The utility of red cell distribution width to predict mortality of septic patients in a tertiary hospital of Nepal.

CURRENT STATUS: UNDER REVIEW

Rajan Ghimire  biplawi.shashi@gmail.com
Nick Simmons Institute
Corresponding Author
ORCiD: 0000-0001-5095-8477

Yogendra Man Shakya
Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University

Tirtha Man Shrestha
Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan

Ram Prasad Neupane
Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University

DOI:
10.21203/rs.2.10110/v2

SUBJECT AREAS
Critical Care & Emergency Medicine

KEYWORDS
red cell distribution width, sepsis, emergency care, mortality
Abstract

Background: Sepsis is a common problem encountered in the emergency room which needs to be intervened early. Predicting prognosis is always a difficult task in busy emergency rooms using present scores, which has a number of variables to calculate. Red cell distribution width (RDW) is an easy, cheap, and efficacious score to predict the severity and mortality of patients with sepsis. Method: This prospective analytical study was conducted in the emergency room of Tribhuvan University Teaching Hospital among the patients age ≥16 years and with a clinical diagnosis of sepsis using qSOFA score. 148 patients were analyzed in the study by using a non-probability purposive sampling method. Result: RDW is more efficacious test to predict mortality in sepsis (Area under the Curve of 0.734; 95% C.I = 0.649-0.818; p-value=0.000) than APACHE II (AUC of 0.728; 95% C.I= 0.637 to 0.819; p-value=0.000) or SOFA (AUC of 0.680, 95% C.I =0.591-0.770; p-value=0.001). Youden Index was maximum (37%) at RDW value 14.75, which has a sensitivity of 83% (positive likelihood ratio=1.81) and specificity of 54% (negative likelihood ratio=0.32). Out of 44 patients with septic shock 16 died (36.4 %) and among 104 patients without septic shock, 24 died (22.9%) which had the odds ratio of 0.713 (p=0.555, 95% C. I= 0.231-2.194). Overall mortality was 27.02% (n=40). RDW subgroup analysis showed no mortality in low RDW (<13.1) subgroup, 3.6% mortality in moderate (13.1 to 14) RDW group, 22.0% mortality in high (14 to >15.6) RDW group and 45.9% mortality in very high (>15.6) RDW group. Significant mortality difference was seen in high and very high RDW subgroups with a p-value of 0.003 and 0.008 respectively.

Conclusion: RDW can be used as a good prognostic score to predict the mortality of patients with sepsis in the emergency room. RDW is a more efficacious test to predict mortality in sepsis than APACHE II or SOFA scores. Keywords: red cell distribution width, sepsis, emergency care, mortality
Background

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The incidence of sepsis varies among different studies with a wide range from 300 to 1000 cases/100,000 persons per year.[1] In one of the studies conducted at Tribhuvan University Teaching Hospital, 10.49% of patients showed bacterial growth in blood or bone marrow samples.[2]

Organ dysfunction in the presence of infection increases in-hospital mortality by 10%.[3]

One of the studies done in Nepal showed overall mortality from sepsis as 39.3% and a higher mortality rate among elderly patients (46.7%).[4] In a comparative meta-analysis, there was 33.2% mortality of severe sepsis patients during 28-days follow up.[5] Ongoing mortality in patients with sepsis remains elevated up to 2 years and beyond.[6]

In today's clinical practice, a number of indicators are being used to predict the prognosis of sepsis. Commonly used prognostic indicators include Acute Physiological and chronic health evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Mortality in Emergency Department Score (MEDS), New York Sepsis severity score. In recent years Red cell distribution Width (RDW) is being investigated for its prognostic value in septic patients.

Red cell distribution width (RDW) is an index of variation of erythrocyte volume (i.e. anisocytosis). It is conventionally included in a standard complete blood count (CBC). The value of this parameter increases parallel with anisocytosis. It is conventionally increased in patients with anemia attributable to iron deficiency[7], folic acid/vitamin B12 deficiency, patients with autoimmune disorders[8], myelodysplastic syndrome, hemolytic anemia, liver impairment, sickle cell disease[9], and blood transfusions.[10] RDW value is increased among the red blood cell transfused patients[11] and a cutoff value of RDW to predict the mortality of critically ill patients was higher in comparison to non-transfused
patients[12]. The normal range of RDW is 11.5% to 14.5% with no clinical scenarios that produce RDW <11.5%. Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW value.

When patients are infected, microbes release various toxins/lipopolysaccharides which activate inflammatory cascade via various interleukins, cytokines.[13] Cytokines are responsible for the clinically observable effects of the bacteremia in the host.[14] These cytokines induce direct red blood cell damage by erythrophagocytosis or apoptosis, interfere with iron homeostasis, inhibit erythropoiesis by myelosuppression and downregulate erythropoietin-receptor expression.[13] These mechanisms are thought to lead to anisocytosis and increased RDW value. [15]

RDW has been utilized in diverse diseases other than traditionally for the interpretation of anemia. In chronic diseases, elevated RDW was associated with all-cause mortality in critically ill patients[15,16] and increased mortality among healthy middle-aged[17] and older adults[18] from the general population and patients with cardiovascular disease[19], stroke[20], heart failure, and chronic dialysis[21]. In acute conditions, RDW can also be used as a mortality predictor among patients with acute pancreatitis[22], subarachnoid hemorrhage[23], acute dyspnea[24] during an emergency department visit[25], out-of-hospital cardiac arrest[26], cardiac arrest in ICU[27], and critical illnesses in an ICU setting. For septic patients, RDW was also found to be an independent indicator of mortality in patients with gram-negative bacteremia, community-acquired pneumonia, severe sepsis, and septic shock.[28,29] For every 1% increase in RDW value, total mortality risk increased by 14% among older adults. [18]

In the emergency condition like sepsis, a tool that can predict the severity and thus the prognosis of a patient is crucial in deciding the modality of treatment including the vasopressor, possible need of ventilator, empiric antibiotics or higher group of antibiotics.
In the resource-limited setting of developing countries like Nepal, and also in busy places like an emergency room, calculating other prognostic indicators like APACHE II, MEDS, SOFA will be costly as well as time-consuming. RDW is a cost-effective and easy tool to predict the prognosis of critically ill patients including sepsis. Only a few studies of this type are conducted in developed nations and as developing nations have different health set up, this prospective analytical observational study is designed to find whether RDW can predict prognosis of septic patients in one of the tertiary centers of Nepal or not. Better efficacy of RDW as a predictive score can help to guide the aggressiveness of treatment as per the severity of a disease.

Methods

The primary aim of this study was to determine the utility of red cell distribution width (RDW) as a prognostic factor in septic patients. The secondary aim of the study was to compare the efficacy of RDW to predict mortality of the septic patients with APACHE II and SOFA scores

Study Design

This prospective observational quantitative study was conducted in Tribhuvan University Teaching Hospital (TUTH), Emergency Room, Maharajgunj, Kathmandu, Nepal from June 2017 to August 2018. Patients ≥16 years with the clinical diagnosis of sepsis in the emergency room of TUTH were included in the study. Sepsis was suspected using qSOFA (quick Sequential Organ Failure Assessment) score. Patients with infection can be predicted to have sepsis if they have at least two of following clinical criteria that together constitute a new bedside clinical score termed as quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation status or systolic blood pressure of 100mmHg or less.[3,30] Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate greater than
2 mmol/L in the absence of hypovolemia.[3] Following patients were excluded from the study:

1. The patient who received blood transfusion within 90 days before emergency admission.
2. The patients who are known to have long-term conditions causing anemia like sickle cell anemia, thalassemia, iron deficiency anemia.
3. Patient with incomplete information and data.
4. The patient who deny consent.

Data collection:
Patients with suspected infection and hence sepsis suggested by qSOFA score were enrolled into the study after getting formal written/oral consent from the patient or legal guardian available at the Emergency room. It was a nonprobability and purposive sampling method, as only septic patients meeting the above-mentioned inclusion and exclusion criteria were enrolled in the study without any randomization of the samples. Patient’s basic demographic information, vital signs on ER arrival, symptoms and underlying diseases, provisional diagnosis and laboratory values required for analysis of RDW, APACHE II, and SOFA score were collected. Outcome (cured/improved and mortality) of patients was followed by phone calls made at 28-day from the day of ER admission. Patients who were in hospital till 28-days were followed in the respective admitted wards or critical care units. Collected data were then analyzed. Data collection was done by the researcher.

Statistical analysis:
Descriptive statistics of demographic and laboratory variables are calculated as mean, median, numbers, and percentages. Patients were further stratified a priori based on RDW results as: RDW $<$13.1% - low; RDW $\geq$13.1% -14% - moderate; RDW $>$14% - 15.6% - high;
RDW ≥15.6% - very high.[25] An odds ratio was used to compare differences in mortality between groups. Binary logistic regression was used to evaluate potential confounding between risk factors, RDW, and mortality. Receiver operating characteristics (ROC) curve analysis was done to evaluate the performance of RDW in predicting mortality within 28-days of ER admission. The area under the ROC curve was compared between different clinical prognosis score viz. RDW, APACHE II, and SOFA. All p-values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS (Statistical Package for Social Sciences) version 25.

Results

A total of 148 patients were analyzed. Mean age was 51.29 years (S. D= 20.22) with a mean age in survival group 48.4 years (S. D =19.94) and in mortality group 59.10 years (S. D=19.1). Maximum number of people lied in age-group 60-70 years (n=28, 18.9%) followed by 20-30 and >70 years both of which have the same numbers. Data is negatively skewed (-0.217). In the study, there were more females (88, 59.5%) than males (60, 40.5%).

Most of the patients lie in a very high RDW group (n=60, 40.5%). (Figure -1). Mean RDW was 15.933 (S.D =2.69), the median was 15 (S. D= 2.69). Data for RDW groups was negatively skewed (-0.678).

As data did not follow normal distribution (negatively skewed) nonparametric test (Mann-Whitney U test) was done to test the difference of distribution of Age, RDW, APACHE II and SOFA across the categories of outcome (improved and mortality). The test showed a significant difference between the improved and mortality group with a p-value of 0.005, 0.000, 0.000, 0.002 for age, RDW, APACHE II, SOFA respectively (Table 1).

Table 1 Mann-Whitney U test for predicting mortality among septic patients.
| Variable       | Mann-Whitney U-Test | p-value |
|---------------|---------------------|---------|
| Age           | 2808.5              | 0.005   |
| RDW           | 3422.0              | 0.000   |
| APACHE II     | 3119.5              | 0.000   |
| SOFA          | 2866.5              | 0.002   |

Binary logistic regression analysis was done to analyze the effect of confounding factors like age, sex, presence of septic shock on mortality. Results showed no significant effect of these confounding factors on mortality except for sex (p=0.029, Odds ratio= 2.950, 95% C.I =1.120-7.773) (Table 2). Among the predictive scores viz. RDW, APACHE II, and SOFA scores; only RDW had a significant difference in predicting mortality with an odds ratio of 1.551 (p=0.000003, 95% C.I =1.292-1.863). So RDW is a better prognostic test to predict mortality in septic patients.

Table 2 Binary logistic regression analysis of confounding factors and prognosis predictive scores

|                  | Outcome |                      |                      | Odds Ratio | 95% C.I   |
|------------------|---------|-----------------------|-----------------------|------------|-----------|
|                  |         | Improved/Cured (N=108) | Mortality (N=40)      | p-value    | Lower     | Upper     |
|                  | Mean    | Row %                 | n                     |            |           |           |
|                  | (S.D)   |                       |                       |            |           |           |
| Age (years)      | 48.4 (19.94) | 73.0%                | 108                   | 59.10 (19.1)| 27.0%    | 40        |
|                  | 0.101   | 1.250                 | 0.958                 | 1          |
| Hematocrit %     | 35.3 (8.8) | 73.0%                | 108                   | 33.6 (10.1)| 73.0%    | 40        |
|                  | 0.315   | 0.979                 | 0.941                 | 1          |
| SOFA             | 6 (3)   | 73.0%                 | 108                   | 8 (3)      | 27.0%    | 40        |
|                  | 0.062   | 1.221                 | 0.990                 | 1          |
| APACHE II        | 16 (7)  | 73.0%                 | 108                   | 21 (7)     | 27.0%    | 40        |
|                  | 0.157   | 1.053                 | 0.983                 | 1          |
| RDW              | 15.2 (2.2) | 73.0%               | 108                   | 17.9 (2.9) | 27.0%    | 40        |
|                  | 0.000003| 1.551                 | 1.292                 | 1          |
| Sex              | Male    | 65.0%                 | 39                    | 35.0%      | 21        |
|                  | Female  | 78.4%                 | 69                    | 21.6%      | 19        |
| Septic shock     | Yes     | 63.6%                 | 28                    | 36.4%      | 16        |
|                  | No      | 76.9%                 | 80                    | 23.1%      | 24        |

Note: 1 indicates the significant level for the analysis.
Patients were further divided into two groups viz. with sepsis and septic shock. Out of 44 patients with septic shock 16 died (36.4 %) and among 104 patients without septic shock, 24 died (23.1%) with odds ratio of 0.713 (p=0.555, 95% C.I= 0.231-2.194)(Table 2). Overall mortality was 27.02% (n=40).

**Table 3 Binary logistic regression of RDW subgroup and outcome**

| RDW Classification | Improved/Cured (N=108) | Mortality (N=40) | Odds Ratio | p-value | 95% C.I
|---------------------|------------------------|------------------|------------|---------|----------|
|                     | N         | %        | N         | %        |          | Lower  | Upper  |
| Low (<13.1)         | 10        | 9.3%     | 0         | 0.0%     | 0.000    | 0.003  | 0.000  |
| Moderate (≥13.1-14) | 27        | 25.0%    | 1         | 2.5%     | 0.00     | 0.999  | 0      |
| High (>14-15.6)     | 39        | 36.1%    | 11        | 27.5%    | 0.042    | 0.003  | 0.005  | 0.332  |
| Very high (≥15.6)   | 32        | 29.6%    | 28        | 70.0%    | 0.332    | 0.008  | 0.139  | 0.746  |

RDW subgroup analysis showed no mortality in low RDW (<13.1) subgroup, 3.6% mortality in moderate RDW (≥13.1-14) group, 22.0% mortality in high RDW (>14-15.6) group and 46.7% mortality in very high (>15.6) RDW group (Table 3). Significant mortality difference was seen in high and very high RDW subgroups with p-value 0.003 and 0.008 respectively. This shows an increasing trend of mortality with the increase in RDW value and vice-versa.

Receiver Operating Characteristic (ROC) curve was used to test the efficacy of different clinical scores viz. RDW, SOFA, APACHE II to predict mortality in septic patients (Figure-2). Area under the ROC curve was analyzed which shows RDW is more efficacious test to predict mortality in sepsis with AUC of 0.734 (95% C.I =0.649-0.818; p-value=0.000) than APACHE II (AUC of 0.728, 95% C.I= 0.637 to 0.819; p-value=0.000) or
SOFA (AUC of 0.680, 95% C.I 0.591-0.770; p-value=0.001) *(Table 4).* AUC of RDW is >0.7 which is considered a fair test.

**Table 4 Area under the ROC curve for RDW, APACHE II, SOFA to predict mortality of sepsis**

| Test  | Variable(s) | Area | Sig. | 95% Confidence Interval |
|-------|-------------|------|------|-------------------------|
|       |             |      |      | Lower Bound | Upper Bound          |
| SOFA  |             | 0.680| 0.001| 0.591       | 0.770                |
| RDW   |             | 0.734| 0.000| 0.649       | 0.818                |
| APACHE II |       | 0.728| 0.000| 0.637       | 0.819                |

RDW value of 15.05 has a sensitivity of 73% (positive likelihood ratio= 1.82) and specificity of 60% (negative likelihood ratio =0.45) while RDW value of 16.1 has sensitivity of 56% (positive likelihood ratio=2.07) and specificity of 73% (negative likelihood ratio = 0.6). Youden Index was maximum (37%) at RDW value 14.75 which has a sensitivity of 83% (positive likelihood ratio=1.81) and specificity of 54% (negative likelihood ratio=0.32). Increasing the value of RDW decreases the sensitivity of the test and increases the specificity of the test.

**Discussion**

This prospective analytical study illustrated the significant differences in RDW levels between mortality and survivor groups of septic patients. The aim of this study was to find the performance of RDW to predict the mortality of septic patients. The performance of RDW to predict mortality in septic patients was found better than other clinical scores like SOFA, APACHE II.

Over 500,000 patients each year present to an emergency department with suspected severe sepsis. [31]Sepsis incidence increases > 100 fold with the age (0.2 per 1000 in children age 10 to 14 years to 26.2 per 1000 in those > 85 years of age).[32] The overall
mortality in septic patients was 27.02% (n=40) and the mortality in septic shock patients was 36.4% which is near to mortality rate shown by a meta-analysis of multicenter randomized- trials by Stevenson EK and et al.[5] This meta-analysis had 33.2% mortality from severe sepsis.

Mortality was high in the septic shock group than patients without septic shock (36.4% vs 23.07%). In another study, among the severely septic patients (n=2110), 13.8% died (n=290), which is significantly higher compared with the non-severe septic group (3.8%, n=187, P< 0.001). [25]

Mortality was more in the very high RDW group (RDW ≥15.6) with 46.7% mortality among patients with RDW≥15.6. Mortality subsequently increased from a low RDW group to a very high RDW group. Kim J et al showed that RDW was a particularly strong predictor of all-cause mortality, 30 days following critical care initiation.[26] RDW had a significant ability to predict mortality in septic patients (p=0.000, Mann Whitney U Test).

The area under the ROC curve of RDW showed a fair capacity of RDW to predict mortality in septic patients (AUC= 0.734) which is better than SOFA and APACHE II (AUC = 0.680 and 0.728). In another study, the area under the receiver operating characteristic curve of RDW to predict mortality was 0.75 (95% confidence interval, 0.72–0.77), which is significantly higher than the areas under the curve of clinical prediction rules (SIRS, MEDS, and CURB65).[25]AUC of RDW is >0.7 which is considered a fair test. [33] However, Fontana et al showed no correlation between RDW and prognosis of septic patients.[34]

The sensitivity of RDW at 15.05 was 73% (Positive likelihood ratio=1.82) and specificity of 60% (Negative likelihood ratio=0.45). Decreasing the value increases sensitivity while decreasing the specificity and vice versa. In a study by Chen et al; using 12% as a cutoff of RDW, the sensitivity in predicting mortality would be 99.4% (negative likelihood ratio: 0.30). On the other hand, the specificity in predicting mortality would be 89.9% if 17%
used as the cutoff of RDW (positive likelihood ratio: 3.16). [25]

There are certain limitations to our study. All the data and patients were collected in a single-center so the findings may not apply in the general population. As a purposive non-probability sampling method was used there is a chance of selection bias. The severity of the disease, patient characteristics, the value of RDW and treatment protocol may vary with different institutes and hence the outcome of patients. Though the findings in patients with hematocrit <36% are also applicable, patients with undiagnosed chronic anemia may have created biases and baseline hemoglobin of patients visiting the emergency room was lacking. Sepsis was diagnosed clinically using qSOFA which has low sensitivity due to which fewer cases might have been enrolled in the study.

RDW is a cheap and widely available test that has efficiency equivalent, if not more than the SOFA or APACHE II score. So it can be used in an emergency room or bedside or in a set-up where arterial blood gas analysis is not available to predict the severity /mortality of septic patients. This study provides level III evidence for its use in day to day life. However, a multicenter study involving different geographical conditions and randomized sampling method will help to reduce biases involved in the study. Separate studies need to be done before using findings to patients with anemia of different causes.

Conclusion

RDW can be used as a good prognostic score to predict the mortality of patients with sepsis in the emergency room. RDW is a more efficacious test to predict mortality in sepsis in comparison to APACHE II or SOFA.

Abbreviations

APACHE II: Acute Physiological and Chronic Health Evaluation II; AUC: Area under the curve; ER: Emergency Room; qSOFA: quick Sequential Organ Failure Assessment; RDW:
red cell distribution width; SOFA: Sequential Organ Failure Assessment

Declarations

**Ethical consideration and consent to participate:**
Ethical clearance was done from the Institutional Review Board of Institute of Medicine, Tribhuvan University. Written/oral consent was taken from the patient or legal guardian.

**Consent for publication**
Not applicable

**Availability of data**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**
The authors declare that they have no competing interests

**Funding**
This study was funded by authors.

**Authors Contributions**
As this study was conducted for partial fulfillment of the requirement of Doctor of Medicine in General Practice and Emergency Medicine, RG conducted the whole of the process of study. YMS, TMS, and RPN guided through the process as a guide and co-guides respectively.

**Acknowledgments**
Not applicable

**Authors details**
1 MD General Practice and Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University. 2 Professor and Head of Department, Department of
General Practice and Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University. 3,4 Department of General Practice and Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University

References

1. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the Incidence and Mortality of Severe Sepsis in the United States. Crit Care Med. 2013;41:1167–74. DOI:10.1097/CCM.0b013e31827c09f8

2. Chaudhary R, Karmacharya S, Shrestha S, Dahal RK, Mishra SK, Banjade NR, et al. Incidence of Bacteremia and Septicemia in patients attending in tertiary care center, Nepal [Internet]. J. Inst. Med. 2012. p. 32–8. Available from: www.jiom.com.np

3. Singer M, Deutschman Clifford S. SCW, Manu S-H, Djillali A, Michael B, Bellomo R, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10. DOI:10.1001/jama.2016.0287.

4. Lakhey S, Karki B, Shrestha B, Shakya S, Pandey SB. Sepsis_ a private hospital experience in Nepal _ Lakhey _ Journal of Institute of Medicine. J Inst Med. 2006;28.

5. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two Decades of Mortality Trends among Patients with Severe Sepsis: A Comparative Meta-analysis Elizabeth. Crit Care Med. 2014;42:625–31. DOI:10.1097/CCM.0000000000000026.

6. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ SJ. Long-term mortality and quality of life in sepsis_ a systematic review. Crit Care Med. 2010;38:1276–86. DOI:10.1097/CCM.0b013e3181d8cc1d

7. Bessman JD, Gilmer PR, Gardner FH. Improved Classification of Anemias by MCV and RDW. Am J Clin Pathol [Internet]. Oxford Academic; 1983 [cited 2020 Feb 17];80:322–6. Available from: https://academic.oup.com/ajcp/article/80/3/322/1803902
8. Hu Z-D. Red blood cell distribution width: a promising index for estimating activity of autoimmune disease. J Lab Precis Med. AME Publishing Company; 2016;1. DOI:10.21037/jlpm.2016.10.02

9. Webster P, Castro O. Red cell distribution width in sickle cell disease. Ann Clin Lab Sci [Internet]. Association of Clinical Scientists; 1986 [cited 2020 Feb 17];16:274–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3740796

10. Lippi G, Plebani M. Red blood cell distribution width (RDW) and human pathology. One size fits all. Clin Chem Lab Med. 2014;1–3. DOI:10.1515/cclm-2014-0585

11. Spadaro S, Taccone FS, Fogagnolo A, Franchi F, Scolletta S, Ragazzi R, et al. The effects of blood transfusion on red blood cell distribution width in critically ill patients: a pilot study. Transfusion. 2018;58:1863–9. DOI:10.1111/trf.14759

12. Fogagnolo A, Spadaro S, Taccone FS, Ragazzi R, Romanello A, Fanni A, et al. The prognostic role of red blood cell distribution width in transfused and non-transfused critically ill patients. Minerva Anestesiol. 2019. p. 1159–67.

13. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus Anti-inflammatory Cytokine Profile in Patients with Severe Sepsis: A Marker for Prognosis and Future Therapeutic Options [Internet]. J. Infect. Dis. 2000. p. 176–80. Available from: https://academic.oup.com/jid/article-abstract/181/1/176/892417

14. Kobayashi M, Tsuda Y, Yoshida T, Takeuchi D, Utsunomiya T, Takahashi H, et al. Bacterial Sepsis and Chemokines. Curr Drug Targets. 2006;7:119–34. DOI:10.2174/138945006775270169

15. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. Crit Care Med. 2011;39:1913–21. DOI:10.1097/CCM.0b013e31821b85c6
16. Musikasinthorn C, Harvey S, McKnight CL, Inouye D, Kuroda J, Nakamura C, et al. Red cell distribution width (RDW) as predictor of hospital mortality in critically ill patients. Crit Care Med. 2014;42:466.

17. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort: NHANES III: RDW and mortality risk. Arch Intern Med. 2009;169:588-94. DOI:10.1001/archinternmed.2009.55

18. Patel K V, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al. Red Cell Distribution Width and Mortality in Older Adults : A Meta-analysis. J Gerontol A Biol Sci Med Sci. 2010;65A:258-65. DOI:10.1093/gerona/glp163

19. Uyarel H, Isik T, Ayhan E, Ergelen M. Red Cell Distribution Width ( RDW ) : A novel risk factor for cardiovascular disease. Int J Cardiol [Internet]. Elsevier Ireland Ltd; 2011;351-2. Available from: http://dx.doi.org/10.1016/j.ijcard.2011.10.126 DOI:10.1016/j.ijcard.2011.10.126

20. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci [Internet]. Elsevier B.V.; 2009;277:103-8. Available from: http://dx.doi.org/10.1016/j.jns.2008.10.024 DOI:10.1016/j.jns.2008.10.024

21. Sicaja M, Pehar M, Star B, Vuleti V, Bo V. 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;54:25-32. DOI:10.3325/cmj.2013.54.25

22. Şenol 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. DOI:10.1016/j.ajem.2012.12.015
23. Fontana V, Bond O, Spadaro S, Annoni F, Nobile L, Badenes R, et al. Red Cell Distribution Width after Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. Lippincott Williams and Wilkins; 2018;30:319-27.
DOI:10.1097/ANA.0000000000000459

24. Hong N, Oh J, Kang S, Kim S, Won H, Chan J, et al. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. Clin Chim Acta [Internet]. Elsevier B.V.; 2012;413:992-7. Available from: http://dx.doi.org/10.1016/j.cca.2012.02.024 DOI:10.1016/j.cca.2012.02.024

25. Chen C-K, Lin S-C, Wu C-C, Chen L-M, Tzeng I-S, Chen K-F. The utility of red cell distribution width to predict mortality for septic patients visiting the emergency department. Medicine (Baltimore). 2016;95:e3692.
DOI:10.1097/MD.0000000000003692

26. Kim J, Kim K, Hyuk J, Hwan Y, Eui J, Yun T, et al. Red blood cell distribution width as an independent predictor of all-cause mortality in out of hospital cardiac arrest. Resuscitation [Internet]. European Resuscitation Council, American Heart Association, Inc., and International Liaison Committee on Resuscitation.~Published by Elsevier Ireland Ltd; 2012;83:1248-52. Available from: http://dx.doi.org/10.1016/j.resuscitation.2012.01.038
DOI:10.1016/j.resuscitation.2012.01.038

27. Fontana V, Spadaro S, Villois P, Righy Shinotsuka C, Fogagnolo A, Nobile L, et al. Can red blood cell distribution width predict outcome after cardiac arrest? Minerva Anestesiol. NLM (Medline); 2018;84:693-702. DOI:10.23736/S0375-9393.17.12102-4

28. Jo YH, Kim K, Lee JH, Kang C, Kim T, Rn HP, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. Am J Emerg Med [Internet]. Elsevier Inc.; 2013;31:545-8. Available from:
29. **Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al.** An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. *Crit Care [Internet].* 2013;17:R282. Available from: http://ccforum.com/content/17/6/R282 DOI:

30. **Jones AE, Stephen T, Kline JA.** The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med.* 2009;37:1649–54. DOI:10.1097/CCM.0b013e31819def97

31. **Puskarich, Michael A; Jones AE.** Sepsis. In: Tintinalli, Judith E; Stapczynski, J. Sthephan; Ma, O John; Yealy, Donald M; Meckler, Garth D; Cline DM, editor. *Tintinalli’s Emerg Med A Compr study Guid.* 8th ed. McGraw-Hill; 2016. p. 1021-9.

32. **Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M.** Epidemiology of severe sepsis in the United States _analysis of incidence, outcome, and associated costs of care._ *Crit Care Med.* 2001;29:1303–10.

33. **Tape TG.** The Area Under an ROC Curve [Internet]. Interpret. Diagnostic Test. [cited 2018 Oct 22]. Available from: http://gim.unmc.edu/dxtests/ROC3.htm

34. **Fontana V, Spadaro S, Bond O, Cavicchi FZ, Annoni F, Donadello K, et al.** No relationship between red blood cell distribution width and microcirculatory alterations in septic patients. *Clin Hemorheol Microcirc [Internet].* IOS Press; 2017 [cited 2020 Feb 18];66:131–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28128746 DOI:10.3233/CH-160154

**Figures**
1 histogram of RDW classification; 1=low RDW (<13.1), 2= moderate RDW (≥13.1-14), 3= high RDW (>14-15.6), 4= very high RDW (≥15.6)
Figure 2

Receiver operating characteristics curve analysis for RDW, SOFA, and APACHE II to predict mortality in sepsis