Original Article

Predictive factors for sepsis diagnosis, length of intensive care unit (ICU) stay and mortality in ICU

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Abstract

Background: The incidence of sepsis is worldwide. We aimed to assess the value of enhanced red cell distribution width (RDW) to predict sepsis and evaluate factors affecting length of intensive care units (ICU) stay and in-hospital mortality among sepsis patients.

Materials and Methods: In a prospective study, we had 187 patients, which after exclusion of 27 patients, we included 160 adult patients with suspicious sepsis admitted in the university affiliated Hospital with 33 ICU-beds from 2010 to 2012. Nighty patients were diagnosed with sepsis and the source of infection was defined. Receiver–operating characteristic (ROC) curves were used to examine the sepsis predictions from RDW, APACHE II scores, and combination of them. The primary endpoint of this analysis was ICU mortality. The secondary endpoints were length of stay in ICU and hospital. A linear regression analysis was used to study risk factors for longer ICU stay and we used Logistic regression analysis to predict factors affecting in-hospital mortality.

Results: The addition of elevated RDW value to acute physiology and chronic health evaluation (APACHE) II score in critically illness states enhanced the AUC for predicting sepsis and its differentiation from SIRS. Female patients and those with numerous co-morbidities or AKI and those on mechanical ventilation significantly stayed longer in ICU. Moreover, the patients with higher APACHE II score died significantly more than others.

Conclusion: The addition of elevated RDW value to APACHEII score in critically illness helps to differentiate sepsis from SIRS.

Keywords: Red blood cells distribution width, Intensive Care Unit, Factor

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Introduction

Sepsis is defined as systemic inflammatory response syndrome (SIRS) plus infection (1). The incidence of sepsis worldwide has been reported 1. 8 million each year (2). About 10% of admissions to the intensive care units (ICU) are related to sepsis and septic shock (3). Sepsis with a mortality rate about 30% is still among leading causes of death worldwide (2-4). If sepsis progresses, multiple organs failure might occurring approximately one third of patients (5). Difficulty of diagnosis is one of the key challenges since early diagnosis and subsequent treatment result in more success (2, 6). Multiple

diagnostic tests with different degrees of accuracy are applied to assess these conditions in the patients (3, 7-9). There are some factors to predict the outcomes of sever sepsis such as age, sex, biomarkers and comorbidities (10, 11). Among them, red cell distribution width (RDW) as a prognostic evaluation tool for distinguishing sepsis has been studied less (12).

Red cell distribution width as part of complete blood count (CBC), shows the variability in the size of the red blood cells (10). Mixed cohort studies has shown that elevated RDW in critically ill patients is accompanying with severity of disease and even mortality (13). It is used, not only in the differential diagnosis of anemia but also as a predictive factor of mortality and morbidity in numerous diseases such as chronic heart failure, acute myocardial infarction, pulmonary embolism, and critical illness (10, 14-16). The cause of association between RDW and mortality in the patients is unclear (12). It seems that the mechanism of raised RDW value is the inflammatory markers such as cytokines and interleukins which are produced in the inflammatory process (10, 12). Pro-inflammatory cytokines play an important role in inhibition of erythrocyte maturation and proliferation of reticulocytes into the peripheral circulation (10, 17). In addition, the oxidative stress which is produced by activated leukocytes lead to diminishing the half-life of RBCs (12). RDW is also increased by nutrition deficiency (Iron, B12, folate), blood transfusions, renal dysfunction, any medication and chronic inflammation (18).

The aim of the current study is to assess whether the elevated RDW at initiation of critical care is associated with in-hospital mortality in sepsis patients and to evaluate whether it can predict sepsis and differentiation from SIRS.

Methods

In a prospective study, we included 187 adult patients with suspicious sepsis admitted in the university affiliated hospital with 33 ICU-beds from 2010 to 2012. 27 patients, including HIV-positive patients, patients on steroid therapy, or patients with known hematologic malignancy were excluded. Moreover, patients admitted to ICU for less than 48 hours or had a blood transfusion on week prior to admission were excluded. The study was approved by the Institutional Research and Ethics Committee in accordance with the Declaration of Helsinki.

"SIRS" is defined as 2 or more of the following criteria: fever of more than 38°C (100. 4°F) or less than 36°C (96. 8°F), heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO2) of less than 32 mm Hg and abnormal white blood cell count (>12, 000/µL or < 4, 000/µL or >10% immature (band) forms).

Before initiation of antibiotics, blood cultures were performed and growth of aerobic, anaerobic, or fungal organisms was defined as positive blood culture. Primary site infection was categorized as pulmonary, urinary, blood (primary) and other or multiple sites. Infection was confirmed by positive culture of responsible germ(s) drawn from blood, urine or tracheal tube secretions samples "Sepsis" is defined as SIRS as a result of confirmed infection.

We collected demographic data as well as information on medications and co-morbidities, including thyroid disease, liver disease, pulmonary disease, diabetes, hypertension, congestive heart failure, cerebrovascular accidents, and cancer. We recorded hemodynamics, the need for mechanical ventilation, primary site of infection, laboratory values and microbiological data.

Acute physiology and chronic health evaluation (APACHE) II score was calculated within the initial 24 hours of ICU admission for disease severity assessment. APACHE II was calculated using age and 12 acute routine physiological measurements within 24h of ICU admission. These variables include; temperature, mean arterial pressure, heart rate, respiratory rate, AaDO2 or PaO2, pH arterial, serum sodium and potassium, creatinine, hematocrit, white blood cell count, and Glasgow coma scale. It ranges from 0 to 71, with higher scores indicating more severe illness.

A Sysmex America XT 1800 (Mundelein, IL, USA) analyzer was used by the hospital laboratory to determine RDW, hemoglobin level, and mean corpuscular volume (MCV) during the study. The normal reference range for RDW in our laboratory was 11. 6% – 14. 5%. First admission day's erythrocyte sedimentation rate (ESR) and C-reactive

protein (CRP) were recorded.

The primary endpoint of this analysis was ICU mortality. The secondary endpoints were length of stay in ICU and hospital.

Statistical analysis

Continuous variables were reported as means ± standard deviation or median (interquartile ranges (IQR)) and compared using Student's t-test or Mann Whitney U test respectively. The Kolmogorov-Smirmov test was used to assess normality distribution of continuous variables and the comparison test was chosen depending on the normality distribution of variables. Categorical variables were presented as frequency with percentages and compared using the Chi square test or Fisher's exact test, as appropriate. Descriptive statistics were calculated for patients with diagnosis of SIRS versus those with septic diagnosis. Within each group (SIRS and sepsis), patients were divided into those with normal RDW (11. 5%-14. 5%) and high RDW (>14. 5%), then compared using appropriate statistical tests. Receiver–operating characteristic (ROC) curves were used to examine the sepsis predictions from RDW, APACHE II scores, and combination of them. The area under the ROC curve was used as a measure of discrimination of RDW, APACHE II scores, and combination of them for sepsis diagnosis.

Univariate analysis was done to find potential risk factors for length of hospital stay. Then a linear regression analysis was used to study risk factors for the longer ICU stay. For linear regression analysis, serum creatinine, albumin, number of morbidities, sex and mechanical ventilation were entered in the model. Moreover, after univariate analysis, we used Logistic regression analysis by potential factors such as age, APACHE II, the number of morbidities, RDW, serum creatinine, albumin and mechanical ventilation for hospital mortality.

Two-sided comparing and statistically significant level of p values less than 0. 05 were considered in the present study. All statistical analysis was performed using SPSS 16. 0 (SPSS, Chicago, IL, USA).

Results

A total of 183 patients with suspected diagnosis of sepsis in ICU enrolled in the study.

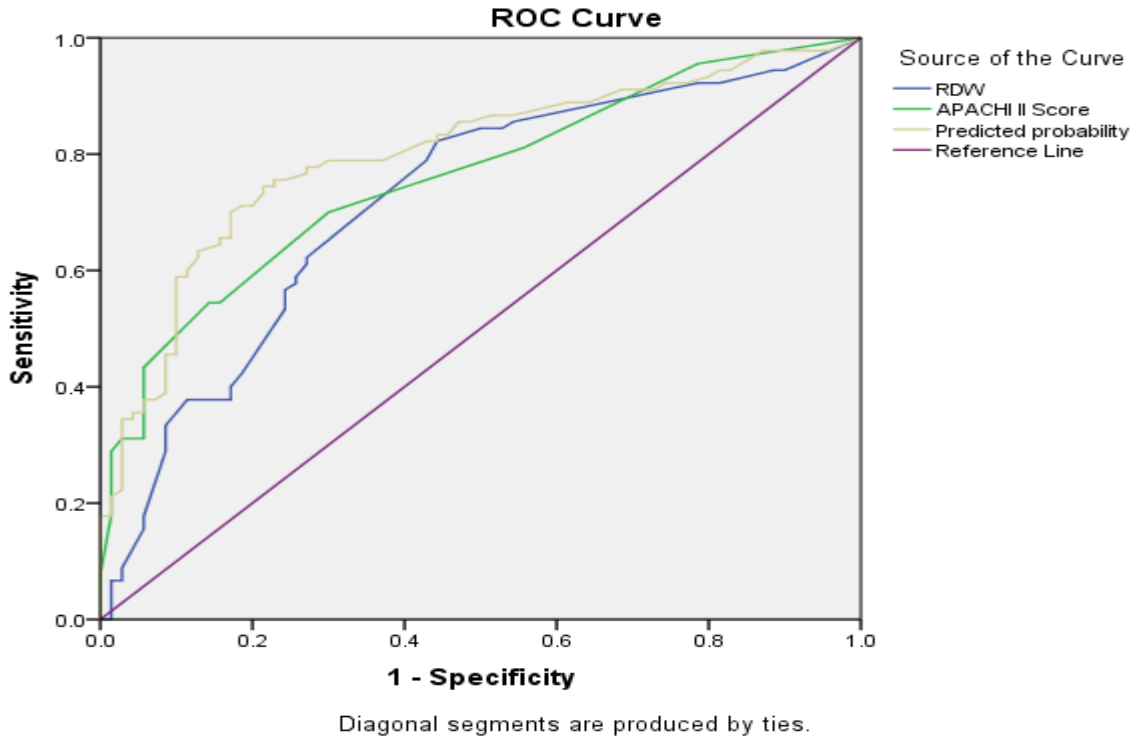

Figure 1. Receiver operating characteristics (ROC) curve for Diagnosis of sepsis; RDW, APACHI II and combination of RDW, APACHI II.

Table 1: Demographic, clinical and laboratory findings in patients with SIRS and Sepsis.

	SIRS (70)	SEPSIS (90)	p-value
Age	55 (20)	70 (18)	<0.001
Sex (Male)	34 (48.6%)	59 (65.6%)	0.036
APACHEII	8 (4)	12 (10)	<0.001
Comorbidities			
Diabetes	23 (32.9%)	46 (51.1%)	0.025
Chronic Renal Failure	0 (0%)	12 (13.3%)	0.001
Hypertension	11 (15.7%)	40 (44.4%)	<0.001
Congestive Heart Failure	10 (14.3%)	14 (15.6%)	>0.999
Cerebrovascular Accident	3 (4.3%)	6 (6.7%)	0.732
Cancer	13 (18.6%)	4 (4.4%)	0.008
Chronic Liver disease	10 (14.3%)	13 (14.4%)	>0.999
Chronic respiratory diseases	47 (67.1%)	67 (74.4%)	0.379
Biochemical data			
ESR	34 (40)	55 (43.25)	0.001
CRP	30 (19.25)	39 (26.5)	<0.001
Hb (g/dL)	10.61 (3.8)	11.15 (4.0)	0.388
WBC(10^3 /mm^3)	10.52 (4.9)	10.95 (5.1)	0.591
RDW	14.4 (1.85)	16 (3)	<0.001
Albumin (g/dL)	3.08 (0.8)	2.95(1.40)	<0.001
Creatinine (mg/dL)	1 (0.4)	1.5 (0.8)	<0.001
Acute Kidney Injury	7 (10%)	34 (37.8%)	<0.001
Mechanical Ventilation	19 (27.1%)	72 (80%)	<0.001
Total length of ICU stay	5 (4)	8 (7)	<0.001
Total length of hospital stay	14 (8.25)	12.5 (8)	0.871
Mortality	2 (2.9%)	28 (31.1%)	<0.001

Twenty three patients were excluded due to HIV, steroid therapy, hematologic malignancy, blood transfusion in the week before and ICU admission for less than 48 hour. Finally a total of 160 patients (58. 1% male; median age 60 years) were eligible for this study.

RDW ranged from 13% to 23% (median 15% mean 15.75± 2.11%) on the day of admission. The average APACHE-II score was 10. 82±5. 8 on the day of ICU admission. Approximately 91% of patients had at least one organ failure.

90 (53.3%) of patients were diagnosed with sepsis due to positive blood culture. The 2 most frequent primary sites of infection were respiratory (71.7%) and urinary tracts (6.7%). The baseline clinical and laboratory characteristics of SIRS and sepsis groups are listed in table 1. Compared with SIRS patients, sepsis patients were significantly older, with higher APACHE II, and higher ESR, CRP, serum creatinine and RDW. Sepsis patients stayed in ICU for longer time and more frequently needed mechanical ventilation. Approximately 18% of patients died during stay at hospital, which was significantly higher in sepsis group.

To assess the value for APACHE-II score and RDW to predict diagnosis of sepsis in comparison with SIRS, a receiver–operating characteristic (ROC) curve analysis was used (Figure 1). The AUC was calculated as 0.719±0.80 ($p<0.001$) and 0.759±0.73 ($p<0.001$) for RDW and APACHE-II score, respectively. Combination of RDW and APACHE II score increased AUC to 0.799±0.70 ($p<0.001$) for predicting diagnosis of sepsis. In order to predict sepsis diagnosis, the optimal cutoff value for RDW was 14.65 with sensitivity of 82.2% and specificity of 55.7%. Similarly the optimal cutoff value for

Table 2: Multiple linear regression for factors determining length of hospital stay.

	Beta co-efficient	P value
Sex (male)	-4.124	0.002
Serum Albumin	0.705	0.445
Serum Creatinine	-0.641	0.353
Mechanical ventilation	4.341	0.018
Number of comorbidities	1.328	0.036
Acute Kidney Injury	2.878	0.039

APACHE II was 10.5 which gave 54.4% and 85.7% sensitivity and specificity, respectively.

There was no correlation between "length of ICU stay" in sepsis patients and factors such as age (p=0.22), APACHE II (p=0.091), RDW (p=0.382), ESR (p=0.510), and CRP (p=0.995). There was a positive correlation between "length of ICU stay" and serum creatinine (r=0.287, p=0.006) and also number of morbidities (r=0.289, p=0.006). The correlation between "length of ICU stay" and albumin (r=-0.230, p=0.029) was negative.

Female patients stayed in ICU longer than male patients (10vs.8, p=0.002). Moreover the ICU stay days were more among patients on mechanical ventilation (9vs.5, p<0.001).

We entered sex, serum creatinine, albumin, number of morbidities, AKI and mechanical ventilation in a multiple linear regression model to evaluate factors affecting the length of ICU stay amongst sepsis patients (r square = 0.266). Analysis showed that female patients, patients with higher number of co-morbidities or AKI and those on mechanical ventilation significantly stayed longer in ICU (Table 2).

We entered age, APACHE II, the number of morbidities, RDW, serum creatinine, albumin and mechanical ventilation in a logistic regression model to evaluate factors affecting mortality of sepsis patients (r square = 0.657) (Table 3). Analysis showed that patients with higher APACHE II died significantly more than others (Table 4).

Discussion

The current study presented that high level of RDW (on day of admission) as an independent risk factor was unrelated to in-hospital mortality and prolonged ICU stay at multiple regression analysis. Moreover, the patients with higher APACHE II score died significantly more than others. To continue, female patients and those with numerous co-morbidities or AKI and those on mechanical ventilation significantly stayed longer in ICU. Furthermore, the addition of elevated RDW value to APACHEII score in critically illness states enhanced the AUC for predicting sepsis and its differentiation from SIRS.

In this study, we observed that there was no significant association between RDW and in-hospital mortality. In addition, APACHE II score had a great importance in mortality risk in sepsis patients. However, RDW value in combination with APACHEII score could predict sepsis diagnosis in a higher sensitivity. The elevated RDW in sepsis may be due to high oxidative stress. The activated leukocytes can generate the reactive oxygen types and consequently high oxidative stress (19). It has been anticipated that the oxidative stress can decrease RBC survival which lead to high releasing of premature RBCs into the peripheral circulation (17, 20). Moreover, another reason should be noted that the frequency of renal injury in our sepsis group was more than SIRS group. The studies have demonstrated the relation between elevated RDW and renal dysfunction (17, 21). Renal dysfunction is strictly related with nutritional deficiencies and inflammation which both of them are also associated with increased RDW value (21, 22). To our knowledge, nowadays despite the improvement in treatment and managing of sepsis in intensive care units (ICU), the mortality rate of this group of patients are still high (2, 4). Thus, early diagnosis of sepsis plays a crucial role in modifying the natural history of it. It also improves the cost-effectiveness of the critical care (23). APACHEII score would guide the medical decision-making about the necessary strategies to manage the patients with sepsis (13). Our study in consistent with the previous study described

Table 3: Clinical and laboratory finding in patients with sepsis

Sepsis and Mortality	**Survivor (62)**	**Non-survivor (28)**	**P-Value**
Age	65 (19)	77 (10)	**<0.001**
Sex (male)	38 (61.3%)	21 (75%)	0.239
APACHEII	10 (6)	22 (5.5)	<0.001
Co-morbidities (Number)	2 (2)	3 (2)	<0.001
Infection Site			
Urinary Tract Pulmonary	6 (9.7%)	0 (0%)	
Other	44 (71%)	20 (71.4%)	0.178
	12 (19.4%)	8 (28.6%)	
Biochemical data			
ESR	58(45)	46.5(33.75)	0.348
CRP	38 (28.75)	40 (22)	0.972
Hemoglobin (g/dL)	11.3 (4.1)	10.8 (3.9)	0.588
White Blood Cell(10^3 /mm^3)	11.1 (5.2)	10.6 (4.8)	0.667
RDW	15.7 (2.82)	17 (2.63)	0.043
Albumin (g/dL)	3.6 (1.22)	2.55 (2.2)	<0.001
Creatinine (mg/dL)	1.2 (0.6)	1.9 (0.85)	<0.001
Acute Kidney Injury	20 (32.2%)	14 (50%)	0.158
Mechanical Ventilation	44 (71%)	28 (100%)	0.001

that consideration of RDW in APACHE II score could significantly advance it to predict sepsis as a higher severity risk compared with SIRS (24, 25). The low cost and easy availability of RDW in routine CBC tests, would be valuable in evaluation of severity of illness in clinical utility (26).

Recent studies depicted the association of RDW with mortality in patients with cardiovascular diseases, pulmonary embolism, cardiac arrest, stroke and septic shock in comparison to those with normal

Table 4: Logistic regression for factors affecting mortality.

	OR	**CI**	**P value**
Age	1.104	0.904-1.374	0.331
APACHE II	2.851	1.429-5.687	**0.003**
Number of comorbidities	0.588	0.128-2.705	0.496
RDW	1.957	0.826-4.635	0.127
Serum albumin	0.518	0.042-6.331	0.606
Serum Creatinine	4.992	0.160-156.094	0.360
Mechanical ventilation	0	0	0.998

limits of RDW (5, 13, 17, 27, 28). Meynaar et al. , and Loveday et al. showed the maximum elevations in RDW which were in significant association with probability of mortality in the ICU patients with acute diseases (12, 29). Even so, this association was not confirmed in our study which could be due to small sample size. However, APACHE II score had a great importance in predicting the mortality risk in sepsis patients.

Besides mortality, another important issue amongst septic patients is the length of hospital stay. Since the length of ICU stay is costly and numbers of ICU beds are limited in referral hospital, prediction of ICU stay is crucial for physicians and also hospital managers. According to our study, female patients and those on mechanical ventilation significantly are expected to stay in ICU for longer time. More importantly patients with AKI or higher number of co-morbidities stayed longer in ICU. These factors could help patients to make more accurate decisions about prevention and management of long ICU stay complications such as VAP and tracheostomy.

Conclusion

The addition of elevated RDW value to APACHEII score in critically illness states enhanced the prediction of sepsis diagnosis and its differentiation from SIRS.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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