American Journal of Emergency Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Red blood cell distribution width is associated with mortality in elderly patients with sepsis

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ARTICLE INFO

Article history:
Received 4 September 2017
Received in revised form 15 October 2017
Accepted 24 October 2017
Available online xxxx

Keywords:
Aged
Red blood cell distribution width
Sepsis

ABSTRACT

Introduction: RDW is a prognostic biomarker and associated with mortality in cardiovascular disease, stroke and metabolic syndrome. For elderly patients, malnutrition and multiple comorbidities exist, which could affect the discrimination ability of RDW in sepsis. The main purpose of our study was to evaluate the prognostic value of RDW in sepsis among elderly patients.
Methods: This was a retrospective cohort study conducted in emergency department intensive care units (ED-ICU) between April 2015 and November 2015. Elderly patients (≥65 years old) who were admitted to the ED-ICU with a diagnosis of severe sepsis and/or septic shock were included. The demographic data, biochemistry data, qSOFA, and APACHE II score were compared between survivors and nonsurvivors.
Results: A total of 117 patients was included with mean age 81.5 ± 8.3 years old. The mean APACHE II score was 21.9 ± 7.1. In the multivariate Cox proportional hazards model, RDW level was an independent variable for mortality (hazard ratio: 1.18 [1.03–1.35] for each 1% increase in RDW, $p = 0.019$), after adjusting for CCI, any diagnosed malignancy, and eGFR. The AUC of RDW in predicting mortality was 0.63 (95% confidence interval [CI]: 0.52–0.74, $p = 0.025$). In subgroup analysis, for qSOFA <2, nonsurvivors had higher RDW levels than survivors (17.0 ± 3.3 vs. 15.3 ± 1.4%, $p = 0.044$).
Conclusions: In our study, RDW was an independent predictor of in-hospital mortality in elderly patients with sepsis. For qSOFA scores <2, higher RDW levels were associated with poor prognosis. RDW could be a potential parameter used alongside the clinical prediction rules.

1. Introduction

Red cell distribution width (RDW) is calculated as the standard deviation of red blood cell (RBC) volume divided by the mean corpuscular volume (MCV) and is a quantitate expression of anisocytosis. RDW is a common hematologic parameter and a part of the standard complete blood count which is measured among hospitalized patients. It has been used as a prognostic biomarker in hypertension [1], coronary disease [2,3], stroke [4], pulmonary hypertension [5], and acute kidney injury [6]. RDW is also related to all-cause mortality in the general population and is even independently associated with nutritional status [7].

The exact pathophysiological mechanism underlying RDW and clinical outcomes is not well-understood currently. Elevated RDW has been associated with inflammatory biomarkers [8] and RDW increases with increasing oxidative stress [9]. Inflammation impairs iron metabolism, promotes RBC apoptosis, reduces erythropoietin production, and has a myelosuppressive effect [10,11]. In a previous study, it has been reported that RDW has moderate discriminative power for mortality in critically-ill patients, including medical and surgical patients [12], which indicates that RDW could be a potential biomarker for assessing the severity of sepsis. Increase in RDW from baseline levels during the first three days after ED admission has been associated with mortality in severe sepsis or septic shock [13]. In that study, the mean population age was lower than 65 years. For elderly patients, malnutrition and multiple comorbidities exist, such as chronic heart failure and chronic kidney disease which have been related to the increase in RDW [14]. This could affect the discrimination ability of RDW in sepsis. The main purpose of our

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https://doi.org/10.1016/j.ajem.2017.10.056
0735-6757/

study was to evaluate the prognostic value of RDW in sepsis among elderly patients.

2. Materials and methods

2.1. Study design

This was a retrospective analysis conducted between April 2015 and November 2015 at the Taipei Medical University Hospital, a university-based teaching hospital. The study was conducted in the Emergency Department's intensive care unit (ED-ICU). This study was approved by the Institutional Review Board of the Taipei Medical University, and the requirement for informed patient consent was waived.

Elderly patients (≥65 years old) who were admitted to the ED-ICU from the emergency room with a diagnosis of severe sepsis and/or septic shock according to the International Sepsis Definitions Conference criteria [15] were included in the study. Exclusion criteria included trauma patients, patients transferred from the general wards and postoperative patients.

Demographic data for all the study patients were obtained from the electronic medical records and included age, gender, height, body weight, body mass index (BMI), Charlson comorbidity index (CCI) [16] to represent the comorbidities in different illness categories (malignancy, metastatic or hematologic malignancies, cardiovascular disease, renal insufficiency, hepatic insufficiency, stroke, respiratory insufficiency, and diabetes mellitus), primary site of infection, and Acute Physiology and Chronic Health Evaluation (APACHE) II score [17] at ICU admission obtained within 24 h.

Laboratory parameters such as white blood cell (WBC) count, hemoglobin (Hb) level, hematocrit (Hct), platelet count, sodium, potassium, total bilirubin, albumin, c-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR) and blood gas were measured at initial presentation in the emergency room. RDW values, as a part of the complete blood cell count analysis, were extracted, and compared to the normal laboratory range of RDW in our hospital (11.5% to 14.5%). The main outcome of our study was in-hospital mortality.

2.2. Subgroup analysis

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 introduced the quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score for sepsis definition, which assesses physiologic parameters, as hypotension (systolic blood pressure ≤ 100 mm Hg), tachypnea (respiratory rate ≥ 22/min), and altered mental status [18]. A qSOFA score of 2 or more points can be identified as a poor outcome of sepsis. We also compared the qSOFA score (range, 0 [best] to 3 [worst] points) calculated based on the ED's triage physiological parameters with RDW level and mortality.

2.3. Statistical analyses

All numeric variables were assessed for normality using the Kolmogorov-Smirnov test. Continuous variables were expressed as means and standard deviations, applying the Mann-Whitney *U* test for comparisons. Categorical variables, expressed numerically and as proportions, were compared as applicable via chi-square test or Fisher's exact test. Variables in univariate analysis with a p-value <0.10 were entered into the multivariate analysis. The multivariate analysis was conducted using Cox proportional hazards model.

A receiver-operating characteristic (ROC) curve was generated for predictive accuracy of RDW level, and the area under the curve (AUC) was calculated. Significance was set at $p < 0.05$ in two-sided testing. All analyses were performed using the SPSS version 22 (IBM Corp., Armonk, NY).

3. Results

3.1. Baseline characteristics

A total of 117 patients were included in the study. The mean age was 81.5 ± 8.3 years, and 59.8% (70/117) of the patients were male. The mean length of stay (LOS) in ICU was 5.7 ± 5.8 days. In our cohort, 82.9% (97/117) of patients had underlying cardiovascular disease, 23.9% (28/117) had malignancies, 40.2% (47/117) had diabetes, 40.2% (47/117) had cerebrovascular disease, and 21.4% (25/117) had chronic kidney disease. The mean APACHE II score in our cohort was 21.9 ± 7.1. The primary sites of infection were as follows: 62.3% (73/117) were pneumonia, 22.2% (26/117) were intra-abdominal infections, 14.5% (17/117) were urinary tract infections, and only one was meningitis. Non-survivors had shorter LOS in ICU (4.5 ± 4.1 days vs. 6.2 ± 6.4 days, $p = 0.045$) and total LOS (26.4 ± 39.0 days vs. 11.7 ± 14.1 days, $p < 0.001$). The patients who survived to discharge had a lower prevalence of underlying malignancy with lower CCI (3.6 ± 2.2 vs. 5.1 ± 3.4, $p = 0.056$). There were no significant differences in age, gender, BMI, APACHE II score, and primary site of infection. Detailed demographic characteristics were shown in Table 1.

3.2. Biochemical parameters

Survivors had lower RDW levels (15.5 ± 1.9% vs. 16.7 ± 2.8%, $p = 0.025$), and higher eGFR (66.56 ± 53.91 ml/min/1.73 m^2 vs. 41.48 ± 32.20 ml/min/1.73 m^2, $p = 0.007$) compared to non-survivors. There was no significant difference in RBC count, Hb, platelet count, CRP, and albumin level (Table 1).

Other parameters which were incorporated in the APACHE II scoring system are shown in Table 1. There was no significant difference in APACHE II score between the two groups (21.5 ± 5.9 vs. 22.8 ± 9.2, $p = 0.275$).

3.3. RDW and mortality

In Table 2, higher RDW values, higher CCIs, previous diagnosis of malignancy, and lower eGFR, were associated with mortality. In the multivariate Cox proportional hazards model, RDW level was an independent variable for mortality (hazard ratio: 1.18 [1.03–1.35] for each 1% increase in RDW, $p = 0.019$), after adjusting for CCI, any diagnosed malignancy, and eGFR. The AUC of RDW in predicting mortality was 0.63 (95% confidence interval (CI): = 0.52–0.74, $p = 0.025$).

3.4. Subgroup analysis

Out of 117 patients, 49 (41.9%) had qSOFA scores ≥2. Higher RDW levels in the qSOFA ≥2 group was observed, but there was no significant difference between the qSOFA score <2 and ≥2 (15.7 ± 2.2% vs. 16.0 ± 2.4%, $p = 0.753$) groups. In the group with qSOFA <2, non-survivors had higher RDW levels than survivors (17.0 ± 3.3% vs. 15.3 ± 1.4%, $p = 0.044$). For the qSOFA ≥2 group, non-survivors had slightly higher RDW levels, but there was no significant difference (16.3 ± 2.3% vs. 15.8 ± 2.5%, $p = 0.254$) (Fig. 1). Discrimination of in-hospital mortality using qSOFA was not satisfactory (AUC, 0.56; 95% CI: 0.45–0.67, $p = 0.313$).

4. Discussion

In our study, the RDW level could be an independent predictive factor for mortality in elderly patients admitted to the ICU with sepsis. After adjusting for comorbidities and renal function, for each 1% increase in RDW level as a continuous variable in the multivariate Cox proportional hazards model, mortality rate increased by 18%. The ROC curve showed that RDW had moderate discriminative power for in-hospital mortality.

Please cite this article as: Wang A-Y, et al, Red blood cell distribution width is associated with mortality in elderly patients with sepsis, American Journal of Emergency Medicine (2017), https://doi.org/10.1016/j.ajem.2017.10.056