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ORIGINAL ARTICLE – OPEN ACCESS

The Relationship between Platelet/Lymphocyte and Neutrophil/Lymphocyte Ratios and Mortality in Intensive Care Patients with Crimean-congo Hemorrhagic Fever

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ABSTRACT

Objective: This study aims to examine the platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) values in predicting mortality of Crimean-Congo Hemorrhagic Fever (CCHF) patients in an intensive care unit (ICU).

Materials and Methods: This is a retrospective study, and 34 patients diagnosed with CCHF hospitalized in ICU between 1 January 2016–1 January 2020 were included in this study. Demographic data and PLR, NLR, mean platelet volume (MPV), red cell distribution width (RDW), c-reactive protein (CRP) values in their first blood samples taken in ICU were analyzed. Receiver operating characteristic (ROC) curve analyses for the estimation value of the parameters was carried out. The area under the curve (AUC), sensitivity and specificity were used to evaluate the performance of the diagnostic tests.

Results: The mortality rate was 52% (18 exitus). The average length of ICU stay was 10.8±6.6 days. For the value of 8.40 FL for MPV, sensitivity was 83.3%, and specificity was 68.8%. The sensitivity was 88.9% and the specificity was 81.3% for the value of 13.15% of RDW. For NLR, the sensitivity was 83.3%; and the specificity was 87.5% for the value of 2.73. For PLR, the sensitivity was 81.3%, and the specificity was 100% for the cut-off value of 49.94.

Conclusion: PLR and NLR can give the physician an idea about the mortality in patients with severe CCHF; however, studies with a larger number of patients are needed for full validity.

Keywords: Crimean-congo hemorrhagic fever, mortality, intensive care

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INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is an acute viral infectious disease with symptoms, such as ecchymosis, visceral hemorrhage, hepatic dysfunction, and mortality ranging from 8% to 80% (1, 2). Nairovirus from the Bunyaviridae family, which is the causative agent of the disease, can be found asymptomatically in cattle, sheep, goats, small rats, and birds (3). Many types of ticks can carry the disease. Central Anatolia and the Black Sea region contain suitable conditions for tick life. CCHF was defined in Turkey for the first time in 2002. Later, the disease started to appear in Eastern Europe, Africa, the Middle East and Asia (4). Ten thousand two hundred nineteen cases of CCHF were reported in Turkey between the years of 2002–2016 (5).

CCHF infection has four periods as follows: incubation, pre-hemorrhagic, hemorrhagic and convalescence. The incubation period lasts between the first 3–7 days after tick contact. This period varies depending on the viral dose and the type of exposure. In the pre-hemorrhagic period, sudden rising fever (39–41°C), headache, myalgia, weakness are observed. Fever lasts, on average, 4–5 days, and in some cases, diarrhea, nausea, and vomiting may be accompanied. Findings of hyperemia and conjunctivitis can be found in the face, neck and chest area. The duration of the pre-hemorrhagic period varies between 1 day and 7 days. The hemorrhagic period develops quickly and usually takes 2–3 days. The size of hemorrhage in the hemorrhagic period varies from petechiae to large hematomas on the mucosa and skin. In addition, vaginal bleeding, gingival bleeding and cerebral hemorrhages have been reported in some patients during this period. The most frequent bleeding places in the body during the CCHF hemorrhagic period are the nose, gastrointestinal tract, uterus, urinary tract and respiratory system. In survivors, the period of convalescence is observed and its duration varies between 10–20 days (6).

The diagnosis is made based on anamnesis, laboratory and clinical findings. A definitive diagnosis is made with the polymerase chain reaction (PCR) study performed with virus isolation. Ribavirin, which is known to be the most effective antiviral agent for CCHF, and supportive replacement therapies have an important role in treatment. For the patient to survive the hemorrhagic period, it is necessary to follow up in a center where it is easy to access blood products such as fresh frozen plasma, erythrocyte suspension, platelet apheresis.

Conditions requiring intensive care unit (ICU) hospitalization of patients are bleedings that are seen in the hemorrhagic period. These bleeding can completely disrupt hemodynamics in some patients and cause the disease to be

more mortal. Situations that require hospitalization of CCHF patients in intensive care are central nervous system involvement, liver failure, kidney failure, multiple organ dysfunction, respiratory failure, disseminated intravascular coagulation (DIC), shock and coma (7).

In recent years, mortality estimation has been made in some medical situations using the ratio of neutrophil count and platelet count to lymphocyte count, which are among hemogram parameters (8–10). It is thought that mortality increases due to the disruption between the increased inflammation in the body and the anti-inflammatory mechanism developing against it. Several studies have shown that neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are reliable markers in demonstrating immune activation, oxidative stress damage and inflammation.

Our objective was to research the PLR and NLR values in predicting mortality of CCHF patients in ICU.

MATERIALS and METHODS

Thirty-four patients, who were diagnosed with Crimean-Congo Hemorrhagic Fever hospitalized in Anesthesia Intensive Care Unit between January 1, 2016, and January 1, 2020, were included in this study. Written consents were obtained from the first degree relatives of the patients for the use of clinical and laboratory findings of the patients. This study was performed as a retrospective scan by accessing the patient files from the hospital patient information system and the hospital archive.

The name, surname, age, gender, length of stay and date of hospitalization in the intensive care unit, mean platelet volume (MPV), red cell distribution width (RDW) the ratio of the number of neutrophils to the number of lymphocytes (NLR), and the ratio of the number of platelets to the number of lymphocytes (PLR), c-reactive protein (CRP) values in the first blood samples taken from the patients during the hospitalization were recorded.

Statistical Analysis

The data obtained from our study were evaluated using SPSS 22.0 program. Whether the data were normal or were not determined by the Shapiro-Wilk test was investigated. As a result of the Shapiro-Wilk's test, the MPV variable was suitable for normal distribution ($p>0.05$) and all other numerical variables were not suitable for normal distribution ($p<0.05$). Accordingly, independent sample t-test was used in the examinations made with MPV and the Mann-Whitney U test was used in the examinations carried out with other numerical variables.

Receiver operating characteristic (ROC) curve analyses for the estimation value of the parameters was carried out. The area under the curve (AUC), sensitivity and specificity were used to evaluate the performance of diagnostic tests. ROC was used when determining the estimation value of the parameters with the highest likelihood ratio (Sensitivity/1-Specificity). By finding the point closest to the (0,1) coordinate, the cutting point was decided. By calculating the Euclidean distance to the coordinates of all the points on the line (0,1), it was decided that the closest value is the intercept point. A p-value of less than 0.05 was considered statistically significant.

The prevalence of CCHF in Sivas province between January 2016 and January 2020 varies between 0.1% and 0.02%. On average, 5% of these patients were followed up as intubated in the intensive care unit. Therefore, the prevalence of intubated patients diagnosed with CCHF in this region varies between 0.05% and 0.01%. Accordingly, the power analysis of this research was calculated as 99.3% with the patients (n=34) included in this study.

Table 1. Demographic data of the patients

	Min.	Max.	Mean±SD	p[a]
Age (year)				
Exitus	25	74	52±17	0.157
Living	17	75	42±21	
Length of ICU stay (day)				
Exitus	2	14	7±4	<0.001
Living	5	26	15±6	

a: Mann-Whiyney U test; Min.: Minimum; Max.: Maximum; SD: Standard deviation; ICU: Intensive care unit

Table 2. Comorbidities of the patients

Comorbidities	Exitus patients number (n)	Living patients number (n)	Percentages (%)
Type-2 DM	4	2	17.7
Hypertension	4	1	14.7
COPD	2	0	0.6
CAD	2	0	0.6
Hypothyroidism	1	0	0.3

COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; DM: Diabetes mellitus

RESULTS

The average length of ICU stay of the patients included in this study was 10.8±6.6 days, and the average age was 47.2±19.6 years. Of the patients, 21 were male and 13 were female, 13 of male patients (61.9%) became exitus, and five of women (38.4%) became exitus. The total mortality rate was 52%. There was no statistically significant difference in terms of the gender-mortality relationship (p=0.183). Other demographic data of the patients are shown in Table 1.

When the comorbidities of exitus patients are analyzed, four patients were with diabetes mellitus, four patients were with hypertension, two patients were with chronic obstructive lung disease, two patients were with coronary artery disease and one patient was with hypothyroidism. Two of the living patients had diabetes mellitus and one of the living patients had hypertension. No other comorbidities were detected in living patients. These comorbidities are shown in Table 2.

With the diagnosis of CCHF, eight patients in 2015, seven patients in 2016, six patients in 2017, six patients in 2018, and seven

Table 3. Distribution of the patients admitted to the intensive care unit with the diagnosis of CCHF by years

Year of hospitalization	Patient status	Patient number	Percent (%)	p*
2015	Exitus	1	12.5	0.066
	Living	7	87.5	
2016	Exitus	4	57.1	
	Living	3	42.9	
2017	Exitus	3	50	
	Living	3	50	
2018	Exitus	4	66.6	
	Living	2	33.3	
2019	Exitus	6	85.7	
	Living	1	14.3	

CCHF: Crimean-Congo Hemorrhagic Fever; *: Chi-Square Analysis

patients in 2019 were hospitalized in the intensive care unit. The distribution of mortality by years is shown in Table 3, and the result was not statistically significant (p>0.05).

Average value for CRP was 35.3±31.9 (min: 5.5, max: 126) mg/L, for MPV it was 8.5±0.8 (min: 6.7, max: 10.6) fL, for RDW it was 13.8±1.4 (min: 12.1, max: 17.4) percent, for NLR it was 3.8±2.8 (min: 0.6, max: 11.5) and for PLR it was 54.6±67.2 (min: 6.66, max: 285).

If the mean values of living patients were analysed, for CRP, it was 17.9±15.1 (min: 5.5, max: 54.9) mg/L, for MPV, it was 8.2±0.8 (min: 6.7, max: 10.6) fL, for RDW, it was 12.9±0.7 (min: 12.1, max: 15.1) percent, for NLR, it was 1.8±0.9 (min: 0.6, max: 4.6) and for PLR, it was 94.7±80.9 (min: 12.8, max: 285). When the mean values of exitus patients were analysed, for CRP, it was 50.7±35.3 (min: 6.2, max: 126) mg/L, for MPV, it was 8.8±0.6 (min: 7.2, max: 10) fL, for RDW, it was 14.5±1.5 (min: 12.8, max: 17.4) percent, for NLR, it was 5.7±2.7 (min: 1.9, max: 11.5) and for PLR, it was 19.0±12.3 (min: 6.66, max: 44). These average values are shown in Table 4. When these parameters were compared between living and exitus patients, the differences were statistically significant for CRP, RDW, NLR and PLR (p<0.05). If MPV values were compared between living and exitus patients, the difference was not statistically significant (p>0.05).

Table 4. Laboratory parameters of living and exitus patients

Parameters	Patient status	Min.	Max.	Mean±SD	p
CRP (mg/L)	Exitus	6.29	126.00	50.7±35.3	<0.001[a]
	Living	5.57	54.90	17.9±15.1	
MPV (fL)	Exitus	7.20	10.00	8.8±0.6	0.021[b]
	Living	6.70	10.60	8.2±0.8	
RDW (%)	Exitus	12.80	17.40	14.5±1.5	<0.001[a]
	Living	12.10	15.10	12.9±0.7	
NLR	Exitus	1.96	11.50	5.7±2.7	<0.001[a]
	Living	0.60	4.61	1.8±0.9	
PLR	Exitus	6.66	44	19.0±12.3	<0.001[a]
	Living	12.80	285	94.7±80.9	

a: Mann-Whitney U Test; b: Independent sample t-test; Min.: Minimum; Max.: Maximum; SD: Standard deviation; CRP: C-reactive protein; mg: milligram; MPV: Mean platelet volume; fL: Femtoliter; RDW: Red cell distribution width; %: Percent; NLR: Neutrophil/lymphocyte ratio; L: Liter

According to the ROC analysis, when searching for the cut-off point, for CRP 19.15, sensitivity was 83.3% and specificity was 81.3%, sensitivity 83.3% and specificity 68.8% for the cut-off value of 8.40 FL for MPV, the sensitivity was 88.9% and the specificity was 81.3% for the cut-off value of 13.15% of RDW. For NLR, the sensitivity was 83.3% and the specificity was 87.5% for the cut-off value of 2.73. For PLR, the sensitivity was 81.3% and the specificity was 100% for the cut-off value of 49.94 (Table 5) (Fig. 1, 2).

DISCUSSION

In our study, PLR came to the forefront as the test with the most remarkable results in predicting mortality of patients diagnosed with CCHF. All patients included in this study were in their hemorrhagic period of CCHF. Leukopenia and thrombocytopenia are the two remarkable laboratory findings in the hemorrhagic period of CCHF (6). In severe CCHF, neutrophil counts are higher, but lymphocyte and monocyte counts are lower (11). The number of lymphocyte and thrombocyte starts to decrease in the pre-hemorrhagic period and reaches their lowest values in a hemorrhagic period of the disease (6).

Given that thrombocytopenia is strongly related to the severity of the disease because of its negative clinical outcomes like mild to

Table 5. Cut-off values of laboratory parameters according to ROC curve

Parameters	Area under curve	CI	Cut-off value	Sensitivity	Specificity	PPV	NPV
CRP	0.844	0.703–0.984	19.15 (mg/L)	0.833	0.813	83.3	81.3
MPV	0.776	0.609–0.943	8.40 (fL)	0.833	0.688	83.3	68.8
RDW	0.894	0.783–1.000	13.15 (%)	0.889	0.813	88.9	81.3
NLR	0.944	0.875–1.000	2.73	0.833	0.875	83.3	87.5
PLR	0.884	0.756–1.000	49.94	0.813	1.000	100.0	81.3

CI: Confidence interval; CRP: C-reactive protein; mg: Milligram; MPV: Mean platelet volume; fL: femtoliter; RDW: Red cell distribution width; %: Percent; NLR: Neutrophil/lymphocyte ratio; L: Liter; PLR: Platelet/lymphocyte ratio; PPV: Positive predictive value; NPV: Negative predictive value

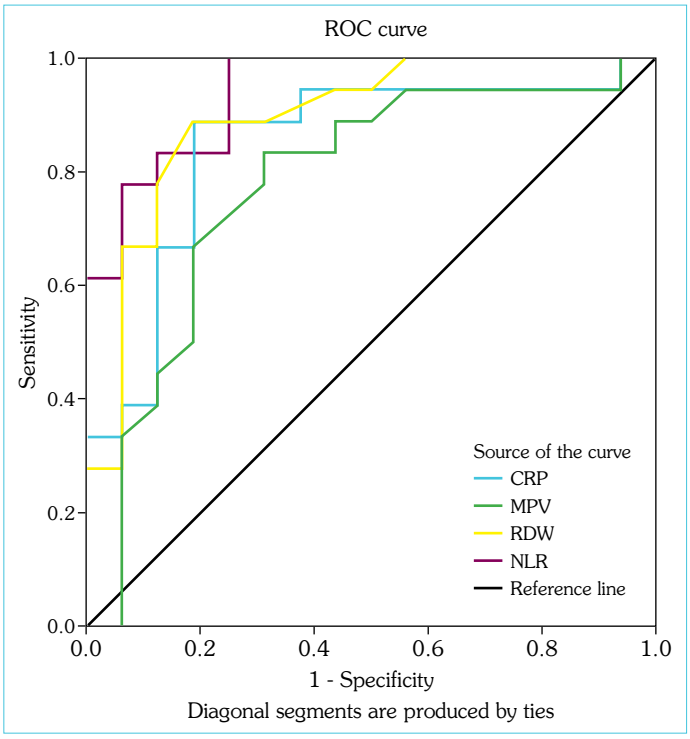

Figure 1. ROC curves for c-reactive protein (CRP), mean platelet volume (MPV), red cell distribution (RDW), neutrophil/lymphocyte ratio (NLR)

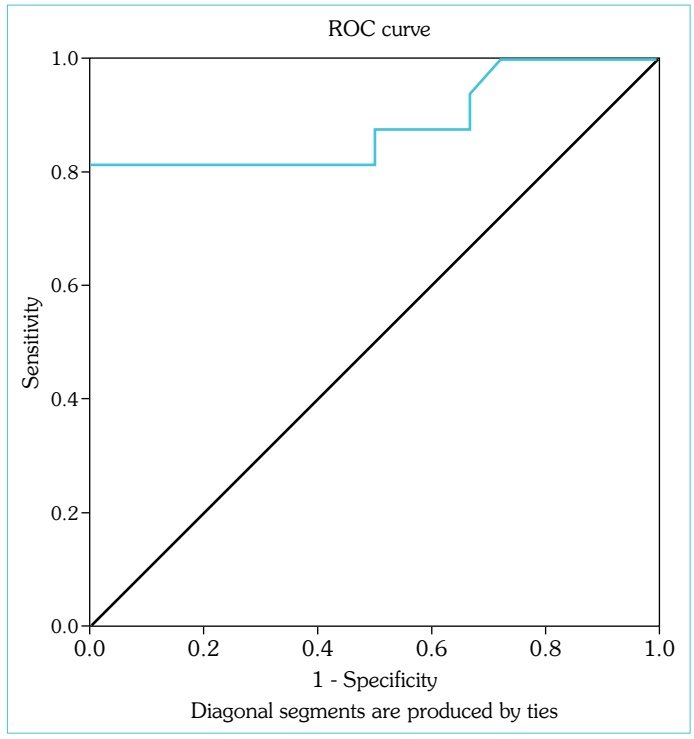

Figure 2. ROC curve for platelet/lymphocyte ratio (PLR)

severe bleedings. Lymphocytopenia also results in immunity and humoral antibody response depletion. An increase in neutrophil numbers may cause excessive cytokine release and these excessive amounts of cytokines can cause endothelial damage, increased vascular permeability, severe hypotension and end-organ damages. Several studies have shown that PLR and NLR can be a prognostic tool in the systemic inflammatory response (8–10, 12). Because of the increase in neutrophil numbers and decrease in lymphocyte numbers, NLR may show the severity of immunity depletion and impaired systemic inflammatory response in CCHF. We think that PLR can also be a predictive tool for mortality in CCHF because clinical worsening is more related to bleedings due to severe thrombocytopenia. Both thrombocyte and lymphocyte numbers show a decrease in CCHF but a decrease in thrombocyte numbers in proportion to lymphocyte numbers, which can be a more precious laboratory sign that shows the patient's exaggerated response to the impaired immune system or the response to the infection directly.

The characteristics of the patient population in our study is important. All of the patients had a CCHF diagnosis confirmed by reverse transcriptase-polymerase chain reaction before hospitalized in an intensive care unit (ICU). All the patients were in their hemorrhagic period with respiratory failure. Because the infectious diseases department of our hospital has its own ICU without mechanical ventilation, only the patients with respiratory failure were accepted in the anesthesia ICU. All of the patients had endotracheal intubation and mechanical ventilation support. The patients in our study had high mortality and were hospitalized in our ICU during their worst hemorrhagic days of CCHF. We can say that, in CCHF patients with endotracheal intubation, the mortality was 52%.

The hemogram parameters that we studied were from the first blood sample that was taken from the patients when they were accepted in ICU. It means they could have received blood product transfusions before they came to ICU. Either they were transfused or not, it is that all of the patients were in their worst clinical phase.

Turcato et al. (9) found NLR and PLR useful for predicting the 30 day-mortality in acute decompensated heart failure. Mısırlıoğlu et al. (10) found PLR as a predictor for mortality in the pediatric intensive care unit. In a study conducted by Shen et al. (8), they also found that high PLR values at admission were associated with an increased risk of mortality in patients with sepsis.

Ertürk et al. (12) conducted a study about the prognostic value of mean platelet volume (MPV) and NLR in CCHF. They divided the patients into two groups in their study. Fifty patients with CCHF constituted the patient group, and 47 healthy people constituted the control group. They found that MPV values were higher in the patient group; however, NLR and PLR parameters were found similar in both groups. They showed that there were no relations between PLR, NLR and hospitalization durations. The most important difference between our study and the study of Ertürk et al. (12) was the patient population. Our study consisted of severe and mortal CCHF patients with respiratory failure, but Ertürk's et al.'s study had patients with CCHF without ICU requirement and the period of the disease of the patients was unknown. We researched the predictive value of PLR and NLR in severe CCHF patients.

Eren et al. (13) also found PLR helpful in determining the prognosis of CCHF patients. They divided the CCHF patients into two groups. Group 1 was decided according to Çevik's score (14). Group 2 consisted of the patients with PLR value lower than 41. Four patients in Group 1 and seven patients in Group 2 died in

their study. As a result, they found that PLR can predict the prognosis of CCHF. They took the cut-off value of PLR as 41 when they decided their patient groups; however, we found the cut-off value of PLR as 49.4 in our study. Our study differs in several ways; for example, we researched the statistical validity of PLR as a clinical test in CCHF. The cut-off value of PLR was decided by our patients as a result of this study.

The patients that had PLR value below 49.9 died in our study. We found the specificity of PLR as 100% for the cut-off value of 49.9. This unexpected result must be confirmed by other studies with a larger patient population. The patient number of our study was a limitation. We had hospitalized CCHF patients with respiratory failure only. This was a single-centered study and this was also a limitation. Regarding the retrospective nature of our study, selection bias may be present. NLR also has a sensitivity of 83% and specificity of 87% for the cut-off value of 2.73.

Comorbidities are always an obstacle for mortality research. Because comorbidities may affect the mortality ratios. In our study, the most common comorbidity was diabetes mellitus (DM), which was seen in six patients with CCHF. Type-2 DM has some effects on hemogram. Kızılgül et al. (15) have found neutrophil, lymphocyte, white blood cell counts higher in type-2 DM patients. Also, Chowta et al. (16) have found elderly type-2 DM patients more anemic in their study. Anemia-DM relation can be based on the effects of DM on renal functions also. Besides this anemia-DM relation, inflammation has a substantial role in the pathogenesis of type-2 DM. Six of the thirty-four patients in our study had type-2 DM. Bilgin et al. (17) studied NLR, PLR, RDW in their recent study about male patients with type-2 DM. They have found strong relations between these hemogram parameters with hemoglobin A1C. They conclude that these parameters can show the relationship between the inflammatory process and blood glucose control. Because type-2 DM may affect these parameters, these six patients with type-2 DM may affect the standardisation of our study. However, these parameters need more confirmations in chronic inflammatory processes like in DM.

Among the comorbidities of our patients, hypothyroidism may also affect hemogram parameters. In a study by Geetha et al. (18), they have found mean corpuscular volume (MCV) increased in hypothyroidism and decreased in hyperthyroidism, and RDW values were increased in both hypothyroidism and hyperthyroidism. In addition to these diseases, uncontrolled hypertension can be a major problem in bleeding diseases like CCHF. Thus, hypertension may increase the mortality of CCHF. No doubt, these comorbidities may affect complete blood count analysis and also may affect mortality. We think that our comorbidity ratios are low, but their existence is a limitation for this study.

According to our results, PLR is more related to mortality than NLR in clinically-severe CCHF patients in ICU. These simple laboratory findings can give the physician an idea about the mortality in patients with severe CCHF; however, studies with a larger number of patients are needed for full validity.

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Ethics Committee Approval: This study was approved by the Ethics Committee of the Non-Interventional Clinical Practices of Cumhuriyet University (2020-02/05) (19/02/2020). This study was designed on the principles of the Helsinki Declaration properly.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – OA, OG; Design – OA, OG; Supervision – OA, OG; Resource – OA, OG; Materials – OA, OG; Data Collection and/or Processing – OA, OG; Analysis and/or Interpretation – OA, OG; Literature Search – OA, OG; Writing – OA, OG; Critical Reviews – OA.

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