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Original Investigation / Özgün Araştırma

Evaluation of the Role of the Relationship Between Red Blood Cell Distribution Width (RDW) and Monocyte on Estimation of Mortality in Surgical Intensive Care Unit

Cerrahi Yoğun Bakım Ünitesinde Kırmızı Kan Hücre Dağılım Genişliği ve Monosit Arası İlişkinin Mortalite Tahminindeki Rolünün Değerlendirilmesi

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Abstract

Objective: The aim of the present study was to assess the usability of the relationship between the red blood cell distribution width (RDW) and the monocyte count, complete blood count (CBC) parameters routinely checked in the intensive care units (ICUs), for mortality prediction in the surgical ICU.

Material and methods: Five hundred thirty-seven patients who were followed up at the surgical ICU between October 1, 2014 and October 1, 2015 were retrospectively assessed. To ensure that the study involves patients who really needed intensive care, patients who were followed up at the ICU for postoperative monitoring were excluded from the study. Patients with a hemoglobin value <10 g/dL were also excluded from the study so that the RDW would not be affected by anemia.

Results: A total of 183 patients were evaluated after the exclusion criteria. The maximum RDW value and the Acute Physiology and Chronic Health Evaluation II score of the patients who died were higher than those of the living patients. On the other hand, a significant decrease in the monocyte values of the dead patients was detected, and there was a statistical difference between dead and living patients ($p<0.01$).

Conclusion: Checking CBC is a routine in the ICUs. Of the CBC parameters, the RDW and monocyte values have been assessed in the present study as being convenient, easily accessible, and practical method for predicting mortality for surgical intensive care patients.

Keywords: Intensive care, surgery, monocytes, mortalities

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Öz

Amaç: Bu çalışmada, yoğun bakımlarda rutin olarak kontrol edilen tam kan sayım parametrelerinden, kırmızı kan hücre dağılım genişliği (RDW) ve monosit sayısı arasındaki ilişkinin, cerrahi yoğun bakımda mortalite tahmininde kullanılabilirliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: 1 Ocak 2014 ile 1 Ocak 2015 tarihleri arasında cerrahi yoğun bakım ünitesinde takip edilen 537 hasta retrospektif olarak değerlendirildi. Çalışmanın gerçek yoğun bakım ihtiyacı olan hastaları kapsaması için, postoperatif monitorizasyon için yoğun bakımda takip edilen hastalar çalışmadan dışlandı. Ayrıca RDW'nin anemiden etkilenmemesi için hemoglobin 10 gr/dL altında olan hastalarda çalışmadan dışlandı.

Bulgular: Dışlanma kriterleri sonrasında toplam 183 hasta değerlendirildi. Mortalite gelişen hastaların maksimum RDW değeri ve APACHE (Acute Physiology and Chronic Health Evaluation) II skoru yaşayan hastalarla karşılaştırıldığında daha yüksekti. Öte yandan ölen hastaların monosit değerlerinde belirgin bir düşüş saptandı. Mortalite gelişen ve hayatta kalan hastalar arasında istatistiksel olarak anlamlı fark bulundu ($p<0,01$).

Sonuç: Tam kan sayımı kontrolü yoğun bakımlarda rutindir. Tam kan sayımı parametrelerinden RDW ve monosit değerleri, bu çalışmada cerrahi yoğun bakım hastalarında mortaliteyi öngörmek için uygun, kolay erişilebilir ve pratik bir yöntem olarak değerlendirilmiştir.

Anahtar kelimeler: Yoğun bakım, cerrahi, monositler, mortaliteler

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Ethics Committee Approval: Ethics committee approval was received for this study from the Hacettepe University Ethics Committee (15/746-25).

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

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Introduction

In intensive care units (ICUs), risk assessment is often based on scoring systems. Among the scoring systems, the most commonly used system for scoring critical patient risk assessment is the Acute Physiology and Chronic Health Evaluation (APACHE) II. Other than the APACHE II, a wide range of scoring systems is available for use in the ICUs (1). However, since scoring systems require the use of both multiple complex logarithmic cross tables and logarithmic formulas, their usefulness in the ICUs is limited. Currently, there remains a need for risk prediction models, which are reliable and can provide more objective numerical evaluations that do not require complex formulas in the ICUs. These models are needed to predict both disease severity and mortality, to evaluate the success of the treatment performed, and to determine the optimal use of medical resources. Red blood cell distribution width (RDW) is a quantitative measurement of anisocytosis, the size of circulating red blood cells. Recent studies have provided growing evidence that RDW has a prognostic value. Until today, most studies on RDW were conducted by the cardiovascular disease group (2). Apart from this, in terms of both mortality and morbidity, a relationship has been shown between RDW and many clinical conditions, such as metabolic syndrome, inflammatory bowel disease, and septic shock (3-5). However, the underlying pathophysiology of this relationship is still unclear. The most widely accepted hypothesis on this subject focuses on the effects of both systemic inflammation and oxidative stress (6). Inflammation has been suggested to increase bone marrow metabolism and lead to the expression of some proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin (IL)-1β, and IL-6, to cause the suppression of erythrocyte maturation and shorten the lifespan of erythrocytes, and consequently, to lead to the presence of new and larger reticulocytes in circulation. It is important to note that as a result of this inflammation, anisocytosis occurred in erythrocytes, and RDW increased (7-13). Monocytes are central mediators of the immune response. After neutrophil infiltration, migration of monocytes to the inflamed area occurs (14). The inflammatory stimulus affects the number of monocytes in the peripheral blood (15). The primary role of monocytes is to survey the environment and to fill the pool of both tissue macrophages and dendritic cells (16). Proliferative activity in the bone marrow that occurred as a response to an inflammatory stimulus leads to an increase in monocytes (17, 18).

Recent studies have shown that peripheral monocyte count is an independent predictive factor for poor prognosis and mortality in cancers of the organs, such as head–neck, cervix, colon, biliary tract, and stomach (19-22).

The aim of the present study was to evaluate the availability of RDW and monocytes as markers to predict mortality and other variable patient characteristics in the surgical ICU and to make these assessments using the APACHE II scoring system that is commonly used in the ICUs.

Material and Methods

In the present study, 537 patients who were hospitalized at the Hacettepe University School of Medicine Surgical Intensive Care Unit between October 1, 2014 and October 1, 2015 were retrospectively evaluated. Ethical approval was obtained from the ethical committee of Hacettepe University (GO 15/746-25) for retrospective analyses. Patients <18 years old were excluded from the study. Patients with a hemoglobin level <10 g/dL were excluded from the study to avoid the effects of anemia. Patients who were admitted to the ICU for postoperative observation and whose hospital stay was <3 days were also excluded from the study to evaluate patients who needed real intensive care.

All patient information was obtained from the Hacettepe University School of Medicine Data Processing System. Age, gender, RDW value (reference range: 11.7%-14.6%), monocyte count (reference range: 0.3-0.9×10^3/μL), hemoglobin value (reference range: 34.5%-46.3%), and the APACHE II score at 24 h after admission to the ICU were recorded in the admission of the patients to the ICU. In addition, the highest RDW value, the lowest and highest monocyte value, and the lowest hemoglobin value were detected during the last 72h of ICU stay. Blood transfusions were also recorded during the intensive care hospitalizations of the patients.

Venous blood samples were collected into K2-EDTA tubes (Becton Dickinson and Company, NJ, USA). Complete blood count (CBC) and differential blood count were performed by a Coulter LH 780 fully automated cell counter (Beckman Coulter GmbH, Krefeld, Germany). Briefly, blood was aspirated, erythrocytes were lysed, and leukocytes were counted based on the impedance of the cell nuclei. In this system, the leukocyte count was performed in three capillaries, and the mean was reported as erythrocytes and platelets. A leukocyte differential count was performed by VCS technology based on the simultaneous measurement of volume, conductivity, and scattering of the laser, and the size of leukocytes, surface structure, granule content, and ratio of the nucleus to the cytoplasm are determined. Cells were classified into five leukocyte populations: lymphocytes, monocytes, neutrophils, eosinophils, and basophils. Cell data were displayed in a matrix and transferred in clusters to a 3D coordinate system. This 3D space presentation allowed the determination of the proportion of leukocyte subpopulations. The absolute numbers of leukocytes could be calculated from the total leukocyte count. The differential count also determined the means for volume, conductivity, and scattered light and the corresponding distribution and widths, including RDW.

Statistical Analysis

Logistic regression analysis and receiver operating characteristic (ROC) analysis were utilized to build a model between monocytes, RDW, and a patient's mortality status. In ROC analyses, both monocyte and RDW measurements during the last 72h of ICU stay that provided the highest area under the curve (AUC) values (minimum monocyte and maximum RDW) were considered. The cut-off points providing optimum sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for minimum monocyte and maximum RDW measurements were determined. According to the determined cut-off values for monocyte and RDW, these variables were categorized into two groups for use in the logistic regression. The relationship between categorical variables and mortality status was analyzed by the Pearson Chi-square or the Likelihood Ratio (LR) Chi-square test. Numerically measured variables were compared using the Mann-Whitney U test to reveal the differences between the two mortality groups. Two different logisticregression models were constructed, using minimum monocyte and maximum RDW as explanatory variables. The first model included only age, minimum monocyte, and maximum RDW as variables. In the second model, all variables with significance on univariate comparisons were included in the logistic regression model, and the variables found in the model were selected based on the backward stepwise regression method.

Table 1. Comparison of patient status with demographic and clinical features RDW, red blood cell distribution width.

	Alive (n=144)		Deceased (n=39)		
	Mean±SD		Mean±SD		p
Age (years)	59.40±17.42		67.85±14.54		0.005
APACHE II score	6.90±3.17		13.87±5.55		0.001
Minimum monocyte ($10^3/\mu L$)	0.45±0.32		0.21±0.28		0.001
Maximum RDW (%)	16.46±3.26		19.36±3.78		0.001
Hemoglobin (g/dL)	12.67±1.78		11.47±1.63		0.001
	Frequency	%	Frequency	%	p
Gender					
Male	88	77.2	26	22.8	0.654
Female	56	81.2	13	18.8	
Focus of infection					
No	71	95.9	3	4.1	0.001
Yes	73	67	36	33	
Intra-abdominal infection					
No	77	87.5	11	12.5	0.009
Yes	67	70.5	28	29.5	
Blood transfusion					
No	105	92.1	9	7.9	0.001
Yes	38	56.7	29	43.3	
Type of treatment					
Medical	37	78.7	10	21.3	1.000
Operation	107	78.7	29	21.3	

Data were presented as mean±SD and median values for numerical variables and frequencies and percentages for categorical variables

Statistical analyses were performed The Statistical Package for Social Sciences, version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) program and R version 3.2.5 (R Development Core Team, Vienna, Austria) statistical programming language. A $p<0.05$ was accepted as statistically significant.

Results

A total of 183 participants were included in the study. There were 114 (62%) men. The median age of the patients was 64 (range, 20-96) years. While 47 patients were treated medically, 136 underwent operation. While 144 patients lived, 39 patients died. The average hospitalization time of the patients was 12 days.

Age, APACHE score, and maximum RDW were higher in dead participants than in patients who survived, whereas minimum monocyte and hemoglobin were lower (Table 1, $p<0.01$). Figure 1 shows the median values and distributions. If the distribution of categorical features in the groups was examined, both focus of infection and intra-abdominal infection were significant compared with the patient's status (survival or death), but there was no significant effect of gender and type of treatment on patient outcome ($p>0.05$).

Results of the ROC analysis

The ROC analysis was applied to determine the cut-off values, which are the critical cut-off points for the minimum monocyte, maximum RDW values, and APACHE II score measurements that are thought to be susceptible to mortality. Table 2 shows the AUC, PPV, and NPV for the determined cut-off values.

The best separator performance was achieved by the APACHE II score (AUC=0.85, sensitivity=0.71). When the best cut-off point for the minimum monocyte was obtained as $0.15\times10^3/\mu L$, the success rate of the diagnosis was found as AUC=0.75, with a mortality of $\leq0.15\times10^3/\mu L$ in the minimum monocyte value. Similarly, when the RDW value is ≥17.15%, the success rate of mortality recognition was obtained as AUC=0.78.

Two different logistic regression models were developed by taking into account the basic variables that were significant as a result of univariate analysis between the patient's status (survival or death) and other clinical variables. The first model is a restricted model with age, minimum monocytes (low/high based on cut-off point), and maximum RDW (low/high based on cut-off point), whereas the second model is a full model that also included the other significant parameters, such as APACHE II score, hemoglobin, focus of infection, intra-abdominal infection, and blood transfusion. The first restricted model was used to elucidate the estimation success of monocyte and RDW measurements on patient outcomes. In contrast, the full model includes variables selected from the backward variable selection method among all the variables. Table 3 shows the outputs of model 1 and model 2 and the results of the log LR test (a comparison of goodness-of-fit) of these models.

In the first restricted model, both the minimum monocyte and the maximum RDW are significant ($p<0.05$, odds ratio=8.84 and 4.03, respectively), whereas the full model does not include the maximum RDW (although there was no important effect of age on mortality in the full model in which the APACHE II score was added, age was also an important factor in the first model). The risk of mortality in the full model was 4.08 times higher in patients whose monocytes were below the cut-off value ($0.15\times10^3/\mu L$), whereas this risk was 8.84 times in the restricted first model.

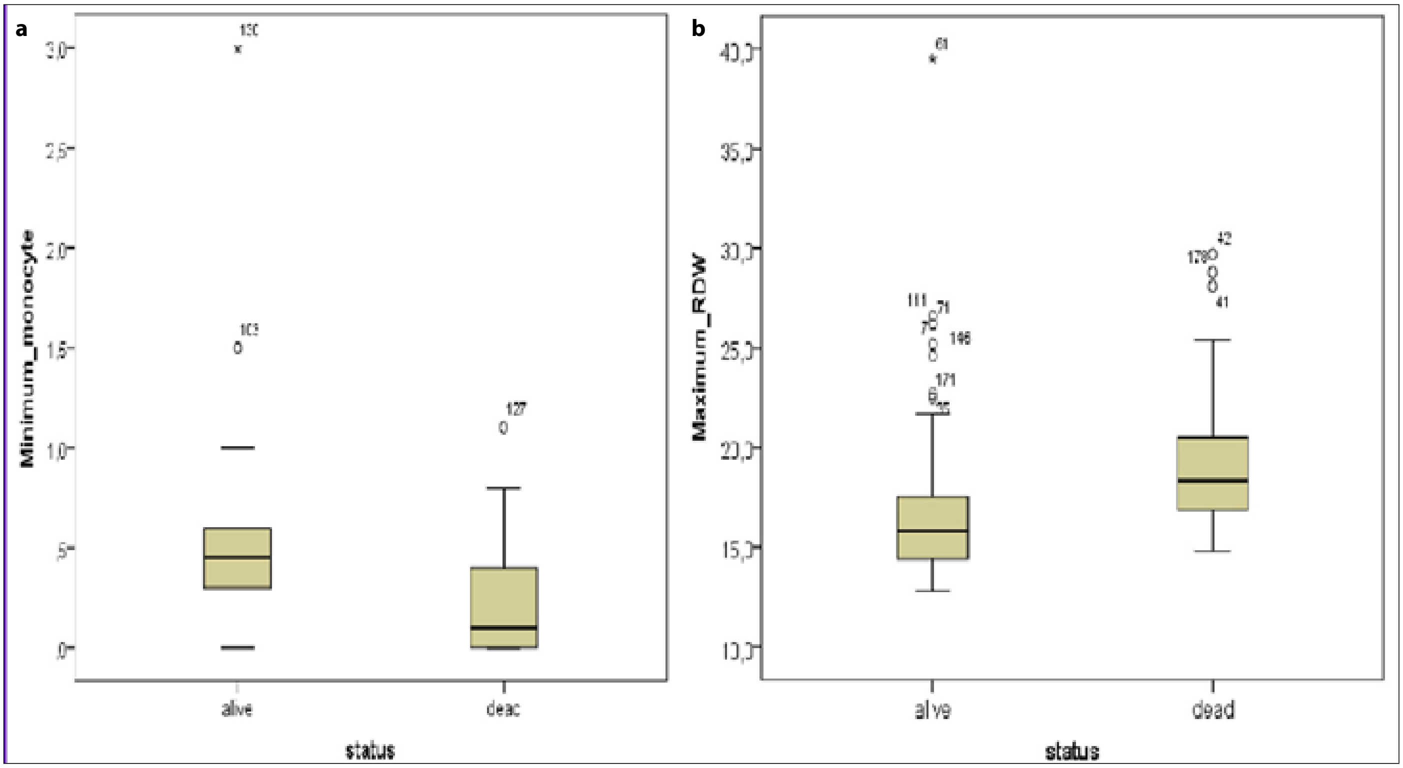

Figure 1. a, b. Distribution of monocyte (a) and RDW measurements according to patient status (b).

Table 2. ROC analysis and cut-off values for mortality expectations and APACHE II score.

Mortality scores	AUC	Sensitivity	Specificity	PPV	NPV
Minimum monocyte (≤0.15×10³/μL)	0.751 (0.65-0.85)	0.62	0.87	0.56	0.89
Maximum RDW (≥17.15%)	0.779 (0.71-0.85)	0.70	0.72	0.40	0.90
APACHE II score (10.50)					

RDW: red blood cell distribution width; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value

Table 3. Restricted and full model results for patient's mortality prediction.

Model 1				
Variable	**p**	**Odds ratio**	**95% CI (lower-upper)**	
Age (years)	0.039	1.03	1.01	1.07
Minimum monocyte	<0.001	8.84	3.16	21.06
Maximum RDW	0.001	4.03	1.70	9.55
Model 2				
Variable	**p**	**Odds ratio**	**95% CI (lower-upper)**	
Minimum monocyte	0.008	4.08	1.45	11.54
APACHE II score	<0.001	1.37	1.20	1.55
Blood transfusion	0.005	4.45	1.55	12.76

Model 1 consists only of age, minimum monocyte, and maximum RDW
In Model 2, analysis was performed by including monocyte, RDW, APACHE II, hemoglobin, focus of infection, intra-abdominal infection, and blood transfusion and a final model containing monocyte, APACHE II and blood transfusion variables, which were found to be significant

The LR test was performed by estimating two models and comparing the fit of one model with the fit of the other. We performed both the full and the restricted models and assessed the difference in fit using the LR test function. Therefore, our LR test statistic was 26.881 (Chi-square distribution), with two degrees of freedom. The associated p-value (p=0.0014) indicated that the model with all eight predictors fit significantly better than the model with only three predictors.

It is clear that the AUC value obtained from the first restricted model (AUC=0.847) was very close to that obtained from the full model (AUC=0.914) even though the full model provided a significant improvement over the restricted model.

Discussion

Complete blood count (CBC) is a routinely used test in the ICUs. In these tests, monocyte count and RDW are routinely reported. In the present study, we established two models for the determination of monocyte count and RDW availability in predicting mortality in surgical intensive care patients. We determined that RDW value and monocyte count were important parameters in the prediction of mortality. RDW value was higher, whereas monocyte count was significantly lower in dead patients than in living patients.

In a study about RDW by Patel et al. (23), they suggested that every 1% increase in RDW results in a 22% increase in mortality. The relationship between different patient groups and RDW has been the focus of many studies. Lorente et al. (24) evaluated the relationship between RDW and mortality in the first week in patients with sepsis. The RDW value was found to be higher in patients who died within the first week than in surviving patients. Weng et al. (25) suggested that RDW is an independent predictive factor for mortality. As a result of the study, the RDW value being ≥14.5% in 98 patients admitted to the emergency department due to necrotizing fasciitis was found to be an independent predictor factor for mortality. In a different study on mortality conducted by Bello et al. (26), they found that RDW >14% is an independent risk factor for long-term mortality in acquired community pneumonia. In a retrospective study of 2915 patients conducted by Meynaar et al. (27), the increase in RDW in the ICU was assessed as an independent risk factor in predicting mortality. In the ROC analysis of the present study, the AUC value was detected as 0.845. In a study conducted by Fujita et al. (28) with 829 patients in the medical ICU, the RDW value >16.1% for all patients was found to be an increased risk for mortality in the ICU. In the present study conducted in the surgical ICU, our results were consistent with the literature. The cut-off value for RDW was found to be 17.15% (AUC=0.78). In our study, similar to the results of other studies, the RDW value was found to be an independent risk factor for mortality in patients in the surgical ICU.

To our knowledge, no studies have been found in the literature for the comparison with our study on monocyte count. However, Kato et al. (29) evaluated leukocyte subtypes in hemodialysis patients. There was a statistically significant increase in mortality in patients with >270/µl monocyte count. In 2014, Lee et al. evaluated 603 patients. In their study, they found that preoperative peripheral blood monocyte ratio >7% is a poor prognostic factor in patients with hepatocellular carcinoma (HCC). As a result of the study, the researchers suggested that preoperative monocyte ratio can be used as a new prognostic biomarker in patients with HCC (30). Rezende et al. (31) investigated the relationship between RDW and blood monocyte counts for the risk of venous thrombosis. They found that an increase of >14.1%, even being in the normal range of RDW, is associated with an increased risk of venous thrombosis; they also showed that a monocyte count $<0.12\times10^9$/L is associated with lower risk of venous thrombosis, and a monocyte count $>0.55\times10^9$/L is associated with an increased risk of venous thrombosis.

Before the present study, we detected in our clinical observations that there was an increase in mortality in our intensive care patients with an increase in RDW and a decrease in monocyte count. We found consistent results with our observations in the present study that was planned as a result of our observations. However, the results of our studies with monocyte counts were interestingly different from the results of monocyte count studies in the literature. Studies in the literature with monocyte counts indicate that the increase in monocyte percentage and number is associated with poor prognosis and mortality. However, in our study, the cut-off value for monocyte count was found to be 0.15×10^3/µL (AUC=0.75), and we detected an increase in mortality in surgical ICU patients with the monocyte count below this value. The mechanism of this result is unclear. However, monocytes are the precursor cells of tissue macrophages and play an important role in the immune system (16). Therefore, this suggests that the decrease in monocyte count can lead to an insufficient immunological response and an increase in mortality.

In our limited model composed of age, RDW, and monocyte (AUC=0.847), we obtained similar results with full model (AUC=0.914) composed of APACHE II, hemoglobin, focus of infection, intra-abdominal infection, and blood transfusion. Although APACHE II is widely used in the management of patients in the ICU and is considered as a gold standard, it is not very practical and requires many data entries (32). The RDW and monocyte counts may be a good alternative to the APACHE II score in predicting the mortality in ICU with the ease of accessibility and lower cost.

Conclusion

Both RDW and monocyte counts in surgical intensive care patients were considered to be an appropriate and practical method for predicting mortality. However, data from the study were obtained retrospectively and included only the patients in the surgical ICU. We believe that more comprehensive and prospective studies are needed in terms of method and number to clarify the results of the study.

References

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13: 818-29. [CrossRef]
2. Jung C, Fujita B, Lauten A, Kiehntopf M, Küthe F, Ferrari M, et al. Red blood cell distribution width as useful tool to predict long-term mortality in patients with chronic heart failure. Int J Cardiol 2011; 152: 417-8. [CrossRef]
3. Fujita B, Strodthoff D, Fritzenwanger M, Pfeil A, Ferrari M, Goebel B, et al. Altered red blood cell distribution width in overweight adolescents and its association with markers of inflammation. Pediatr Obes 2013; 8: 385-91. [CrossRef]
4. Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/undifferentiated colitis. Dig Dis Sci 2008; 53: 2521-3. [CrossRef]
5. Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 2013; 28: 307-13. [CrossRef]
6. Polat V, Iscan S, Etli M, El Kilic H, Gürsu O, Eker E, et al. Red cell distribution width as a prognostic indicator in pediatric heart disease and after surgery. BioMed Res Int 2014; DOI: 10.1155/2014/681679. [CrossRef]
7. Ku NS, Kim HW, Oh HJ, Kim YC, Kim MH, Song JE, et al. Red blood cell distribution width is an independent predictor of mortality in patients with gram-negative bacteremia. Shock 2012; 38: 123-7. [CrossRef]
8. Senol K, Saylam B, Kocaay F, Tez M. Red cell distribution width as a predictor of mortality in acute pancreatitis. Am J Emerg Med 2013; 31: 687-9. [CrossRef]
9. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 2005; 20: 83-90. [CrossRef]
10. Scharte M, Fink MP. Red blood cell physiology in critical illness. Crit Care Med 2003; 31: 651-7. [CrossRef]
11. Chiari MM, Bagnoli R, De Luca PD, Monti M, Rampoldi E, Cunietti E. Influence of acute inflammation on iron and nutritional status indexes in older inpatients. J Am Geriatr Soc 1995; 43: 767-71. [CrossRef]
12. Kolls JK. Oxidative stress in sepsis: a redox redux. J Clin Invest 2006; 116: 860-3. [CrossRef]
13. Ghaffari S. Oxidative stress in the regulation of normal and neoplastic hematopoiesis. Antioxid Redox Signal 2006; 10: 1923-40. [CrossRef]
14. Lee SD, Kim SH, Kim YK, Lee SA, Park SJ. Prognostic significance of preoperative peripheral blood monocyte ratio in patients with hepatocellular carcinoma. World J Surg 2014; 38: 2377-85. [CrossRef]
15. Leithead JA, Rajoriya N, Gunson BK, Ferguson JW. Neutrophil-to-lymphocyte ratio predicts mortality in patients listed for liver transplantation. Liver Int 2015; 35: 502-9. [CrossRef]
16. Jiyeon Y, Lixiao Z, Caijia Y, Xiao-F Y, Hong W. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. Biomark res 2014; DOI: 10.11.1186/2050-7771-2-1

17. Meuret G, Bammert J, Hoffmann G: Kinetics of human monocytopoiesis. Blood 1974; 44: 801-16.
18. Sabrina B, Tommaso M, Giovanna A, Sara AE, Michela S, Mauro V et al. Extended leukocyte differential count and C-reactive protein in septic patients with liver impairment: diagnostic approach to evaluate sepsis in intensive care unit. Ann Transl Med 2015; 3: 244.
19. Sajadieh A, Mouridsen MR, Selmer C, Intzilakis T, Nielsen OW, Haugaard SB. Monocyte number associated with incident cancer and mortality in middleaged and elderly community-dwelling Danes. Eur J Cancer 2011; 47: 2015-22. [CrossRef]
20. Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S. Prognostic value of preoperative peripheral blood monocyte count in patients with hepatocellular carcinoma. Surgery 2006; 139: 755-64. [CrossRef]
21. Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Tominaga M, et al. Prognostic value of preoperative peripheral blood monocyte count in patients with colorectal liver metastasis after liver resection. J Gastrointest Surg 2007; 11: 596-02. [CrossRef]
22. Lee YY, Choi CH, Sung CO, Do IG, Huh S, Song T, et al. Prognostic value of pretreatment circulating monocyte count in patients with cervical cancer: comparison with SCC-Ag level. Gynecol Oncol 2012; 124: 92-7. [CrossRef]
23. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. Arch Intern Med 2009; 169: 515-23. [CrossRef]
24. Lorente L, Martin MM, Gonzales PA, Violan JS, Ferreres J, Labarta L et al. Red Blood Cell Distribution Width during the First Week Is Associated with Severity and Mortality in Septic Patients. PLoS One 2014; DOI: 10.1371/journal.pone.0105436. [CrossRef]
25. 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: 1259-62. [CrossRef]
26. Bello S, Fandos S, Lasierra AB, Minchol_E, Panadero C, Simon AL, et al. Red blood cell distribution width [RDW] and long-term mortality aftercommunity-acquired pneumonia. A comparison with proadrenomedullin. Respir Med 2015; 109: 1193-206. [CrossRef]
27. Meynaar IA, Knook AH, Coolen S, Le H, Bos MM, Dijs F, et al. Red cell distribution width as predictor for mortality in critically ill patients. Neth J Med 2013; 71: 488-93.
28. Fujita B, Franz M, Figulla HR, Pfeifer R, Kabisch B, Fritzenwanger M, et al. Red cell distribution width and survival in patients hospitalized on a medical ICU. Clin Biochem 2015; 48: 1048-52. [CrossRef]
29. Kato A, Takita T, Fruhashi M, Maruyama M, Kumagai H, Hishida A. Blood monocyte count is a predictor of total and cardiovascular mortality in hemodialysis patients. Nephron Clin Pract 2008; 110: 235-43. [CrossRef]
30. Lee SD, Kim SH, Kim YK, Lee SA, Park SJ. Prognostic significance of preoperative peripheral blood monocyte ratio in patients with hepatocellular carcinoma. World J Surg 2014; 38: 2377-85. [CrossRef]
31. Rezende SM, Lijfering WM, Rosendaal FR, Cannegieter SC. Hematologic variables and venous thrombosis: red cell distribution width and blood monocyte count are associated with an increased risk. Haematologica 2014; 99: 194-200. [CrossRef]
32. Breslow MJ, Badawi O. Severity scoring in the critically ill: part 1-interpretation and accuracy of outcome prediction scoring systems. Chest 2012; 141: 245-52. [CrossRef]