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Do Mean Platelet Volume and Red Cell Distribution Width Predict Mortality in Patients with Acute Respiratory Distress Syndrome?

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Abstract

Backround: To investigate the role of mean platelet volume (MPV), red cell distribution width (RDW) and other parameters of complete blood count on predicting mortality in patients withacute respiratory distress syndrome (ARDS).

Materials and Methods: Forty-six patients admitted to the intensive care unit of our institute -a tertiary center- with ARDS between April 2016 and January 2019 were retrospectively recruited in the study. Demographic and clinical data including age, gender, accompanying chronic diseases, the Acute Physiology and Chronic Health Evaluation (APACHE) scores and laboratory test results were retrospectively collected from medical records and electronic databases. The study population was divided into two groups according to the development of mortality as survivors or non-survivors.

Results: Twenty-five subjects died during the in-hospital course (non-survivors) and 21 survived (survivors). APACHE II scores, MPV, RDW andneutrophil–lymphocyte ratio (NLR) were significantly higher in the non-survivors group compared to that of the survivors. Multiple logistic regression analysis revealed that MPV and RDW were independent predictors of mortality in patients with ARDS. ROC curve analysis indicated a cut-off value of 8.11 fl for MPV (sensitivity 88%, specificity86%) and 14.45 % for RDW (sensitivity 84%, specificity86 %) to predict mortality in patients with ARDS.

Conclusions: MPV, as an emerging indicator of preexisting inflammation, and RDW indicating inflammation, independently predict mortality in patients with ARDS. Implementation of MPV and RDW might be useful in identifying patients who will require advanced support during admission for ARDS.

Key words: *Hospital-acquired infections, prevalence, McCabe score, mortality*

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Introduction

The acute respiratory distress syndrome (ARDS) is one of the most important diseases in intensive care unit and a major cause of morbidity and mortality in critically ill patients. ARDS is defined by the association of arterial hypoxemia (partial pressure of arterial oxygen to fraction of inspired oxygen ratio 300 or less with a positive end-expiratory pressure of 5cm H2O or more), presence of bilateral infiltrates on chest radiography and exclusion of cardiac failure as a primary cause (1). Despite improvements in intensive care unit management, ARDS is still a frequent, morbid, and life threatening condition with a mortality rate around 30% (2– 3). Early diagnosis and effective treatment of ARDS can significantly reduce the mortality and improve recovery. Therefore, it is critical to predict the development of ARDS at an early stage in critically ill patients.

Systemic inflammation is an important cause of disease progression, morbidity, and mortalityARDS patients (4-5). Some previous research indicates that simple blood tests of inflammation such as neutrophil–lymphocyte ratio (NLR) performed at admission might predict the mortality in critically ill patients with ARDS (6-7). In previous studies, elevated mean platelet volume (MPV) and red cell distribution width (RDW) values were also found associated with poor outcomes and increased mortality rate in inflammatory diseases such as sepsis, neonatal respiratory distress syndrome, cardiovascular diseases, pulmonary embolism, chronic obstructive pulmonary disease and in critically ill patients (8–17). However, none of these studies investigated the predictive role of MPV and RDW mortality in patients with ARDS.

The purpose of the present study was to investigate the value of MPV, RDW and other parameters of complete blood cell count (CBC)in predicting mortality in patients with ARDS.

Materials and methods

Study population

All consecutive patients admitted to the intensive care unit of our institute -a tertiary center- with ARDS between April 2016 and January 2019 were retrospectively recruited in the study. Informed consent was obtained from all subjects and the study protocol was approved by the local Ethics Committee. Patients admitted to intensive care unit with diagnosis of ARDS based on the 2012 Berlin definition were included in our study if they met the inclusion criteria and none of the exclusion criteria (1). Exclusion criteria were evidence of diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, renal or hepatic dysfunction, chronic lung disease, arterial or venous thrombotic disease, haematological disease, cancer, hypo and hyperthyroidism, auto-immune disease, antithrombotic agents or serotonin reuptake inhibitor drug use, chronic or systemic inflammatory diseases such as asthma bronchial, rheumatoid arthritis and psoriasis.Patients who received a blood transfusion within the last three months were also excluded from the study.

Data collection and outcome measurements

Demographic and clinical data including age, gender, accompanying chronic diseases,the Acute Physiology and Chronic Health Evaluation (APACHE) scores and laboratory test results (Beckman Coulter LH 780 Haematology Analyzer) were retrospectively collected from medical records and electronic databases. In our intensive care unit, CBC is performed daily as part of routine care. White blood cell (WBC) count, neutrophil count, lymphocyte count,

red blood cell count (RBC), hemoglobin (Hb) level, erythrocyte mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets count and mean platelet volume (MPV) were recorded. The neutrophil-to-lymphocyte ratio (NLR) was determined from the blood cytology by dividing the neutrophil count by the lymphocyte count.

The study population was divided into two groups according to the development of mortality as survivors or non-survivors.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v17 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked usingthe Kolmogorov-Smirnov test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent samples t-test was used to compare the groups. Categorical variables were analyzed using Pearson chi-square test. Logistic regression analysis was carried to identify the contributors to in-hospital mortality. ROC curve analyses were performed to determine the cut-off values for selected variables to predict in-hospital mortality. A p-value < 0.05 was assumed statistically significant.

Results

A total of 46 patients with ARDS were enrolled in this retrospective study. Twenty-five subjects died during the in-hospital course and 21 survived. The group of survivors comprised 11 (52.3%) male and 10 (47.7%) female, with a mean age of 49.33±10.91 years.The group of non-survivors comprised 16 (64.0%) male, 9 (36.0%) female, with a mean age of 54.88±18.33 years.There were no significant differences between two groups regarding age and gender distribution. The patient characteristics for survivors or non-survivors are presented in Table 1.

The laboratory characteristics of study populations are presented in Table 1. Mean values of WBC counts, RBC counts, Hb level, MCV, MCH, MCHC, and platelets counts were similar among the groups. However, MPV (9.68±1.54 fl vs. 6.73±1.30 fl, $p < 0.001$), RDW (15.63±1.29% vs. 13.17±1.18%, $p < 0.001$) and NLR (9.51±5.40 vs. 6.13±3.94, $p = 0.021$) were significantly higher in the non-survivors group compared to that of the survivors (Figure 1). APACHE II scores were also significantly higher in the non-survivors group compared to the survivors group (26.80±2.19 vs.24.43 ± 1.80) (Figure 1).

Table 1. Demographic characteristics and laboratory parameters of study groups.

	Survivor n=21	Non-survivors n=25	p value
Age (years)	49.33±10.91	54.88±18.33	0.231
Gender (Male/Female)	11/10	16/9	0.550
APACHE II Scores	24.43 ± 1.80	26.80±2.19	<0.001*
Hb level (g/dL)	10.29±2.10	10.96 ±4.16	0.509
WBC count ($x10^3$/µl)	17.55± 8.80	17.73± 8.83	0.943
Platelet count ($x10^3$/µl)	276.48 ±55.73	281.80±59.35	0.757
RBC count($x10^3$/µl)	3.80±0.73	3.66±0.90	0.583
RDW (%)	13.17±1.18	15.63±1.29	<0.001*
MCV(fl)	85.75±8.46	83.49±7.72	0.354
MCH (pg)	27.66±4.04	28.61±3.77	0.412
MCHC (%)	32.35±2.73	33.04±2.38	0.369
NLR	6.13±3.94	9.51±5.40	0.021*
MPV (fl)	6.73±1.30	9.68±1.54	<0.001*

Data are presented as mean ± standard deviation. Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; Hb, hemoglobin; WBC, white blood cell; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume. * $p < 0.05$.

The laboratory characteristics of study populations are presented in Table 1. Mean values of WBC counts, RBC counts, Hb level, MCV, MCH, MCHC, and platelets counts were similar among the groups. However, MPV (9.68±1.54 fl vs. 6.73±1.30 fl, $p < 0.001$), RDW (15.63±1.29% vs. 13.17±1.18%, $p < 0.001$) and NLR (9.51±5.40 vs. 6.13±3.94, $p = 0.021$) were significantly higher in the non-survivors group compared to that of the survivors (Figure 1). APACHE II scores were also significantly higher in the non-survivors group compared to the survivors group (26.80±2.19 vs.24.43 ± 1.80) (Figure 1).

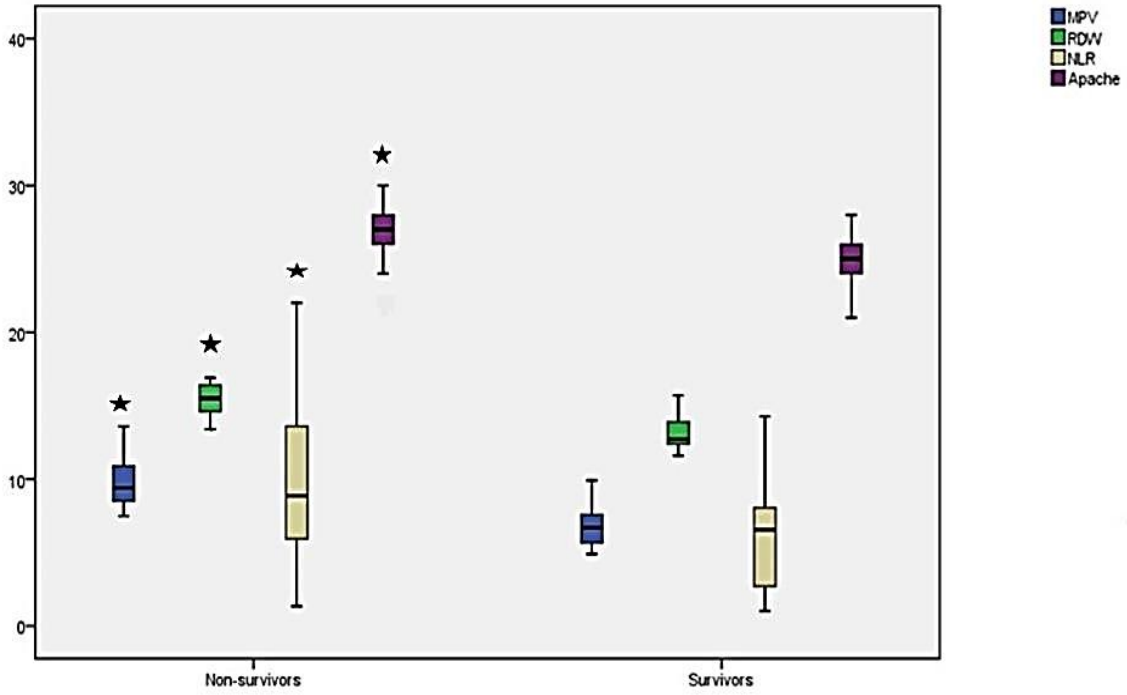

Figure 1. Comparison of mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR) and APACHE II scores in non-survivor and survivor groups (* indicates p<0.05).

Multiple logistic regression analysis revealed that MPV (OR:6.894, 95 % CI: 1.023-46.434, p=0.047) and RDW (OR:5.810, 95 % CI: 1.224-27.582, p=0.027) were independent predictors of mortality in patients with ARDS (Table 2).

Table 2: Predictors of in-hospital mortality.

	OR	95%CI	p value
APACHE II Scores	2.921	0.679-12.562	0.150
RDW	5.810	1.224-27.582	0.027*
NLR	1.360	0.873-2.118	0.174
MPV	6.894	1.023-46.434	0.047*

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; RDW, red cell distribution width; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume.* p < 0.05.

ROC curve analysis indicated a cut-off value of 8.11fl for MPV (sensitivity 88%, specificity 86%) and14.45 % for RDW (sensitivity 84%, specificity86%) to predict mortality in patients with ARDS (Figure 2).

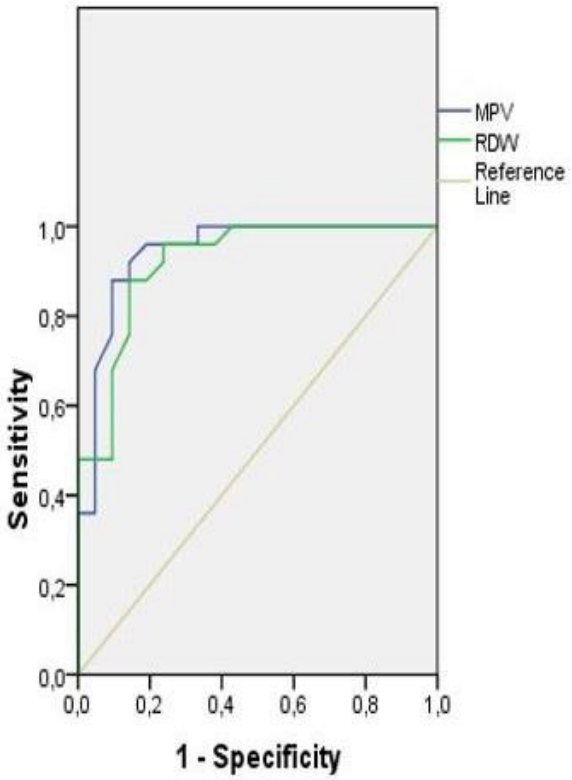

Figure 2. Receiver operating characteristic (ROC) curves demonstrating the predictive value of MPV and RDW for mortality.The area under curve (AUC) of MPV and RDW were 0.942 and 0.920, respectively.

Discussion

The present study demonstrates that APACHE II scores, MPV, RDW and NLR are significantly higher among non-survivors compared to survivors in patients with ARDS. Our findings also indicate that MPV and RDW are predictive for in-hospital mortality in these patients.

ARDS is characterized by diffuse alveolar epithelial and lung endothelial injury leading to increased permeability of alveolar capillary barrier, then a large of acute inflammatory cells and red blood cells penetrate the alveoli, which causes deteriorated gas exchange and loss of aerated lung tissue (1,18). It is also well established that the incidence of ARDS is associated with massive systemic inflammatory response. Systemic inflammation is associated with the development and progression of ARDS (19). Previous studies have reported increased levels of inflammatory biomarkers were associated with poor outcomes in ARDS (20).Although many studies have evaluated the prognosis of ARDS, no biomarker is considered perfect (21).

Mean platelet volume (MPV), the most common used measure of platelet size, is a potential marker of platelet reactivity (22). Large platelets contain a greater number of dense granules and are enzymatically and metabolically more active, and thus have greater prothrombotic potential (23). Besides their role in hemostasis, platelets also initiate inflammation by releasing various kinds of cytokines and adhesion molecules directly activating responses for monocytes, neutrophils, and T-lymphocytes. They also activate the complement system that augments the inflammatory responses (24). MPV has emerged as

an alternate marker for several clinical conditions which explicit with acute or chronic inflammation. In previous studies, elevated MPV value was associated with poor outcomes and increased mortality rate in diseases such as sepsis, neonatal respiratory distress syndrome, myocardial infarction, pulmonary embolism and chronic obstructive pulmonary disease where inflammation plays a critical role in development and progression of the these diseases(8-12). Zhang et al. showed that a higher MPV level is a significant risk factor for higher mortality in critically ill patients (25). Lastly, Sezgiet al. showed that discharge MPV levels increased in the non-survivorintensive care unit patients (13). In the present study, MPV levels were found significantly higher in the non-survivors group compared with in the survivors group. Furthermore, we found that the MPVis an independent predictor of mortality in patients with ARDS (cut-off value of 8.11 fl showed sensitivity 88% and specificity 86%).

Red cell distribution width (RDW) reflects the variation of red blood cell volume. In general, RDW is reflective of inflammation (26). Some previous research indicates that RDW was an independent prognostic factor in patients with congestive heart failure, sepsis, chronic lower respiratory tract disease, acute pulmonary embolism andcritically ill patients (14-17). Although the mechanism of a RDW-mortality association is unclear, the association may be related to inflammation and the contribution of inflammation to the pathophysiology of disease (26). Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW. Elevations in RDW may have negative impact on patient survival by reflecting the extent of inflammation. Recently, retrospective data reported by Xiao et al. revealed that increased RDW was an independent predictor for the development of ARDS in severe burn patients (27). Moreover, they reported that the increase of 1% RDW corresponded to the increase of 29% in the risk of developing ARDS after severe burn. In the present study, RDW levels were found significantly higher in the non-survivors group compared with in the survivors group in ARDS patients. Furthermore, we found that the RDW is an independent predictor of mortality in patients with ARDS (cut-off value of 14.45 % for RDW showed sensitivity 84%, specificity 86 %).

Neutrophil-lymphocyte ratio (NLR) is defined as the number of neutrophils in whole blood divided by the number of lymphocytes in whole blood (28). NLR is an indicator of systemic inflammation and a high NLR may indicate that a patient has severe inflammatory progression (29). High NLR in patients were associated with high levels of inflammation, de Jager et al. showed that NLR predicted bacteremia was better than conventional inflammation markers like C-reactive protein, white blood cell count and neutrophil count (30). NLRhas been found to be a useful biomarker for predicting mortality in various disease ranged from cancers to cardiovascular diseases and other inflammatory related diseases (31-33). Also, high blood NLRlevels is demonstrated that association with development and outcome in patients with ARDS due to military tuberculosis (34). In addition, NLR has been investigated in critically ill patients with ARDS and may prove to be a prognostic biomarker. Li et al. revealed that high NLR was associated with poor outcome in critically ill patients with ARDS and it was an independent risk factor for predicting 28-day mortality in ARDS patients (6). Similarly, another retrospective study reportedthatNLR was higher in the group of non-survivors than in the survivors and it measured at 24 hours after ARDS diagnosis was an independent risk factor of mortality in patients with ARDS (7). In our study, we found that NLR was higher in the group of non-survivors than that of the survivors which is in accordance with their results.However,we

haven't foundany significant role of NLR levels for on predicting mortality. This could have been due to the small sample size.

While the underlying mechanism explaining why elevated MPV and RDW is associated with poor course and outcomes, oxidative stress may also be a contributing factor with increased inflammationin ARDS patients. High oxidative stress is present in ARDS via the generation of reactive oxygen species by activated leukocytes.High oxidative stress contributing to elevated RDW and MPV by reducing red blood cell and platelet survival, and increasing release of large premature red blood cells and large immature platelets into the peripheral circulation (17,35).

As a matter of fact, there are some limitations of our study that we have to mention. First, the small size of our patient sample represents an important limitation. Second is theretrospective design of the study. Finally, the present study is a single center study with a single ethnicity study population, and it remains unclear whether our results could be generalized to other ethnicities.

Conclusion

MPV, as an emerging indicator of preexisting inflammation, and RDW, indicative of systemic inflammation independently predict mortality in patients with ARDS. Implementation of MPV and RDW might be useful in identifying patients who will require advanced support during admission for ARDS. Further studies, especially prospective studies with large sample size, are needed to confirm these findings and elucidate the underlying mechanism in exploring the role of MPV and RDW in patients with ARDS.

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Informed Consent: NA
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