Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Jan 01; 11(B):38-45.
https://doi.org/10.3889/oamjms.2023.11097
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Intensive Care*

Evaluation of Dynamic Variation in Red Cell Distribution Width as a Septic Marker in Comparison with Procalcitonin Levels and Clinical Scores in Patients with Sepsis or Septic Shock: A Prospective Observational Study

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Edited by: Mirko Spiroski
Citation: Fawzy M, Gawish MA, Abdelsamie S, Elsherif M, Ibrahim GHA, Ahmed W. Evaluation of Dynamic Variation in Red Cell Distribution Width as a Septic Marker in Comparison with Procalcitonin Levels and Clinical Scores in Patients with Sepsis or Septic Shock: A Prospective Observational Study. Open Access Maced J Med Sci. 2023 Jan 01; 11(B):38-45. https://doi.org/10.3889/oamjms.2023.11097
Keywords: Acute physiology and chronic health evaluation II score; Sequential organ failure assessment score; Red cell distribution width; Procalcitonin; Sepsis; Septic shock
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Received: 11-Oct-2022
Revised: 22-Nov-2022
Accepted: 22-Nov-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Sepsis is a dysregulated host response to infection resulting in potentially life-threatening organ dysfunction. Elevation in red cell distribution width (RDW), a simple routinely done investigation, could be a prognostic marker in these patients.

AIM: We performed this prospective observational study to assess role of dynamic variation of RDW in predicting 30-day mortality in patients with sepsis or septic shock presenting and getting admitted in intensive care unit (ICU) in Fayoum, Egypt.

METHODS: Between January 2019 and January 2021, 150 patients with sepsis or septic shock at admission were prospectively evaluated for association between RDW value on admission, on day 4, on day 7, and 30-day mortality. To find out factors associated independently with 30-day mortality, we applied multivariate logistic regression analysis and used the analysis to develop nanogram for prediction of mortality on admission.

RESULTS: Among 150 patients, 89 (59.3%) were male. Mean age of the patients was 59.6 ± 12.28 years. Regarding RDW on admission (RDW-0), the mean was 14.1 ± 1.9 while on day 4 (RDW-4), the mean was 14.5 ± 1.97, and on day 7 (RDW-7), the mean was 14.4 ± 2.03. Seventy-four (49.3%) patients died during the period of 30 days follow-up. Multiple logistic regression models for the parameters associated with the mortality outcome at admission were done, for age, higher age was associated with higher probability of mortality, OR = 1.07 (95% CI: 1.02, 1.13). Male sex was associated with lower probability of mortality as compared to females, OR = 0.02 (95% CI: 0.06, 0.80). Higher acute physiologic assessment and chronic health evaluation (APACHE) II score, RDW value, and procalcitonin level, all were associated with higher mortality probability. For APACHE II score, higher level was associated with higher odds of mortality, OR = 1.16. For RDW value on admission, higher value was associated with higher odds of mortality, OR = 1.66. For procalcitonin level at admission, higher level was associated with higher odds of mortality, OR = 1.54. Odds for mortality for those who showed any increase in RDW in day 4 as compared to day 0 are higher as compared to those who showed a decrease or no change in RDW, OR = 2.8, p-value = 0.007.

CONCLUSIONS: We found that an increase in RDW value on admission and on day 4 is significantly associated with mortality. And that, an increase in RDW value from day 0 to day 4 is also significantly associated with mortality Therefore, a combination of baseline RDW value and an increase in serial RDW values can be a promising independent prognostic marker in patients with sepsis or septic shock.

Introduction

Sepsis is redefined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite advances in antibiotic therapy and modern life support, the fatality rate of patients with sepsis has remained as high as 20%–60% worldwide [2]. Early identification of patients at high risk of dying from sepsis may help initiate rapid and appropriate therapeutic interventions and may have a great impact on sepsis-related morbidity and mortality. However, an accurate assessment of patients at risk for poor clinical outcomes is challenging for clinicians.

Red blood cell (RBC) distribution width (red cell distribution width [RDW]) is a quantitative measure of anisocytosis and is routinely reported as a component of the complete blood count analysis which makes it a very simple and available marker [3].

Proinflammatory cytokines found in patients with SIRS including tumor necrosis factor-α, interleukin (IL)-6, and IL-1β are noted to suppress erythrocyte maturation, allowing newer, larger reticulocytes to enter the peripheral circulation and increase RDW. Further, proinflammatory cytokines can have direct inhibitory effects on half-life of RBC circulation and deformability of the RBC membrane which, in turn, can manifest as an increase in RDW [4].

These observations provide support for the potential usefulness of RDW as a marker of inflammation in sepsis. Although not routinely utilized in critical care, in recent years, RDW has been demonstrated to significantly associate with mortality and other adverse

outcomes in various clinical conditions, including sepsis [4], [5], [6].

RDW is routinely provided within the CBC done by automated analyzers. Inexpensive, routinely available, and rapidly measurable prognostic tools have clinical utility in the identification of subset of patients with sepsis who need aggressive management. RDW could be a useful tool in prognostication of cases with sepsis as described in recent studies [4]. Contemplating above points, we performed this prospective observational study to assess role of dynamic variation of RDW in predicting 30-day mortality in patients with sepsis or septic shock presenting and getting admitted in intensive care unit (ICU) in Fayoum, Egypt.

Methods

The protocol of this study was approved from the Ethics Committee in Faculty of Medicine, Cairo university in August 2018 and it was further approved from faculty council in August 15, 2018. The study was carried out in Fayoum University Hospitals and Fayoum General Hospital in the period between January 2019 and January 2021. An informed consent form was taken from patients or legally acceptable representative (where a participant was not able to give informed consent) and the form was approved by the Institutional Ethics Committee. The study was observational with no interference in management and it included 150 patients who were admitted with diagnosis of sepsis or septic shock according to the new **"Sepsis 3"** definition which was created by the **ESICM-SCCM Sepsis Redefinitions Task Force** in **2016**.

Sepsis was defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. Organ dysfunction was defined as an increase of two points or more in the Sequential Organ Failure Assessment (SOFA) score. Septic shock was defined as sepsis and both of persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg, and lactate ≥2 mmol/L, despite adequate volume resuscitation.

The aim of this study was to investigate whether serial RDW measurements could predict prognosis in patients with sepsis and septic shock and to compare RDW as a prognostic marker to procalcitonin level and to clinical severity scores (Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] II and SOFA).

A simple data collection form was designed so that information could be easily entered and analyzed. Data collection was carried out over 24 months. Patients were followed for a total of 30 days. All patients were subjected to the following, full history and clinical examination, and daily routine laboratory investigations. APACHE II score was calculated to all patients on admission, while SOFA score was calculated on admission, on day 4 and on day 7. Procalcitonin was measured for all patients on admission, and on day 4. Procalcitonin level was measured by "ECLIA" electrochemiluminescence immunoassay using Elecsys BRAHMS PCT kit and Cobas e 411 analyzer from ROCHE diagnostics with measuring range from 0.02 to 100 ng/ml and the following normal value: ≤0.046 ng/mL (95th percentile). RDW was measured for all patients on admission, on day 4 and on day 7, the RDW value comes from the measurement of the erythrocyte histogram which is expressed in the form of RDW-SD (fL unit) or RDW-CV (%).

APACHE II Scoring System was calculated according to the modification done to the original APACHE I model to create the APACHE II score in 1985.

SOFA score was calculated according to its original development following a consensus meeting in 1994.

This study had a prospective design. All patients were managed under similar settings with uniform management protocol based on latest Surviving Sepsis Campaign Guidelines. There was uniformity in the time of measurement of RDW, that is, at admission in emergency medical services. Hence, baseline RDW was not affected by medical management during hospitalization. By reviewing transfusion records before admission, patients with history of transfusion of blood products were not included. Blood transfusion is an important confounder for raised RDW.

Statistical analysis

Sample size calculation was done using Medcalc version 17 using alpha of 0.05 and power of 80% to distinguish between two ROC curves with AUC of 0.8 and 0.9. The estimated sample size was 150 patients.

Descriptive statistics is presented in the form of mean and standard deviation for normally distributed numeric variables, while median and the interquartile range are used for the non-normally distributed numeric variables. Numbers and percentages are used to present categorical variables.

Chi-square test was used to compare the characteristics of patients who died and those who survived, while independent samples t-test was used to compare the numeric variables. ROC curve and area under the curve were used to identify the best predictors and to determine the cutoff value. Sensitivity and specificity are presented for the chosen cutoff values. Pearson's correlation was used to test the association between RDW values and other parameters (procalcitonin level and clinical scores). Multiple logistic regression models were done for the parameters

associated with the mortality outcome. A nomogram was developed to be used for calculating the mortality probability based on the developed regression model.

IBM SPSS software for windows, version 28 was used for the statistical analysis and Stata 17 was used for the development of the nomogram. $p < 0.05$ was considered statistically significant.

Results

The mean age of the patients is 59.6 ± 12.3 years. Regarding gender, 89 patients (59.3%) were male. Regarding risk factors, 69 patients (46%) were diabetics, 94 patients (62.7%) were hypertensive, while 56 patients (37.8%) were smokers.

The most common source of sepsis was respiratory in 53 patients (35.3%) followed by urosepsis in 37 patients (24.7%). Other less common sources were skin and subcutaneous tissues in 27 patients (18%), abdominal in 15 patients (10%), infected prothesis, or CRBSI in 6 patients (4%). Multiple sources of sepsis were found in 12 patients (8%). Blood culture showed no growth in 87 patients (58%), while 26 patients (17.3%) showed Gram-positive organisms and 37 patients (24.7) showed Gram-negative organisms. Urine culture showed no growth in 114 patients (76.0%), while five patients (3.3%) showed Gram-positive organisms and 31 patients (20.7%) showed Gram-negative organisms. Sputum culture showed no growth in 82 patients (54.7%), while it showed Gram-positive organisms in 31 patients (20.7%) and it showed Gram-negative organisms in 37 patients (24.7%).

A total of 108 patients (72%) required use of vasopressors during their course of stay. A total of 80 patients required mechanical ventilation during their course of stay.

Regarding APACHE II score, the mean was 19 ± 8. Regarding SOFA score on admission (SOFA-0), the mean was 10 ± 3, while on day 4 (SOFA-4), it was 10 ± 3, and on day 7 (SOFA-7), it was of 10 ± 4.

Regarding procalcitonin level on admission (PCT-0), the mean was 5.5 ± 3, while on day 4 (PCT-4), it was 6.2 ± 3.9.

Regarding red cell distribution width on admission (RDW-0), the mean was 14.1 ± 1.9, while on day 4 (RDW-4), it was 14.4 ± 1.97, and on day 7 (RDW-7), it was 14.4 ± 2.03.

Mortality rate was 49.3% (74 patients). The mean ICU length of stay was 12.4 ± 5.1 days.

There was a statistically significant difference in age among survivors and non-survivors, $p < 0.001$ as in survivors the mean age was 54.2 ± 12, while, in non-survivors, the mean was 65.1 ± 10. There was a statistically significant difference in gender among survivors and non-survivors, $p = 0.049$. The percentage of mortality among female patients was 59%, while, in male patients, it was 42.7%.

Table 1: Comparisons of different clinical scores between survivors and non survivors

Group	Survivors (n = 76)		Non-survivors (n = 74)		p-value
	Mean	SD	Mean	SD	
APACHE II	14.04	4.14	24.95	7.57	<0.001
SOFA-0	8.37	2.25	11.54	2.92	<0.001
SOFA-4	8.39	2.49	12.00	2.88	<0.001
SOFA-7	7.04	3.04	12.93	3.34	<0.001

The result of blood culture showed statistically significant difference, $p < 0.001$, as mortality among patients with bacterial growth was 68.3%, while mortality among patients with no bacterial growth was 35.6%. On contrast, the results of sputum and urine cultures did not show statistically significant difference regarding mortality outcome.

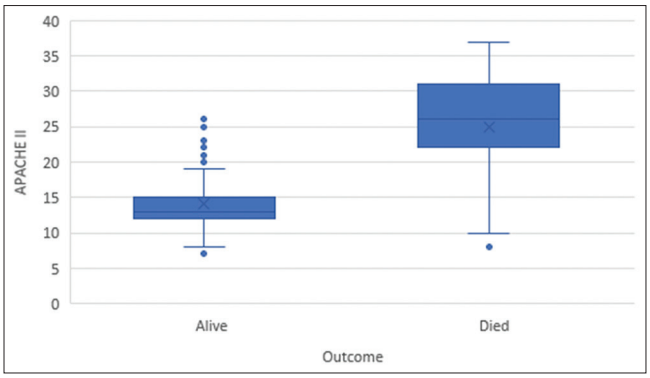

Figure 1: Boxplot comparing APACHE II among the outcome

Vasopressors usage did not show statistically significant difference regarding mortality outcome. On the other hand, mechanical ventilation usage showed a statistically significant association with mortality, $p = 0.014$, mortality among patients who were on MV was 58.8%, while among those who did not use MV were 38.6%.

Comparisons of different clinical scores between survivors and non-survivors were done using independent samples t-test and showed a statistically significant difference in all parameters. All scores were higher in the non-survivors [Figures 1 and 2].

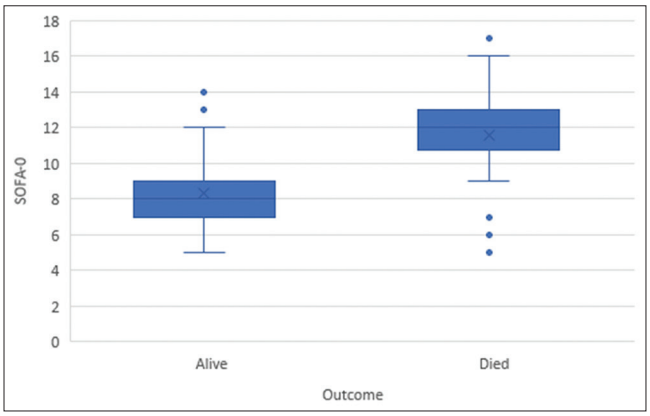

Figure 2: Boxplot comparing SOFA-0 among the outcome

There was a statistically significant difference in RDW 0, RDW 4 and RDW 7 in relation to mortality outcome [Figure 3]. Odds for mortality for those who showed any increase in RDW in day 4 as compared to day 0 were

higher as compared to those who showed a decrease or no change in RDW, OR = 2.80 (95% CI: 1.33–5.87), p = 0.007. For ROC curve, the highest AUC is observed for the RDW score at 4 days of admission [Figure 4].

Table 2: Difference in RDW 0, RDW 4 and RDW 7 in relation to mortality outcome

Group	Survivors (n = 76)		Non-survivors (n = 74)		p-value
	Mean	SD	Mean	SD	
RDW 0	13.07	1.57	15.14	1.58	<0.001
RDW 4	13.27	1.46	15.65	1.68	<0.001
RDW 7	13.19	1.50	15.71	1.70	<0.001

	p-value	OR	95% CI for OR	
RDW change direction	0.007	2.80	1.33	5.87

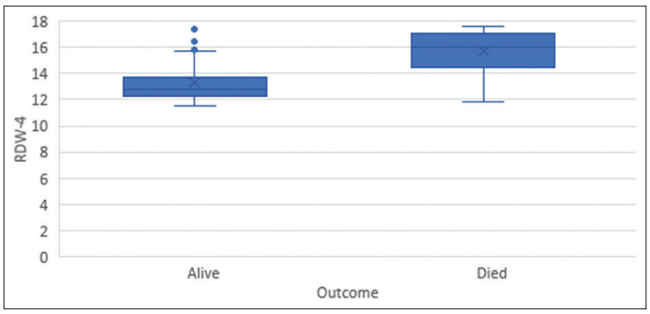

Figure 3: Boxplot comparing RDW-4 across the outcome

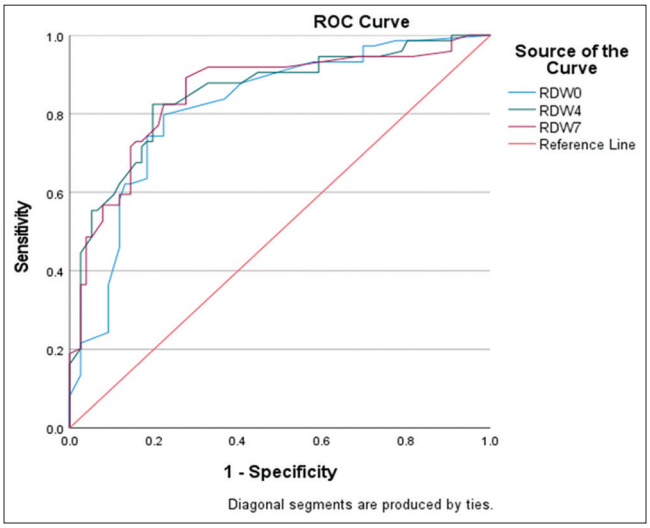

Figure 4: ROC curve comparing serial RDW values with outcome

Parameter	AUC	Cutoff point	Sensitivity (%)	Specificity (%)
RDW-0	0.816	14	70	78
RDW-4	0.855	15.5	74	80
RDW-7	0.851	15.5	73	79

There are statistically significant strong correlations between RDW and clinical scores. The strongest correlations were found between RDW7 and APACHE II score and also between RDW7 and SOFA 7 score.

Table 3: Correlations between RDW and clinical scores

	APACHE II	SOFA-0	SOFA-4	SOFA-7	Procal-0	Procal-4
RDW-0						
Correlation coefficient	0.574	0.502	0.592	0.603	0.186	0.446
p-value	<0.001	<0.001	<0.001	<0.001	0.023	<0.001
RDW-4						
Correlation coefficient	0.651	0.548	0.666	0.695	0.222	0.493
p-value	<0.001	<0.001	<0.001	<0.001	0.006	<0.001
RDW-7						
Correlation coefficient	0.703	0.571	0.707	0.748	0.275	0.512
p-value	<0.001	<0.001	<0.001	<0.001	0.001	<0.001

Table 4: Multiple logistic regression model for the parameters associated with the mortality outcome at admission

	OR	p-value	95% C.I. for OR	
Age	1.07	0.011	1.02	1.13
Sex (male)	0.22	0.021	0.06	0.80
APACHE II	1.16	0.002	1.06	1.28
RDW0	1.66	0.001	1.21	2.27
Procal 0	1.54	0.002	1.18	2.02

Multiple logistic regression models for the parameters associated with the mortality outcome at admission were done and are presented in table.

A nomogram was generated for calculation of mortality probability on admission based on parameters obtained from the logistic regression model as presented in the figure 5.

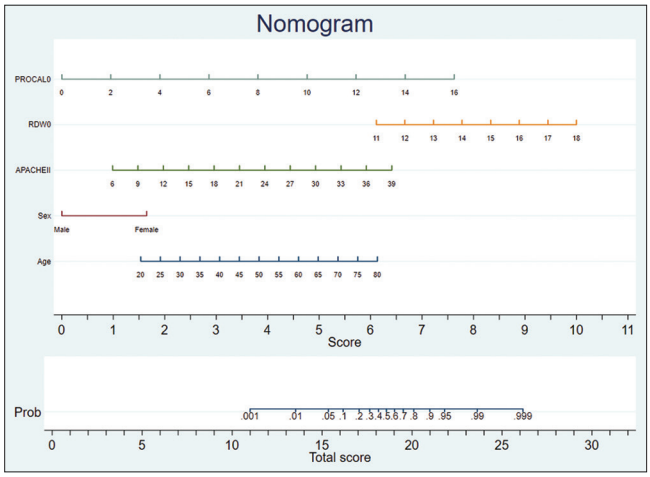

Figure 5: Nomogram for mortality prediction on ICU admission

Discussion

Sepsis, redefined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1], is a life-threatening clinical condition that has cost humanity heavily since time immemorial. Prognostication in severe sepsis may facilitate aggressive management of particular patient groups.

RDW represents the variation in size of all the RBCs in an individual patient. It is elevated when excess of reticulocytes is released into the circulation. Over and above its role in the evaluation of anemia, RDW has been found to be an important prognostic marker in the patients with cardiovascular disorders, pulmonary embolism, community-acquired pneumonia, and critical illness [4], [5], [6], [7], [8], [9]. The association was independent of covariates such as nutritional status, anemia, and comorbidities.

Inflammation and oxidative stress have been suggested to reduce RBC survival and suppress their maturation resulting in release of large premature RBCs into circulation, contributing to elevated RDW. Inflammation and oxidative stress are the essential components of sepsis cascade [4].

RDW could be a useful tool in prognostication of cases with sepsis as described in recent studies. Contemplating above points, we performed this prospective observational study to assess role of elevated RDW in predicting mortality in patients with sepsis or septic shock presenting and getting admitted to ICUs in Fayoum general hospital and Fayoum university hospitals. The aim of the present study was to investigate whether serial RDW measurements could predict prognosis in patients with sepsis and septic shock and to compare RDW as a prognostic marker to procalcitonin level and to clinical severity scores (APACHE II and SOFA).

A total of 150 patients were enrolled, in all patients, the diagnosis was sepsis with or without septic shock. Sepsis and septic shock were defined according to sepsis three criteria. APACHE II score was calculated for all patients on admission, with SOFA score calculated on admission, on day 4 and day 7. RDW was measured on admission, on day 4 and day 7, while procalcitonin was measured on admission.

Regarding age, the mean age of the study group was (59.57 ± 12.28). There was statistical significance when comparing age with outcome in ICU as the mean age among survivors was 54.22 (11.96), while the mean age among non-survivors was 65.07 ± 10.04 with $p < 0.001$.

This was in agreement with Karlsson *et al*., 2006 [10] who found that in patients admitted with sepsis, age was an independent predictor of mortality, while this was in contrast to Boumendil *et al*., in 2012 [11], who perform a study that included 2646 patients, with a median age of 87 years, and found that predictors of in-hospital death were more related to immediate severity conditions (severity score, condition potentially warranting ICU admission, and decubitus ulcers) than the age itself. This hypothesis was confirmed by Flaatten *et al*., 2017 [12] in another study involving over 5000 patients older than 80 years (VIP1 study), where it was demonstrated that age had a smaller impact on survival in ICU and other factors could predict better the risk of mortality among these patients.

Regarding gender, 89 of our patients were male (59.3%) with small but statistically significant trend to increased mortality among female gender. The study was not designed to primarily investigate the effect of gender on sepsis-related mortality; however, this was in agreement with Papathanassoglou *et al*., in 2017 [13], who performed a systematic review on gender dependent outcome in sepsis and found that available research data points toward a small disadvantage for survival in women, but they also noted that due to the paucity of well-designed studies and large heterogeneity across reports, results are so far inconclusive.

Regarding source of infection among the study group, the two most common sources were respiratory infection 53 patients (35.3%) and urosepsis 37 patients (24.7%). Other sources identified were skin and subcutaneous tissues infection, abdominal infection, infected prothesis, and CRBSI. This was in agreement with Mohamed *et al*., in 2017 [14], who found that the most common source of sepsis among ICU patients was respiratory infection.

Regarding culture results, in blood culture, 87 patients showed no growth (58%), while 26 showed Gram-positive organisms (17.3%) and 37 showed Gram-negative organisms (24.7%). Bacterial growth in blood culture was statistically significant with outcome with higher incidence of mortality among patients with positive blood culture. This was in contrast to Mohamed *et al*., in 2017 [14], who found that neither blood culture positivity nor isolation of multiple organisms was significantly related to mortality. In sputum culture, 82 patients (54.7%) showed no growth, while 37 patients (24.7%) showed Gram-negative growth and remaining 31 patients (20.7%) showed Gram-positive growth. In urine culture, 114 patients showed no growth (76%), while 36 patients showing bacterial growth (24%). There was no statistically significance difference between survivors and non-survivors regarding results of sputum or urine cultures.

Regarding mechanical ventilation use among study group, MV was used in 80 patients (53.3%). There was statistically significant difference among survivors and non-survivors in regard to MV use with its use being associated with a high mortality. This was in agreement with Vincent *et al*., in 2006, who found that MV use was significantly associated with mortality and with Mohamed *et al*., in 2017 [14], who found that low platelet count, high CRP, and elevated levels of serum lactate along with need for invasive mechanical ventilation were found to be a clear predictor of mortality in severely septic patients.

The APACHE II score was showing statistically significant association with mortality with mean of 14.04 ± 4.14 among survivors compared to 24.95 ± 7.57 among non-survivors. The AUC for APACHE II score ROC curve was 0.86 with cutoff point of 16 giving sensitivity of 0.82% and specificity of 0.79% for outcome prediction. In logistic regression analysis, higher APACHE II score was associated with higher odds of mortality OR 1.32 (95% CI: 1.13, 1.54).

This was in agreement with Sadaka *et al*., in 2017 [15], who studied a total of 2054 septic patients and found that the average APACHE II score was 19 ± 7, and that both APACHE II and APACHE III scores were higher in n on survivors. ROC area under the curve (AUC) was 0.80 (95% confidence interval [CI]: 0.78–0.82) for APACHE II. This was also in agreement with Mohamed *et al*., in 2017 [14], who concluded that APACHE II and SOFA score of more than 25 and 8.5, respectively, at the time of admission to the ICU with severe sepsis were identified as independent predictors of mortality. In a 3rd study by Mohamed *et al*., in 2017 [14], the difference of mean APACHE II scores between the survivors and non-survivors was significant and was

identified as an independent predictor of mortality in severe sepsis, a cutoff for APACHE II score of 21.5 was associated with higher mortality with a sensitivity of 87% each and specificity of 81%. Zanon *et al*., in 2008 [16], in their Brazilian study, had found APACHE II score cutoff of 18 had sensitivity of 67.6% and specificity 66.6%. Finally, this was in agreement with Singh *et al*., in 2019 [17], who compared APACHE II, SAPS II, and SOFA score in predicting mortality among patients with sepsis and septic shock. They found that all the three scoring systems perform well in mortality prediction with APACHE II showing the higher specificity (0.766) for outcome prediction.

Regarding SOFA score among the study group, the score was measured at day 0 (day of admission or sepsis diagnosis), day 4 and day 7. The range of SOFA 0 was 5 to 17, while the range of SOFA 4 was 4 to 16 and the range of SOFA 7 was 3 to 18. SOFA score was significantly associated with mortality with mean among survivors of 8.37 ± 2.25, 8.39 ± 2.49, and 7.04 ± 3.04 at 0, 4, and 7, respectively, compared with 11.54 ± 2.92, 12 ± 2.88, and 12.93 ± 3.34 among non-survivors in the same days. The highest AUROC observed for SOFA 7 and it was estimated to be 0.876 with sensitivity of 0.892% and specificity of 0.829% at cutoff point of 9.

In a study Ferreira et al., in 2001, to determine the usefulness of repeated measurement of the Sequential Organ Failure Assessment (SOFA) score for prediction of mortality in intensive care unit (ICU) patients, he studied a total of 352 patients and concluded that evaluation of SOFA score throughout the ICU stay is a good prognostic indicator especially the mean and the highest SOFA scores and that independent of the initial value an increase in the initial SOFA score in the first 48 hours of ICU admission, predicts mortality rate of atleast 50%. Independent of the initial value, an increase in the SOFA score during the first 48 h of ICU admission, predicts a mortality rate of at least 50%. Another study by Rivera-Fernández *et al*., in 2007 [19], demonstrated that 28-day mortality was related to mean and maximum daily SOFA scores in a cohort of patients who were critically ill with an AUROC of 0.95. This was also in agreement with Jones *et al*., in 2009 [20], who found that SOFA score provides potentially valuable prognostic information on in-hospital survival when applied to patients with severe sepsis with evidence of hypoperfusion at the time of ED presentation, while Seymour *et al*., in 2016 [21], concluded that among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS but was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis.

Finally, Karakike *et al*., in 2019 [22], studied data from two previously published randomized controlled trials: the first reporting on patients with severe Gram-negative infections as a derivation cohort and the second reporting on patients with ventilator-associated pneumonia as a validation cohort. Only patients with sepsis according to the Sepsis-3 definition were included in this analysis. SOFA scores were calculated on days 1, 2, 3, 5, 7, 14, and 28. They included 448 patients within the derivation cohort and 199 within the validation cohort. Mean SOFA scores on day 1 were 6.06 ± 4.07 and 7.84 ± 3.39, and 28-day mortality 22.8% and 29.6%, respectively. In the derivation cohort, the earliest time point where Δ_{SOFA} score predicted mortality was day 7 (AUROC [95% CI] 0.84 [0.80–0.89]; $p < 0.001$). The best tradeoff for prediction was found with 25% changes (78% sensitivity and 80% specificity); <25% decrease of admission SOFA was associated with increased mortality (odds ratio for death 14.87). This finding was confirmed in the validation cohort. They concluded that Δ_{SOFA} on day 7 is a useful early prognostic marker of 28-day mortality and could serve as an endpoint in future sepsis trials alongside mortality.

Regarding RDW value among the study group, the parameter was measured at day 0, day 4, and day 7. There was statistically significant association with mortality with mean among survivors in 0, 4, and 7 days of 13.07 ± 1.57, 13.27 ± 1.46, and 13.19 ± 1.50, respectively, compared with mean among non-survivors in the same days of 15.14 ± 1.58, 15.65 ± 1.68, and 15.71 ±1.7. The AUROC was 0.816 for RDW0 and 0.855 for RDW4, 0.851 for RDW7. The sensitivity for outcome prediction was estimated to be 0.743% and specificity of 0.803% at cutoff point of 15.5. Using this cutoff point for survival analysis using Kaplan–Meier analysis (Log rank test) in our study comparing time to event (death) between the group who had RDW on admission <15.5, and those who were ≥15.5 showed that median survival time for the <15.5 group was 16 days which is longer than the ≥15.5, 14 days, $p = 0.002$. In logistic regression analysis in our study, higher RDW value on admission was associated with higher odds of mortality, OR = 1.66 (95% CI: 1.21, 2.27).

In a study by Jo *et al*., in 2013 [23], a total of 566 patients were included, and overall mortality was 29%. RDW was significantly higher in non-survivors than in survivors, and the corresponding mortality of patients with an RDW of 14% or less, 14.1% to 15.7%, and 15.8% or greater was 13.1%, 30.1%, and 44.9%, respectively ($p < 0.001$). In Cox proportional hazards analysis, groups with higher RDW are independently associated with 28-day mortality compared with groups with an RDW of 14.0% or less: RDW 14.1% to 15.7% (hazard ratio, 1.66; 95% confidence interval [CI], 1.00–2.76) and RDW of 15.8% or greater (hazard ratio, 2.57; 95% CI, 1.53–4.34). The area under the receiver operating curve of RDW was 0.68 (95% CI, 0.63–0.72). They concluded that RDW is associated with 28-day mortality in patients with severe sepsis and septic shock.

Another study by Kim *et al*., in 2013 [24], who enrolled 329 patients with severe sepsis and septic shock and found that patients with increased RDW at baseline and ΔRDW 72 h-adm >0.2% exhibited the highest risks of 28-day and 90-day mortality, whereas

the patients with normal RDW level at baseline and ΔRDW 72 h-adm ≤0.2% had the lowest mortality risks. For 90-day mortality, a significantly higher mortality risk was observed in the patients whose RDW increased within 72 h of ED admission (normal RDW at baseline and ΔRDW 72 h-adm >0.2%), compared to the reference group. These associations remained unaltered even after adjusting for age, sex, SOFA score, Charlson Comorbidity Index, renal replacement therapy, albumin, hemoglobin, lactate, C-reactive protein, and infection sites in multivariable models.

In a retrospective study by Mahmood *et al*., in 2014 [25], who studied, 349 patients admitted with sepsis or septic shock and compared initial RDW level (within 24 h of admission) to APACHE II score and founded that RDW ≥16% was independently associated with an APACHE II score of ≥15. They suggested that septic patients with a RDW ≥16% may have a higher severity of illness. In addition, they found that RDW ≥16% was independently associated with mortality.

We investigated the correlation between RDW on days 0, 4, and 7 among cases and APACHE II score on admission, and we found that there was a significant linear strong correlation between RDW value and APACHE II score with the strongest correlations in day 7 with $p < 0.001$. This was in agreement with the study done by Jo *et al*., in 2013 [23], who performed a retrospective analytic study that 566 patients were included to assess the role of RDW as a predictor of mortality in intensive care septic patients and investigated the correlation between RDW and APACHE II score and they found that there is positive correlation with $p < 0.001$. Similarly, Sadaka *et al*., in 2017 [15], performed that a retrospective cohort study included 279 patients to assess the role RDW as a prognostic factor in septic shock patients; they found that RDW was significantly correlated with the APACHE II score. In the same context, Mahmood *et al*., in 2014 [25], found that RDW was associated weakly ($r = 0.27$) but significantly ($p = 0.0001$) with the APACHE II score.

We investigated the correlation between RDW in days 0, 4, and 7 and SOFA score in the same days and we found that there was a statistically significant strong linear correlation between SOFA score and RDW in days 0 and 4 with $p < 0.001$ with the strongest correlation between RDW in day 7 and SOFA in day 7. Similarly, to our study, Lorente *et al*., in 2014 [26], investigated whether there is positive correlation between RDW at days 1, 4, and 8 and SOFA score at the same days and they found that there is a statistically significant positive correlation with $p = 0.007$, 0.002, and <0.001 on day 1, 4, and 8, respectively. In addition, the study done by Kim *et al*., in 2013 [24], investigated the correlation between RDW at days 1 and 3 and SOFA score at the same days and they found that that there was a statistically significant positive correlation with $p < 0.001$. Furthermore, this was in agreement with the study done by (Sadaka *et al*., 2017 [15]) as they found that there was a positive correlation between RDW and SOFA score at day 1 with $p = 0.04$.

Contrary to our study, Jandial *et al*., in 2017 [27], concluded that in severe sepsis patients, RDW though showed a graded relationship with 30-day mortality, was not found to be an independent predictor of 30-day mortality. ROC curve analyses only revealed marginal discriminatory power of RDW (AUC 0.606) for predicting 30-day mortality as compared to APACHE II score (AUC 0.822).

A meta-analysis by Vincent *et al*., in 2003 [28], involving 90 cohort studies with 291,433 total patients evaluated prognostic significance of hypoalbuminemia and other parameters. RDW, though indicator of many adverse processes, was not independently associated with 30-day mortality.

Conclusions

The previous results support the usefulness of admission RDW value and serial change in RDW as a simple readily available parameter to predict the outcome among patients admitted with sepsis or septic shock. A combination of baseline RDW value and an increase in serial RDW values can be a promising independent prognostic marker in patients with sepsis or septic shock.

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