



## DETERMINATION OF THE EFFECTS OF INFLAMMATORY MARKERS ON MORTALITY IN INTENSIVE CARE PATIENTS

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### Abstract

**Aim:** Mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), red cell distribution width (RDW) plays important role as effective factors in predicting mortality and morbidity in various diseases. In the present study we aimed to assess and compare MPV, NLR, PLR and RDW of survived and non-survived patients by examining the blood samples taken within the first hour after admission to our intensive care unit.

**Methods:** This retrospective study included 672 patients who were hospitalized in a mixed 16 bed intensive care unit (ICU) between January 2019 and January 2020. By examining our hospital's computer-based data system, patient data of the survived and non-survived patients who were treated in the ICU were analyzed.

**Results:** The demographic parameters of the patients (gender), concomitant disease, and laboratory parameters including HTC, PLT, WBC, MPV and PLR were not significantly different between the survived and non-survived patients. RDW, albumin, CRP and NLR were found statistically different between the study groups.

**Conclusions:** The elevated RDW, NLR and CRP levels were found more significant than the other inflammatory markers for determining mortality of the critically ill patients. In addition, evaluation of albumin level was found important in defining the prognosis of the intensive care unit patients.

**Keywords:** Mean platelet volume, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, red cell distribution width, intensive care, mortality

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## Introduction

Critical diseases treated in intensive care unit such as ARDS, pneumonia, exacerbations of chronic lung disease, sepsis, multi-organ failure, cardiovascular disease, cerebrovascular accident etc. cause inflammatory response with high mortality rates in patients. Although Acute Physiological and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA) are important to predict mortality in critically ill patients, RDW, MPV, NLR and PLR are easily accessible, non-invasive and cost-effective indicators in the ICU.

In this retrospective study, we investigated the association between RDW, MPV, NLR, PLR values and mortality in critically ill patients. Many studies have been conducted to show the effect of these markers in determining mortality but to our knowledge there's no study comparing all of these markers together in ICU patients.

Red cell distribution width (RDW) has been shown to be elevated in various diseases including coronary artery disease, heart failure, atrial fibrillation, stroke and cancer<sup>1</sup>. The association between RDW and mortality can be explained with stressed erythropoiesis and variations in RBC survival<sup>2</sup>. RDW may be an appropriate marker for the differentiation of various diseases.

MPV is an indicator of platelet activation and has been shown to increase with cardiovascular diseases related to atherosclerosis, hypertensive disease and malignant tumors<sup>3,4</sup>. Increased platelet volume and size indicates the presence of a thrombotic and inflammatory activity. For this reason, MPV has been used in various inflammatory disorders such as rheumatoid arthritis and ankylosing spondylarthritis to determine the effectiveness of anti-inflammatory therapy and disease activity<sup>5,6</sup>.

The neutrophil to lymphocyte ratio (NLR), is a rapidly accessible marker and has been shown to be useful in determining prognosis in oncological diseases including lung,

ovary and breast<sup>7-9</sup>. Also, NLR is a prognostic factor for many conditions such as predicting the mortality of septic patients, outcomes of cardiovascular diseases<sup>10,11</sup>.

Jilma et al. reported a 300 % increase in circulating neutrophils 4 to 6 hours after inflammation, while a 96 % reduction in monocytes and 85 % reduction in lymphocytes<sup>12</sup>. Elevated NLR levels indicate an imbalance in the inflammatory response resulting from increased neutrophil and decreased lymphocyte counts. The platelet to lymphocyte ratio (PLR) can also be presented to the clinician as a diagnostic criterion for inflammation in various diseases (pneumonia, bacteremia) and for survival prediction<sup>1</sup>.

The target of this study was to analyze RDW, MPV, NLR and PLR values together in the intensive care unit patients and we found that elevated RDW levels were more significant than the other inflammatory markers for determining mortality.

## Materials and Methods

### *Study design*

In the present study we investigated whether RDW, MPV, NLR and PLR levels together on admission could predict the mortality of the patients in the intensive care unit. After obtaining Local Ethics Committee approval with the protocol number 2017-KAEK-1892020.07.22.02, we retrospectively analyzed the data of intensive care unit by examining our hospital's computer based data system. Helsinki Declaration guidelines were followed throughout the study.

The patients were divided into two groups; survived patients (patients discharged from ICU) and non-survived (patients who died in the ICU). Demographic data of the patients including age, gender, length of stay in the intensive care unit, comorbidities were collected from the medical records. Hematocrit (HCT), white blood cell counts (WBC), platelet counts (PLT), mean cor-

puscular volume (MCV), red cell distribution width (RDW), neutrophil/lymphocyte count ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein (CRP) and albumin were determined. The laboratory data of the patients consist of blood samples taken when they are admitted to the intensive care unit. NLR was calculated by division of the neutrophil count by the lymphocyte count. PLR value was obtained by division of the platelet count by the lymphocyte count.

### Statistical analysis

Number and percentage for classified variable, mean  $\pm$  standard deviation or median, minimum and maximum values were used for continuous variable data. Conformity of permanent variables to normal distribution was interpreted by Kolmogorov-Smirnov test. Chi-square test was used for intergroup comparisons of categorical variables. Student t test or Mann Whitney U test was used for comparison of continuous variables between two groups.

Evaluation of RDW, albumin, CRP and NLR values used to estimate patient's prognosis (survivor / non survivor) were made by ROC analysis. The obtained "area under the curve" values and confidence intervals are presented. The  $P < 0.05$  value was considered statistically significant.

## Results

A total of 672 patients were examined in the study. After admission to the intensive care unit, 169 of these patients were dead and 503 were survived. There was no gender difference between the survived and dead patients ( $P=0.268$ ). Of the 361 male patients, 264 were survived and 97 were dead. Of the 311 female patients, 239 were survived and 72 were dead. Comorbidities of the deceased and survived patients were found similar ( $P=0.109$ ). 131 of 169 deceased patients (26.8%) had comorbidities and 358 of 503 survived patients (73.2%) had comorbidities.

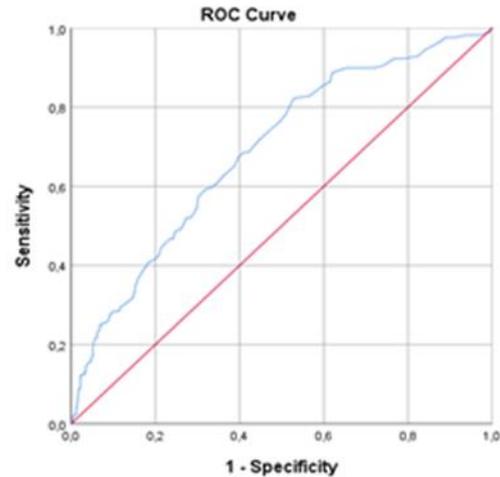
**Table 1.** General characteristics and laboratory data of the study groups

Gender, n (%)		Survived Group	Exitus Group	P
Men		264(73.1%)	97(26.9%)	0.268
Women		239(76.8 %)	72(23.2%)	
Comorbidities (%)		358(73.2%)	131(26.8%)	0.109
Age (years)		63.08 $\pm$ 20.27	73.25 $\pm$ 14.32	<0.001
Hb, g/dL	Mean (SD)	12.54 $\pm$ 2.33	11.80 $\pm$ 2.35	<0.001
Htc, %		38.11 $\pm$ 7.11	36.95 $\pm$ 7.62	0.072
WBC, $\mu$ /mm <sup>3</sup>		12.63 $\pm$ 6.0	14.18 $\pm$ 7.4	0.009
RDW		14.60 $\pm$ 2.35	16.35 $\pm$ 3.10	<0.001
MPV, fL		10.30 $\pm$ 0.98	10.43 $\pm$ 1.03	0.184
Duration in ICU (Days)		2(1-260)	11(1-270)	<0.001
PLT, $\mu$ /mm <sup>3</sup>	Median (min-max)	228(30-693)	210(40-722)	0.146
NLR		7(1-112)	9(1-63)	0.014
PLR		166(8-1745)	194(9-1208)	0.061
C-reactive protein		17.30(0.60-544)	51.50(0.60-438)	<0.001
Albumin (gr/dL)		36.70(15.60-56.20)	32.80(15.40-49)	<0.001

RDW; red cell distribution width, CRP; C reactive protein, HCT; hematocrit, WBC; white blood cell counts, PLT; platelet counts, MCV; mean corpuscular volume, NLR; neutrophil/lymphocyte count ratio, PLR; platelet to lymphocyte ratio, SD; standard deviation

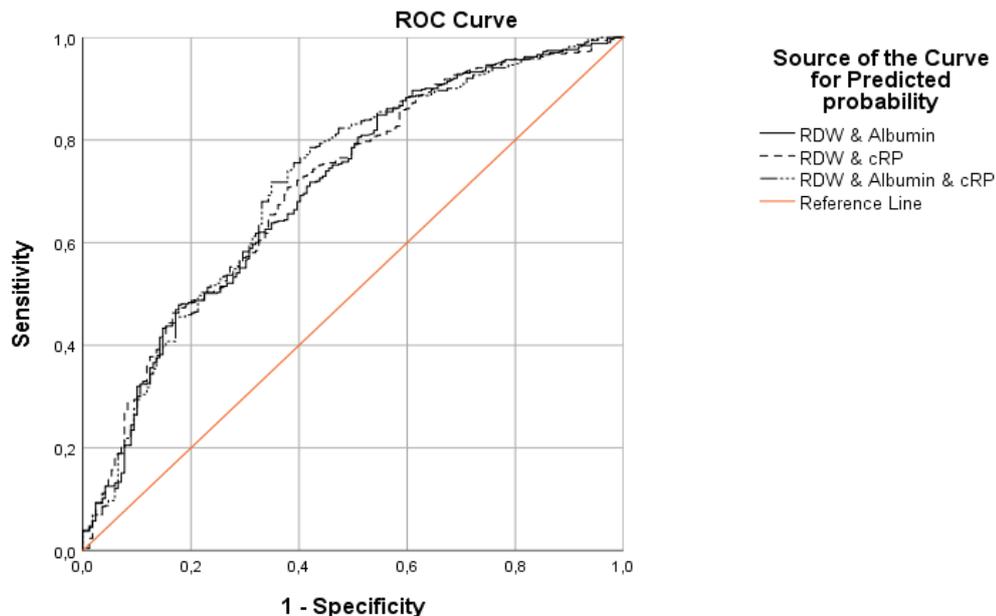


The mean ages of the deceased patients were higher than the survived patients ( $P < 0.001$ ). While the mean age of the deceased patients was found 73.25, the mean age of the survived patients was 63.08. Durations in ICU of the survived and deceased patients were statistically different ( $P < 0.001$ ). The medium length of stay in the ICU of the survived and deceased patients were found 2(1-260) and 11(1-270) days, respectively (Table 1). HTC, PLT and MPV levels were not significantly different between the survived and deceased patients ( $P > 0.05$ ). However, RDW ( $P < 0.001$ ), albumin ( $P < 0.001$ ), CRP ( $P < 0.001$ ), NLR ( $P = 0.014$ ) and WBC ( $P = 0.009$ ) were found statistically different between the study groups. The mean RDW of the survived patients (14.60) were found lower than the deceased patients (16.35) ( $P < 0.001$ ). Serum albumin levels of the survived patients were found higher than the deceased patients ( $P < 0.001$ ). Serum CRP levels of the survivors were found lower than the deceased patients ( $P < 0.001$ ). NLR and PLR of the survived patients were found lower than those of the deceased patients.



**Figure 1.** ROC curves analysis for predicting mortality by RDW.

However only the difference in NLR values were found statistically significant between the deceased and survived patients ( $P = 0.014$ ). There was no statistically significant difference in terms of MPV values between the deceased and survived patients ( $P = 0.184$ ). The demographic parameters of the patients (age, gender), comorbidities and laboratory data were shown in Table 1.



**Figure 2.** Relationship between inflammation-based markers and survival of the patients in the ICU. RDW, red cell distribution width; CRP, C reactive protein; albumin.

Evaluation of RDW, albumin, CRP and NLR values used to determine patient's prognosis (ex/surviving) were made by Roc analysis. RDW was found to be more significant marker than the other markers used to determine the mortality of the patients (Fig.1). The obtained "area under the curve" values and confidence intervals are presented in Fig.2. The area under the curve shows the accuracy-strength of the estimation. While examining albumin and RDW values together has a 70% accuracy in determining mortality of the patients in the ICU, evaluating RDW, albumin and CRP values together provides 71% accuracy.

108 patients admitted to the ICU due to acute respiratory failure, n=22 patients' acute cardiac failure, n= 131 patients cerebrovascular disease, n=28 patients intoxication, n=18 patients infectious reasons, n=54 patients traumatic or non-traumatic brain injury, n=22 patients renal failure, n=279 other reasons (postoperative patient, diabetic ketoacidosis, trauma, gastrointestinal bleeding, tetanus etc.). Also 10 patients had more than one concomitant disease.

Patients' length of stay in the intensive care unit was found longer in the deceased patients ( $P<0.001$ ). Comorbidities of the survived and deceased patients were found similar. 131(77%) of 169 deceased patients had comorbidities. 358(71.2%) of 503 survived patients had comorbidities.

## Discussion

In the present study, we observed that elevated RDW, NLR and CRP levels were more significant than the other inflammatory markers for determining mortality of the critically ill patients. Also, albumin level of the patients was found to be valuable in determining the prognosis of intensive care patients.

Pilling et al. investigated red cell dispersion breadth and common disease onsets in a large population of healthy volunteers and they have stated that increased RDW are important in determining all-cause mortality<sup>2</sup>. It has been shown that high RDW lev-

els are associated with increased incidence of hospital recorded cardiovascular diseases such as HT, heart failure, atrial fibrillation, peripheral vascular disease and stroke<sup>2</sup>. In another study, Lionte et al., showed that, inflammation related indices based on CBC count such as RDW, NLR and MLR (monocyte-lymphocyte ratio) were associated with hospital mortality in acutely poisoned patients<sup>14</sup>. Akcal et al. investigated the impacts of post-operative changes in inflammatory markers such as RDW, MPV, PLR and NLR on mortality rate of the patients operated for hip surgery and found that, only the increase in RDW levels were statistically significant in the non-survivor group in comparison with the survivor group postoperatively<sup>15</sup>. Similar to this study, we found that RDW levels were more significant in determining the mortality of the patients in intensive care unit compared with other markers.

Neutrophil/lymphocyte ratios are accepted as potential markers to classify high risk of death in patients with stage 1 lung cancer, breast cancer or epithelial ovarian cancer<sup>7,8,9</sup>. Ham et al. have found both higher NLR and MPV/platelet ratio in the non-survivor group than in the survivor group and they have declared that MPV/platelet ratio independently associated with an increased mortality at one year in critically ill patients<sup>16</sup>. Zhai et al. conducted a study on cardiac intensive care unit patients to investigate the relationship between PLR and hospital mortality. The patients were grouped according to PLR quartiles. They showed that hospital mortality increased as PLR quartiles increased<sup>17</sup>. In our study, although increased NLR and PLR levels were found in the non-survivor group, only the increase in the NLR levels were statistically significant.

Mean platelet volume (MPV), is an indicator of platelet function and is calculated as the ratio of plateletcrit to platelet count<sup>18</sup>. Zhang et al, investigated the association of platelet volume indices and mortality in intensive care unit patients and found that higher MPV and PDW (platelet distribution width) values are associated with increased

risk of death<sup>19</sup>. In another study, Wang et al showed that MPV and PDW values were decreased in the patients with slight cognitive impairment and Alzheimer's disease<sup>20</sup>. Also confounding factors such as diabetes mellitus, hypertension and many drugs (statins, clopidogrel and angiotensin-converting enzyme inhibitors) may affect MPV levels<sup>21,22</sup>. In our study, MPV of the non-survivor group was found higher than the survivor group but the difference was not found statistically significant. In the present study, the mean age of the deceased patients was higher than the survivor group. Comorbid systemic diseases including slight cognitive spoiling, Alzheimer's disease, medications used by the patients, may have affected their MPV values.

Serum albumin level has been shown to be sensitive marker of protein deficiency malnutrition<sup>23</sup>. Yildiz et al found that geriatric patients with low albumin levels (<3.2 g/dL) in the ICU had higher mortality rates, longer hospital stays and microbiologically documented infection than those with normal albumin levels<sup>24</sup>. In the present study, albumin levels were observed lower in the exitus group. Evaluating albumin and RDW values together has been found to have a 70% accuracy in determining mortality of the patients in the ICU.

Previous studies have shown that CRP was a predictor marker in determining prognosis of intensive care patients<sup>25,26</sup>. Similar to these studies, in the present study CRP level of the deceased patients was found higher than the survivor group.

There are several limitations in this study. First of all, this study was retrospective and only one center study. For this reason, the result may not be generalizable to other institutions. Also, all critically ill patients were included for analysis and there were many factors that affected patient admission to the ICU. Our results may be applicable to mixed ICU patients.

## Conclusion

RDW was found to be a strong predictor of mortality in ICU patients. While RDW alone is 68 % reliable in determining mortality in intensive care patients, the rate increases to 71% when albumin, CRP and RDW values are evaluated together.

### Author contributions

Concept: TH, MH; Design: TH, MH; Supervision: AEŞ, TH; Data Collection and/ or Processing: APÇ, HÖ; Analysis and/ or Interpretation: TH, MH; Literature Search: MH,TH; Writing Manuscript: TH,MH Critical Review: MH,AEŞ,TH

### Conflict of interest

The authors declare that they have no conflict of interest.

### Funding

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### Ethical approval

This study was reviewed and approved by Yozgat Bozok University institutional review board (Protocol number 2017-KAEK-189\_2020.07.22. \_02, date: 22.07.2020)

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