Iran Red Crescent Med J. 2016 July; 18(7):e24319. doi: 10.5812/ircmj.24319.

Published online 2016 May 21. **Research Article**

Association Between Complete Blood Count Parameters and Urinary Stone Disease

Ozay Demiray,[1] Erdem Cevik,[2,*] and Ferhat Cuce[3]

[1]Department of Urology, Van Military Hospital, Van Askeri Hastanesi, Altintepe, Van, Turkey
[2]Department of Emergency Medicine, Van, Military Hospital, Van Askeri Hastanesi, Altintepe, Van, Turkey
[3]Department of Radiology, Van Military Hospital, Van Askeri Hastanesi, Altintepe, Van, Turkey

[*]*Corresponding author*: Erdem Cevik, Department of Emergency Medicine, Van Military Hospital, Van Askeri Hastanesi, Altintepe, Van, Turkey. Tel: +90-4322223329, E-mail: cevikerdem@yahoo.com

Received 2014 October 03; **Revised** 2015 January 02; **Accepted** 2015 March 31.

Abstract

Background: Complete blood count (CBC) parameters may associated with multiple diseases. Urinary stone disease is common public problem. Predictive value of CBC parameters may be associated with urinary stone disease
Objectives: To analyze the association between complete blood count (CBC) parameters and urinary stone disease.
Patients and Methods: This study was a retrospective observational study of 3,099 patients who were admitted to the urology outpatient clinic or diagnosed with urinary stone disease in the emergency services department. There were 353 patients included in the study that had ultrasonography (USG) and/or non-contrast computerized tomography (NCCT) and a CBC. Patients who had non-urinary system inflammatory disease in USG or NCCT, had fever, non-urinary system infection, anemia or diagnosed hematologic malignancy were excluded (n = 27). Patients were divided into two groups: a stone group (n = 74) and a control group (n = 252). Data of patients were retrieved from the hospital database and statistical analysis was performed.
Results: An increase in RDW, MPV, PDW, WBC, granulocyte percentage and a decrease in lymphocyte percentage is statistically associated with urinary stone disease ($P < 0{,}001$, $P < 0.001$, $P = 0.006$, $P < 0.001$, $P = 0.003$, $P = 0.034$, respectively). Microscopic hematuria is associated with urinary stone disease and the odds ratio for urinary stone prediction is 67.7 ($P < 0.001$). In addition, none of the CBC parameters were associated with stone burden.
Conclusions: When evaluating flank pain in patients, it is important to remember that CBC parameters may support urinary stone disease, and considering CBC results may be useful in the diagnosis of urinary stone disease.

Keywords: Urinary Calculi, Blood, Cell Count, Diagnosis

1. Background

Diagnosis and treatment of urinary stone disease is an important health care problem worldwide. The lifetime risk of stone formation for men is 12% and for women is 6%, and this risk has increased in the last quarter of the 20th century (1). Urinary stone disease is responsible for significant economic cost (2).

Although the era of minimally invasive techniques for urinary stones has begun, recurrent stone formation continues to be an important problem. There are multiple theories about stone formation, but none completely explains the mechanisms of stone formation. One of these mechanisms is related to reactive oxygen radicals and oxidative stress and is important, especially in calcium oxalate stones (3). Multiple oxidative stress markers, such as changes in 8-hydroxy-deoxyguanosine calgranulin, α-defensin and myeloperoxidase are apparent in calcium oxalate stone formation (4, 5).

With modern instruments, circulating blood cells can be counted and sized. These instruments can estimate the average cell volume and distribution of cell volume. Red blood cell distribution width (RDW) is a parameter that is calculated by dividing the standard deviation of red blood cell (RBC) volume by the mean corpuscular volume (MCV) multiplied by 100. The main usage of RDW is to differentiate the cause of anemia. Besides differential diagnosis of anemia, recent studies have shown that elevated RDW values are associated with a prognosis of heart failure, sepsis, acute myocardial infarction, and cardiac arrest (6-10). The mechanism of this relationship is still unknown, but inflammation and oxidative stress are suggested for the increase in RDW. Also, recent reports have shown RDW is related with other inflammatory markers such as interleukin-6 and tumor necrosis factor (11, 12).

Mean platelet volume (MPV) is another parameter that can be estimated by complete blood count. The association between MPV and function and activation of platelets has been reported (13). An increase in MPV has been shown in some inflammatory diseases such as inflammatory bowel

diseases, rheumatoid arthritis and ankylosing spondylitis (14-16).

2. Objectives

The aim of this study was to evaluate whether there was a relationship between urinary stone disease, and RDW and MPV as inflammatory markers.

3. Patients and Methods

This retrospective observational study was conducted in a urology outpatient clinic and emergency service of a second-step hospital with a yearly admission of 60.000 patients. Included in this study were patients admitted to the hospital from January 2010 to May 2014. Before the study, approval of the local ethics committee was obtained.

3.1. Patient Selection

The 3,069 adult patients who were admitted to the urology outpatient clinic with CBC and USG and/or whole abdomen NCCT, and who were diagnosed with urinary stone disease by the emergency service between the study dates were included. The patients who had non-urinary system inflammatory disease in USG or NCCT were excluded because of possible changes in CBC. Also, the patients who had fever, non-urinary system infection, anemia or diagnosed hematologic malignancy were excluded, but stone-related urinary system infection patients were included in the study. The 326 patients who were included in the study were grouped as follows: the stone group, who had a stone in USG and/or NCCT, and the control group, who did not have a stone in USG and/or NCCT (Figure 1).

3.2. Data Collection

Demographic data, symptoms and medical history of the patients were taken from the examination form. CBC, USG and/or NCCT results were found in the hospital database, and stone burden was calculated from the data that was previously recorded.

3.3. Measurement Methods

CBC values were measured with the flow cytometry technique. Reference values used were: RBC 4.30 - 6.10 106/mm^3; RDW 10% - 21%; mean corpuscular volume (MCV) 80 - 90 μm^3; platelet (PLT) 150 - 450 103/mm^3; MPV 6 - 5 μm^3; platelet distribution width (PDW) 0.1 - 99.9 μm^3; and creatinine 0.6 - 1.3 mg/dL. Stone burden was calculated as the sum of the longest axis diameters of stones in millimeters in USG and/or NCCT. Erythrocyte or leukocyte count was positive if more than three were counted in a high power field in microscopic analysis of spot urine.

3.4. Outcome Measures

Our primary outcome was the effect of CBC parameters in stone diagnosis. Secondary outcomes were the relations between spot urine analysis, creatinine values, CBC parameters and stone diagnosis or stone burden.

3.5. Statistical Analysis

Continuous variables were examined with the Kolmogorov-Smirnov test for normal distribution. Values with normal distribution were expressed as mean with standard deviation (SD) and values that were not normally distributed were expressed as median with interquartile range (IQR). The Student's t-test or mann-whitney U test was performed, depending on the normality distribution of the variables. Categorical variables were described as a frequency with percentage and compared using the χ^2 test.

We performed multivariate binary logistical regression analysis to determine the independent factors related with urinary stone disease. Variables that had a P value less than 0.05 in univariate analyses between the stone and control groups were included for multivariate analysis.

A two-tailed P value less than 0.05 was considered statistically significant. All analyses were performed using SPSS 21.0 for macintosh (SPSS Inc., Chicago, IL).

4. Results

The stone group had 74 patients and the control group had 252 patients. There were no statistical differences by age and gender between the two groups (Table 1).

4.1. Primary Outcome

Between the stone group and the control group RDW, MPV, PDW, WBC, lymphocyte percentage and granulocyte percentage are statistically different (Table 1). The area under the ROC curves (AUC) in predicting urinary stones for CBC parameters is shown in Figure 2. AUC values for RDW were 0.72 (95% CI 0.65 - 0.78) and for MPV were 0.64 (95% CI 0.57 - 0.71). Binary multiple logistic regression analysis with CBC parameters statistically related with urinary stone disease was performed. RDW, MPV and WBC positively related in our regression model to urinary stone disease prediction (Table 2). Stone risk was increased 1.8-fold (95% CI 1.3 - 2.4) for a one point increase in RDW and 1.6-fold (95 % CI 1.1 - 2.4) for a one point increase in MPV. The sensitivity and specificity of the CBC parameters to predict urinary stones are 95.6% and 27%, respectively.

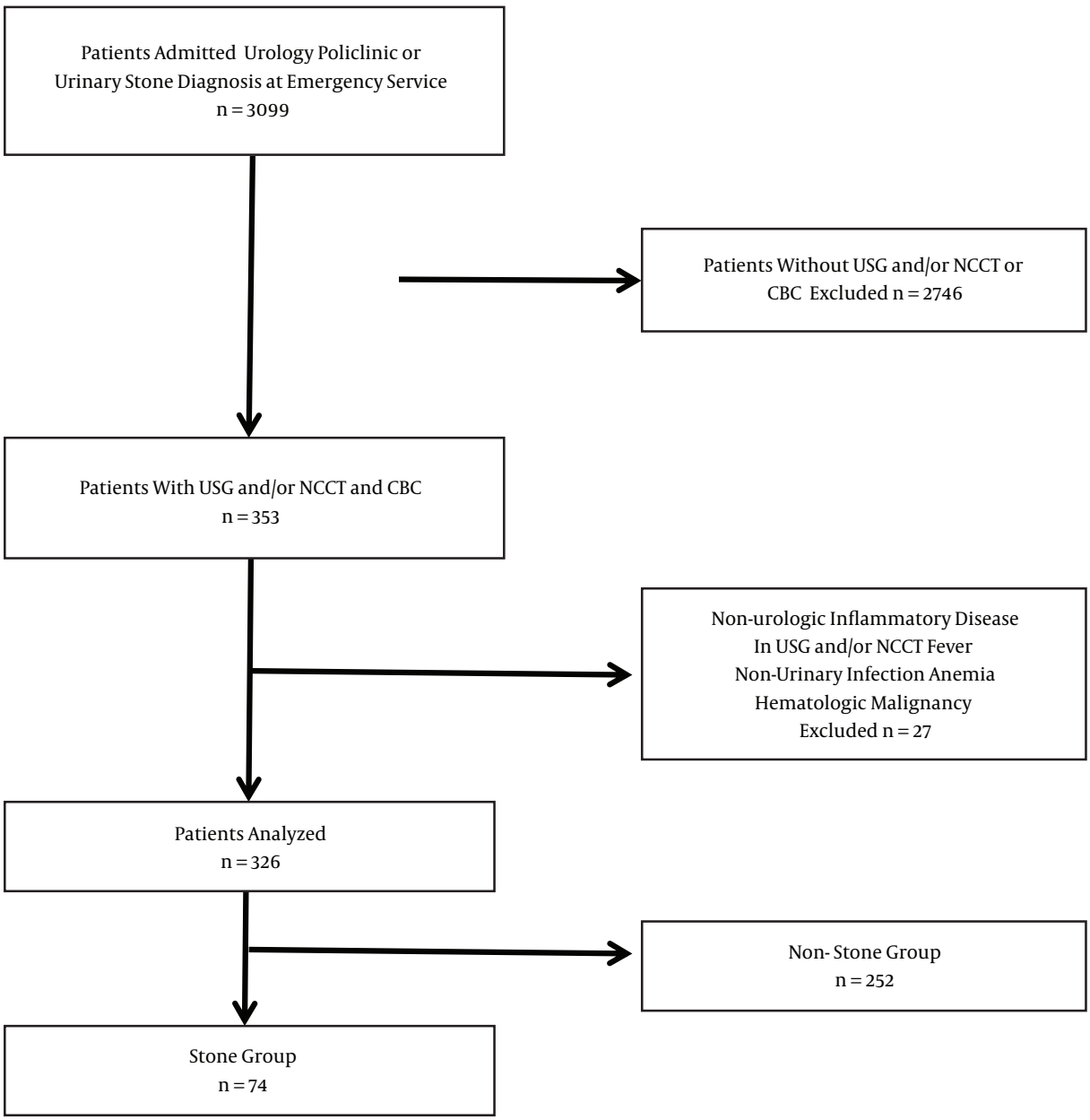


Figure 1. Flow Chart

4.2. Secondary Outcome

The stone group patients were 35% erythrocyte positive in urine analysis, and the control group were 0.7% erythrocyte positive ($P < 0.001$). As a predictive marker, a positive urine erythrocyte demonstrated that the odds ratio (OR) for urinary stone prediction was 67.7 (95% CI 15.5 - 294.7). The creatinine values of the two groups were statistically different (median: 1.0 IQR 0.8 - 1.0 vs. 0.9 IQR 0.9 - 1.1; $P = 0.019$). There is no relationship between any of the CBC parameters and stone burden.

5. Discussion

In this retrospective study, we analyzed the association between CBC parameters and urinary stone disease, we found that RDW, MPV, PDW, WBC and granulocyte per-

Table 1. CBC Parameters of Stone and Control Groups

	Stone Group (N = 74)	Control Group (N = 252)	P Value
Age	28.5 ± 11.7	23.9 ± 6.7	0.24[a]
Gender Female, No. (%)	8 (10)	13 (5)	0.075[a]
RBC	5.30 ± 0.52	5.38 ± 0.43	0.222[a]
MCV[b]	86.8 (82.75-89.25)	87.0 (84.0-90.0)	0.206[c]
RDW[b]	12.7 (12.2-13.5)	11.9 (11.5-12.7)	< 0.001[c]
PLT[b]	252.2 (221.5-295.2)	266.0 (234.2-299.7)	0.199[c]
MPV	8.3 ± 0.8	7.9 ± 0.8	< 0.001[a]
PDW[b]	12.5 (11.5-13.6)	11.9 (10.8-13.0)	0.006[c]
WBC[b]	7.9 (7.0-9.9)	6.9 (5.8-8.0)	< 0.001[c]
LYMPH%[b]	27.6 (16.6-34.0)	30.8 (25.2-35.3)	0.003[c]
GRANU%	64.2 ± 11.9	60.9 ± 9.4	0.034[a]

[a] Student's t-test.
[b] Values are expressed as median (IQR) unless otherwise indicated as mean ± SD.
[c] Mann-whitney-U test P < 0.05 is statistically significant.

Table 2. Binary Multiple Regression Analysis

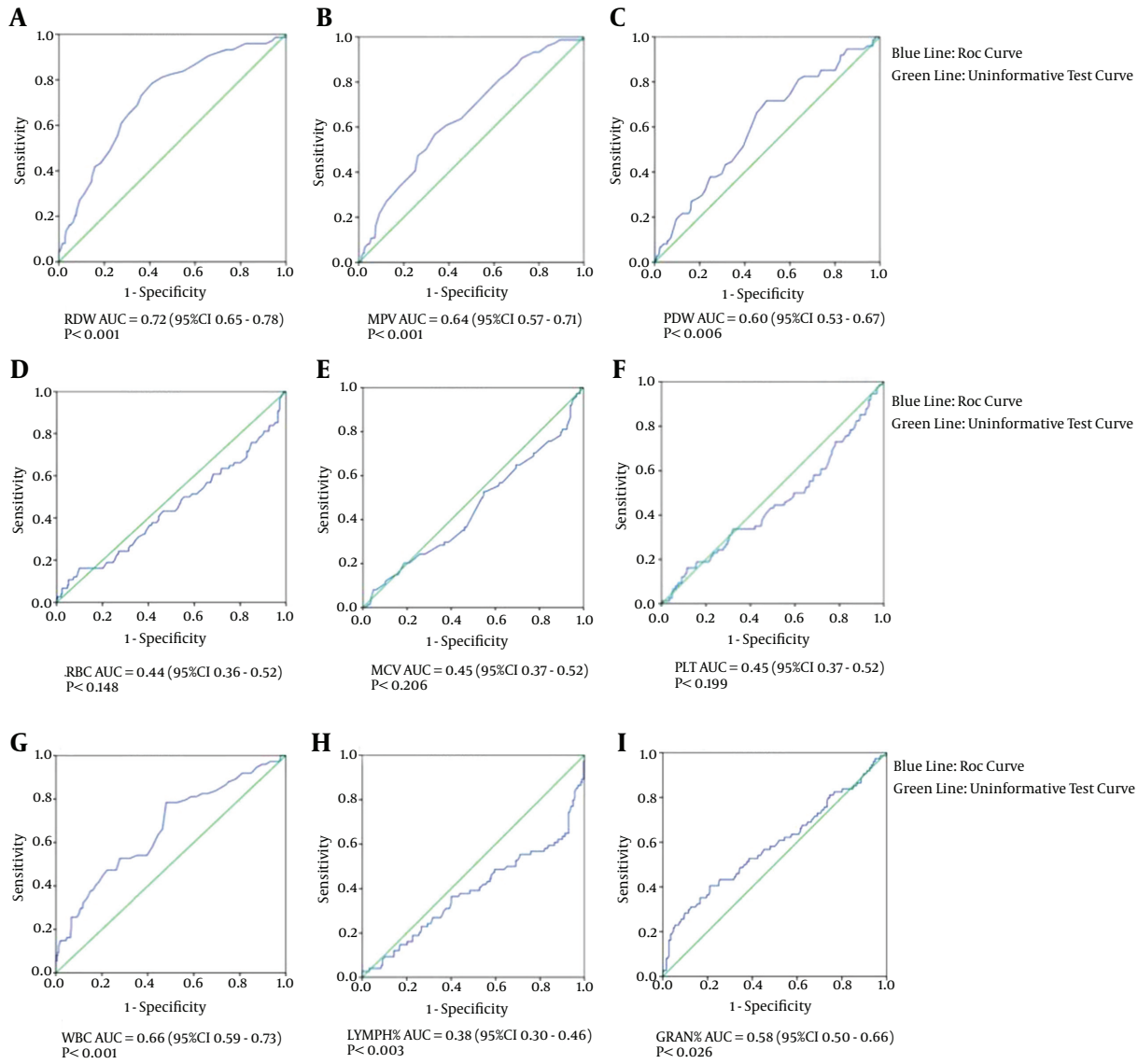
CBC Parameter	P Value[a]	B (95% CI)
RDW	< 0.0001	1.8 (1.3 - 2.4)
MPV	0.008	1.6 (1.1 - 2.4)
PDW	0.616	0.9 (0.8 - 1.1)
WBC	0.001	1.3 (1.1 - 1.5)
Lymphocyte, %	0.504	0.9 (0.9 - 1.0)
Granulocyte, %	0.671	1.0 (0.9 - 1.0)

[a] P < 0.05 is statistically significant.

centage values were increased in urinary stone disease patients, and lymphocyte percentage values were decreased. An increase in RDW is seen in ineffective red blood cell production or increased destruction. Several cytokines, such as tumor necrosis factor α, interleukin-6 and interleukin-1β, could also cause increased destruction of red blood cells and immature red blood cell release (12, 17). In the literature, RDW is associated with the prognosis of acute heart failure, risk and prognosis of a cardiovascular event, risk of mortality in stroke patients and risk of mortality in chronic dialysis patients (7-10). In a recent study, Baysal et al. reported thrombolysis treatment failure in ST-segment elevation myocardial infarction that was associated with an increase in RDW (18). Jo et al. (6) reported that RDW is associated with a prognosis of sepsis in patients and concluded that inflammation may be the cause of an increase in RDW. Also, in inflammatory bowel disease RDW is associated with the activity of the disease (11). Aktas et al. reported the diagnostic value of increased RDW in Hashimoto's thyroiditis patients (19). RDW has also been associated with prediction of mortality in necrotizing fasciitis patients (20). The literature also shows that RDW increase is associated with several inflammatory diseases. RDW increase in urinary stone disease could be associated with inflammation of the uroepithelium. In our study, like other studies, inflammatory markers are increased in patients who have urinary stone disease, and these results are compatible with the literature.

Platelets express mediators for coagulation, thrombosis and inflammation. An increase in MPV is associated with other platelet activation markers such as thromboxane and β-thromboglobulin (13). The relationship with MPV and the prognosis of bloodstream infection as inflammatory markers in active pulmonary tuberculosis and Parkinson's disease has been shown in the literature (21-23). MPV increase is also seen in varicocele patients, as re-

Figure 2. ROC Curves for CBC Parameters



A, ROW AUC = 0.72 (95% CI 0.65 - 0.78) P < 0.001; B, MPV AUC = 0.64 (95% CI 0.57 - 0.71) P < 0.001; C, PDW AUC = 0.60 (95% CI 0.53 - 0.67) P < 0.006; D, RBC AUC = 0.44 (95% CI 0.36 - 0.52) P < 0.148; E, MPV AUC = 0.64 (95% CI 0.57 - 0.71) P < 0.001; F, PLT AUC = 0.45 (95% CI 0.37 - 0.52) P < 0.199; G, WBC AUC = 0.66 (96% CI 0.59 - 0.73) P < 0.00l; H, LYMPH% AUC = 0.38 (95% CI 0.30 - 0.46) P < 0.003; I, GRAN% AUC = 0.58 (95% CI 0.50 - 0.66) P < 0.026.

ported in two studies (24, 25). A recent study of cerebral infarction patients showed that C-reactive protein was correlated with MPV values (26). In this study, we associated urinary stone disease with an increase in MPV values, but this may also be related with inflammation caused by the urinary stone.

Microscopic or macroscopic hematuria is a well-known phenomenon in urinary stone disease and used in scoring to predict ureteral stones (27). We also found that microscopic hematuria is well-related with urinary stone disease.

We concluded that inflammatory markers of CBC parameters could be related with stone burden, but no relationship was found. It may be that the inflammatory process is independent from the stone burden, but further investigations are needed.

Although creatinine levels were in the normal range in both groups, the increase of creatinine levels in the stone

group patients was statistically significant. It was shown that urinary stone history is associated with an increased risk of chronic kidney disease (28). An increase of creatinine in stone patients could be related with renal function deterioration.

5.1. Limitations

The most important limitation of our study was the retrospective study design. Other limitations were the low number of patients, USG was user-dependent and a single radiologist performed all the USG. Also, the negative predictive value of USG is 49. 5% - 61.7%, as some stones could be expelled (29). We did not study any other inflammatory markers.

5.2. Conclusion

Our study showed that CBC parameters, such as RDW and MPV, are associated with urinary stone disease. When evaluating flank pain patients, it is important to remember that CBC parameters could support urinary stone disease, and that considering CBC results may be useful in the diagnosis of these patients.

Footnotes

Authors' Contribution: Study concept and design: Ozay Demiray, Erdem Cevik and Ferhat Cuce; analysis and interpretation of data: Ozay Demiray, Erdem Cevik and Ferhat Cuce; drafting of the manuscript: Ozay Demiray and Erdem Cevik; critical revision of the manuscript for important intellectual content: Ozay Demiray, Erdem Cevik and Ferhat Cuce; statistical analysis: Ozay Demiray and Erdem Cevik.

Financial Disclosure: We declare that we have no commercial, financial or other relationships in any way related to the subject of this article that might create any potential conflict of interest.

References

1. Curhan GC. Epidemiology of stone disease. *Urol Clin North Am.* 2007;**34**(3):287–93. doi: 10.1016/j.ucl.2007.04.003. [PubMed: 17678980].
2. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol.* 2010;**12**(2-3):e86–96. [PubMed: 20811557].
3. Khan SR. Reactive oxygen species as the molecular modulators of calcium oxalate kidney stone formation: evidence from clinical and experimental investigations. *J Urol.* 2013;**189**(3):803–11. doi: 10.1016/j.juro.2012.05.078. [PubMed: 23022011].
4. Boonla C, Wunsuwan R, Tungsanga K, Tosukhowong P. Urinary 8-hydroxydeoxyguanosine is elevated in patients with nephrolithiasis. *Urol Res.* 2007;**35**(4):185–91. doi: 10.1007/s00240-007-0098-0. [PubMed: 17541572].
5. Mushtaq S, Siddiqui AA, Naqvi ZA, Rattani A, Talati J, Palmberg C, et al. Identification of myeloperoxidase, alpha-defensin and calgranulin in calcium oxalate renal stones. *Clin Chim Acta.* 2007;**384**(1-2):41–7. doi: 10.1016/j.cca.2007.05.015. [PubMed: 17610860].
6. Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. *Am J Emerg Med.* 2013;**31**(3):545–8. doi: 10.1016/j.ajem.2012.10.017. [PubMed: 23380094].
7. van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi JL Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. *Eur J Heart Fail.* 2010;**12**(2):129–36. doi: 10.1093/eurjhf/hfp179. [PubMed: 20026456].
8. Chen PC, Sung FC, Chien KL, Hsu HC, Su TC, Lee YT. Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. *Am J Epidemiol.* 2010;**171**(2):214–20. doi: 10.1093/aje/kwp360. [PubMed: 20008450].
9. Sicaja M, Pehar M, Derek L, Starcevic B, Vuletic V, Romic Z, et al. Red blood cell distribution width as a prognostic marker of mortality in patients on chronic dialysis: a single center, prospective longitudinal study. *Croat Med J.* 2013;**54**(1):25–32. [PubMed: 23444243].
10. Kim J, Kim K, Lee JH, Jo YH, Rhee JE, Kim TY, et al. Red blood cell distribution width as an independent predictor of all-cause mortality in out of hospital cardiac arrest. *Resuscitation.* 2012;**83**(10):1248–52. doi: 10.1016/j.resuscitation.2012.01.038. [PubMed: 22322281].
11. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med.* 2009;**133**(4):628–32. doi: 10.1043/1543-2165-133.4.628. [PubMed: 19391664].
12. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion.* 2005;**20**(2):83–90. [PubMed: 15918445].
13. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis.* 1996;**7**(2):157–61. [PubMed: 8735807].
14. Kapsoritakis AN, Koukourakis MI, Sfiridaki A, Potamianos SP, Kosmadaki MG, Koutroubakis IE, et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. *Am J Gastroenterol.* 2001;**96**(3):776–81. doi: 10.1111/j.1572-0241.2001.03621.x. [PubMed: 11280550].
15. Yazici S, Yazici M, Erer B, Erer B, Calik Y, Ozhan H, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. *Platelets.* 2010;**21**(2):122–5. doi: 10.3109/09537100903474373. [PubMed: 20050760].
16. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. *Joint Bone Spine.* 2008;**75**(3):291–4. doi: 10.1016/j.jbspin.2007.06.016. [PubMed: 18403245].
17. Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med.* 2003;**31**(12 Suppl):S651–7. doi: 10.1097/01.CCM.0000098036.90796.ED. [PubMed: 14724462].
18. Baysal E, Cetin M, Yaylak B, Altntas B, Altndag R, Adyaman S, et al. Roles of the red cell distribution width and neutrophil/lymphocyte ratio in predicting thrombolysis failure in patients with an ST-segment elevation myocardial infarction. *Blood Coagul Fibrinolysis.* 2015;**26**(3):274–8. doi: 10.1097/MBC.0000000000000227. [PubMed: 25396765].
19. Aktas G, Sit M, Dikbas O, Tekce BK, Savli H, Tekce H, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis?. *Exp Clin Endocrinol Diabetes.* 2014;**122**(10):572–4. doi: 10.1055/s-0034-1383564. [PubMed: 25380549].
20. Weng CL, Wang CH, Chen IC, Hsiao KY, Chang KP, Wu SY, et al. Red cell distribution width is an independent predictor of mortality in necrotizing fasciitis. *Am J Emerg Med.* 2014;**32**(10):1259–62. doi: 10.1016/j.ajem.2014.08.001. [PubMed: 25178850].

21. Kitazawa T, Yoshino Y, Tatsuno K, Ota Y, Yotsuyanagi H. Changes in the mean platelet volume levels after bloodstream infection have prognostic value. *Intern Med.* 2013;**52**(13):1487–93. [PubMed: 23812196].
22. Gunluoglu G, Yazar EE, Veske NS, Seyhan EC, Altin S. Mean platelet volume as an inflammation marker in active pulmonary tuberculosis. *Multidiscip Respir Med.* 2014;**9**(1):11. doi: 10.1186/2049-6958-9-11. [PubMed: 24581084].
23. Kocer A, Yaman A, Niftaliyev E, Duruyen H, Eryilmaz M, Kocer E. Assessment of platelet indices in patients with neurodegenerative diseases: mean platelet volume was increased in patients with Parkinson's disease. *Curr Gerontol Geriatr Res.* 2013;**2013**:986254. doi: 10.1155/2013/986254. [PubMed: 24382959].
24. Coban S, Keles I, Biyik I, Guzelsoy M, Turkoglu AR, Ozgunay T, et al. Is there any relationship between mean platelet volume and varicocele?. *Andrologia.* 2015;**47**(1):37–41. doi: 10.1111/and.12220. [PubMed: 24387241].
25. Bozkurt Y, Soylemez H, Sancaktutar AA, Islamoglu Y, Kar A, Penbegul N, et al. Relationship between mean platelet volume and varicocele: a preliminary study. *Urology.* 2012;**79**(5):1048–51. doi: 10.1016/j.urology.2012.01.019. [PubMed: 22381251].
26. Lee JH, Kwon KY, Yoon SY, Kim HS, Lim CS. Characteristics of platelet indices, neutrophil-to-lymphocyte ratio and erythrocyte sedimentation rate compared with C reactive protein in patients with cerebral infarction: a retrospective analysis of comparing haematological parameters and C reactive protein. *BMJ Open.* 2014;**4**(11):e006275. doi: 10.1136/bmjopen-2014-006275. [PubMed: 25412865].
27. Moore CL, Bomann S, Daniels B, Luty S, Molinaro A, Singh D, et al. Derivation and validation of a clinical prediction rule for uncomplicated ureteral stone–the STONE score: retrospective and prospective observational cohort studies. *BMJ.* 2014;**348**:g2191. doi: 10.1136/bmj.g2191. [PubMed: 24671981].
28. Shoag J, Halpern J, Goldfarb DS, Eisner BH. Risk of chronic and end stage kidney disease in patients with nephrolithiasis. *J Urol.* 2014;**192**(5):1440–5. doi: 10.1016/j.juro.2014.05.117. [PubMed: 24929140].
29. Ray AA, Ghiculete D, Pace KT, Honey RJ. Limitations to ultrasound in the detection and measurement of urinary tract calculi. *Urology.* 2010;**76**(2):295–300. doi: 10.1016/j.urology.2009.12.015. [PubMed: 20206970].