** Platelet distribution width (PDW) as a significant correlate of COVID-19 infection severity and mortality. *Clin Chem Lab Med* 2024;62:385-395. doi: 10.1515/cclm-2023-0625.
47. **Dwaya A, Urayet A, Milad MB, Alkout AM.** Platelet Count as Useful Indicator for Gram-Type of Bacteria Causing Urinary Tract Infection in Women. *Iberoam J Med* 2022;4:24-29. doi: 10.53986/ibjm.2022.0006.
48. **Akya A, et al.** Platelet Indices as Useful Indicators of Urinary Tract Infection. *Iran J Pediatr Hematol Oncol* 2019;9:159-165. doi: 10.18502/ijpho.v9i3.1165.