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The Prognostic Importance of the Systemic Immune-inflammation Index in Patients with Crimean-Congo Hemorrhagic Fever

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Abstract

Aim: To evaluate the power of the systemic immune-inflammation index (SII) in the prediction of mortality in patients with Crimean-Congo hemorrhagic fever (CCHF) presenting at the emergency department (ED).

Materials and Methods: The study included patients who presented at the ED between April 2020 and November 2022 and were hospitalized for treatment in the Infectious Diseases Department. The demographic data, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and SII were recorded. Categorical data were analyzed with the chi-square test and continuous data with the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to determine the factors predicting the risk of mortality.

Results: The SII value ($p=0.010$) and NLR ($p<0.001$) were determined to be significantly higher and the PLR ($p=0.015$) was significantly lower in CCHF patients who developed mortality compared to those who did not. ROC analysis showed the NLR and SII parameters to be significant in the prediction of mortality.

Conclusion: SII at the time of presentation at the ED can be used for predicting the mortality in CCHF patients.

Keywords: Emergency department, Crimean-Congo hemorrhagic fever, systemic immune-inflammation index, mortality

Introduction

The Crimean-Congo hemorrhagic fever (CCHF) virus is a member of the Nairovirus strain of the Bunyaviridae family (1). CCHF was first described in 1944 in the Crimean region of the Soviet Union and then in 1956 in the Belgian Congo (now the Democratic Republic of the Congo) (2). Turkey, Iran, Pakistan, Russia and Iraq are the countries with the greatest disease burden, with reports of sporadic human cases and outbreaks of varying magnitude (3,4). The disease occurs in humans through tick bites or exposure to the blood or other bodily fluids of an infected animal or CCHF patient (2). Approximately 90% of infections are asymptomatic or have no significant clinical effect and progress with nonspecific subfebrile fever (5). At a lower rate, it can progress to a hemorrhagic phase in which petechiae, hematoma, or generalized bleeding are seen following a short incubation period of approximately 1 week. In this phase, a severe and generally fatal hemorrhagic disease develops with multiple organ failure characterized by high fever, fatigue, myalgia, vomiting, and diarrhea (1,6). The reported mortality rates vary between 4% and 20% depending on the geographic region and the quality of the healthcare services (7).

Early prediction of the clinical course of a CCHF patient can be lifesaving. It is important that clinicians are aware of CCHF disease and the clinical and laboratory characteristics predicting the future course of CCHF, which would require transfer of the patient to a tertiary level hospital for intensive care and appropriate treatment and management planning (8).

High neutrophil and low lymphocyte/monocyte values are generally seen in CCHF patients with high mortality rates. An increase in neutrophils leads to cytokine overexpression, and a decrease in lymphocytes and monocytes causes the depletion of immunity and a humoral antibody response (9). This irregular overexpression of cytokines causes endothelial cell damage and vasodilatation, which can result in hypotension, shock, multiple organ dysfunction, and death (10).

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Thrombocytopenia is one of the most important laboratory parameters for CCHF disease (11). In recent years, the neutrophil count and ratio of platelet count to lymphocyte count, which are among the hemogram parameters, have been used in the prediction of mortality (12-14). The systemic immune-inflammation index (SII), calculated with the formula of peripheral platelet count neutrophil count/lymphocyte count, has been defined in some recent studies as a new index used in the prediction of mortality (15-17). It increases as a marker of inflammation (16). It has also been reported that SII can be more sensitive than the existing methods that use only one or two cell subtypes in the prediction of prognosis of certain cancer patients (18). In CCHF disease, the virus passes to the epithelium after a tick bite, then reaches endothelial cells and damages the cells (10,19). This damage created in the endothelial cells results in the activation of the immunological and inflammatory pathways either directly with the effect of the virus or indirectly (19-21). As the immunological and inflammatory pathways are activated in CCHF disease, SII is expected to have diagnostic value. As far as we could search in the literature, we could not find any article giving information about the efficiency of SII for prognosis among CCHF patients. The aim of this study was to determine the importance of SII in predicting mortality in CCHF patients presenting at the emergency department (ED).

Materials and Methods

Study Setting

This study included 296 patients who presented at the ED between April 1, 2020 and November 1, 2022, were diagnosed with CCHF and were hospitalized in the infectious diseases department.

Participants of the Study

The study was conducted as a retrospective screening of data retrieved from the hospital patient information system and patient records in the hospital archives. Patients were excluded from the study if they were aged <18 years, were using anticoagulant or thrombocyte aggregation inhibitor drugs that could affect the laboratory values, had hematological disease, malignancy, or any chronic disease such as chronic obstructive pulmonary disease or hepatobiliary disease, or if medical information could not be accessed from the hospital automated information system.

Data Collection

The information was recorded of patient age, gender, the length of stay in hospital, and final status in the infectious diseases department (discharged, exitus). From the first blood samples taken on admission of the patients, the values were recorded of white blood cell (WBC), neutrophil, lymphocyte, platelet, mean platelet volume (MPV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

SII was calculated as: Platelet count x Neutrophil count / lymphocyte count

This study is an observational study and ethics committee approval was obtained from the Sivas University Non-Interventional Clinical Research Ethics Committee with the date of 19.10.2022 and the decision number 2022-10/30.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM Statistical Package for Social Sciences (SPSS) statistics version 22 software (IBM SPSS Corp., Armonk, NY, USA). The conformity of the data to the normal distribution was assessed with the Kolmogorov-Smirnov test. All numerical variables were seen not to conform to a normal distribution. Categorical data were analyzed with the chi-square test and ordinal data with the Mann-Whitney U test. To determine the factors predictive of the risk of mortality, receiver operating characteristic (ROC) curve analysis was performed. A value of $p<0.05$ was set as statistically significant.

Results

Evaluation was made of 296 patients comprising 185 (62.5%) males and 111 (37.5%) females with a mean age of 48.7±16.1 years. A mortal course was observed in 19 patients, of which 8 (2.7%) were female. Gender was not determined to be significant for mortality.

The mean age of the patients with a mortal course of the disease was determined to be significantly higher (Table 1).

The distribution according to the months of patients is given in Figure 1. The highest rate was recorded in July (87 patients). In spite of the higher mortality number observed in July, there wasno statistically significant difference when the mortality rates were compared according to the months ($p=0.389$).

The length of hospital stay of CCHF patients with a mortal course was found to be shorter than that of surviving patients ($p=0.039$). The values of WBC ($p=0.007$), neutrophil count ($p<0.001$), MPV ($p<0.001$), AST ($p<0.001$), ALT ($p<0.001$), INR ($p<0.001$), SII ($p=0.010$), and NLR ($p<0.001$) were determined to be significantly higher and the lymphocyte ($p<0.001$), platelet ($p<0.001$), and PLR ($p=0.015$) values were determined to be significantly lower in the non-survivor CCHF patients than in the surviving patients (Table 1).

The optimum cut-off values for neutrophil count, MPV, INR, NLR, and SII were determined by ROC analysis. The optimum neutrophil cut-off values were determined as 1.96 for neutrophil count [area under the curve (AUC): 0.851; 95% confidence interval (CI): 0.767-0.935; sensitivity 73%; specificity 76%], 11.45 for MPV (AUC: 0.770; 95% CI: 0.629-0.911; sensitivity 72%; specificity 73%), 1.08 for INR (AUC: 0.821; 95% CI: 0.700-0.942; sensitivity 77%; specificity 79%), 3.54 for NLR (AUC: 0.928; 95% CI: 0.887-0.969; sensitivity 83%; specificity 85%), and 147.87 for SII (AUC: 0.681; 95% CI: 0.573-0.789; sensitivity 1%; specificity 62%). ROC analysis results of neutrophil, MPV, INR, NLR, and SII parameters were found to be statistically significant in patients with CCHF who died (Table 2, Figure 2).

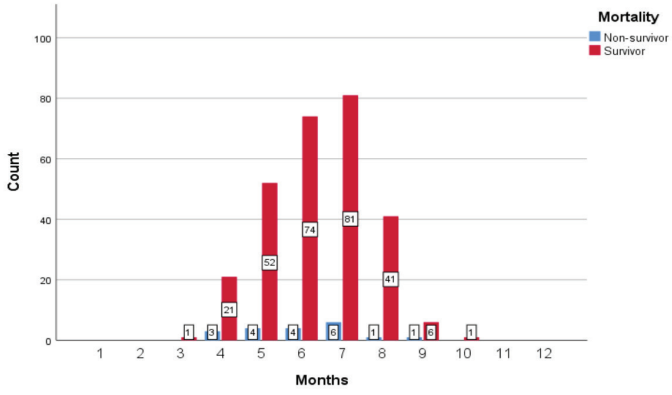

Figure 1. The distribution of patients according to the months of admission

Discusssion

Despite the advances in the pathogenesis and treatment of CCHF disease, there remains a need for the development of rapid, reliable, and simple biomarkers that can make an early and definitive prediction of disease prognosis and be of guidance in patient management strategies. As far as we could search in the literature, we could not find any article giving information about the efficiency of SII for prognosis among CCHF patients.

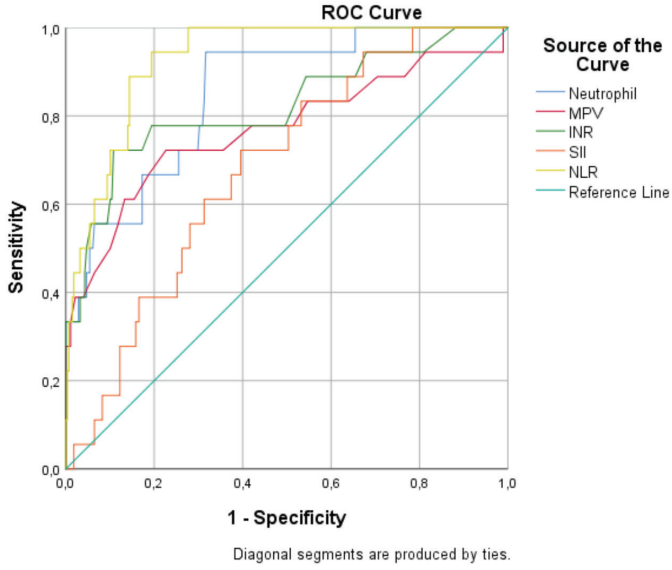

Figure 2. ROC curves for neutrophils, MPV, INR, SII, and NLR

ROC: Receiver operating characteristic, MPV: Mean platelet volume, INR: International normalized ratio, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio

Table 1. Laboratory parameters and hospitalization time compared according to the survivor and non-survivor groups

Characteristics	Survivor	Non-survivor	p
	Mean±SD (min-max)	Mean±SD (min-max)	
Age (mean±SD)	48,14±16.08 (18-86)	57.61±14.63 (18-79)	0.011
Hospitalization time (day)	6.70±2.48 (3-20)	5.44±3.34 (1-15)	0.039
WBC (10^3/µL)	3.26±1.38 (0.60-8.92)	5.91±4.30 (1.92-16.45)	0.007
Neutrophil (10^3/µL)	1.63±0.98 (0.20-6.40)	4.95±4.03 (1.12-14.60	0.001
Lymphocyte (10^3/µL)	1.24±0.64 (0.21-4.24)	0.64±0.27 (0.17-1.24)	0.001
Platelet (10^3/µL)	92.69±34.90 (36.00-192.00)	32.27±9.55 (16.00-48.00)	0.001
MPV (fL)	10.87±0.86 (8.10-13.00)	11.94±1.30 (8.80-13.90)	0.001
AST (U l^{-1})	113.35±104.76 (10.00-719.00)	429.88±411.69 (57.00-1373.00)	0.001
ALT (U l^{-1})	79.59±74.50 (7.00-543.00)	276.16±285.19 (33.00-876)	0.001
INR	1.03±0.11 (0.85-1.57)	1.42±0.43 (0.94-2.34)	0.001
SII	181.47±221.31 (11.08-1484.33)	260.32±230.40 (48.28-1003.71)	0.010
NLR	1.83±1.82 (0.11-12.17)	7.75±5.57 (1.93-24.48)	0.001
PLR	104.08±86.67 (17.04-508.33)	66.99±59.52 (12.90-276.47)	0.015

MPV: Mean platelet volume, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White blood cell, INR: International normalized ratio, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SD: Standard deviation, min-max: Minimum-maximum

Table 2. Cut-off values of laboratory parameters according to ROC curve

Parameters	AUC	CI	Cut-off value	Sensitivity	Specificity
Neutrophil	0.851	0.767-0.935	1.96 (10^3/µL)	0.73	0.76
MPV	0.770	0.629-0.911	11.45 (fL)	0.72	0.73
INR	0.821	0.700-0.942	1.08	0.77	0.79
NLR	0.928	0.887-0.969	3.54	0.83	0.85
SII	0.681	0.573-0.789	147.87	0.61	0.62

MPV: Mean platelet volume, fL: Femtoliter, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

The results of the current study emphasize the importance of SII as an indicator of mortality in patients who presented to the ED and were hospitalized in the infectious diseases department.

In our study, it was observed that the mortality number was high in June and July when the disease was prevalent. According to the data of studies conducted in Iran and Turkey, CCHF disease is more common in summer (22-24). Our results are consistent with other studies in the literature.

In this study, the mortality rate was 6.4% and the mean age of patients with mortality was higher compared with the survivors group. The mortality rate in CCHF patients is between 5% and 30% (2). Ozkurt et al. (25) found that the mortality rate was 5.4%, and Tekin and Engin (26) found that mortality rate 6.1%. In some studies, mortality was associated with the viral load of CCHF disease and advanced age at presentation (6,27). Our data were compatible with the literature.

When we compared the duration of hospitalization of the patients, it was significantly shorter in patients with a mortal course. A previous study conducted in an intensive care unit in Turkey evaluated the length of stay in hospital, and the mean length of stay was found to be significantly shorter for exitus patients (28). Our results support these data.

The results of the current study showed that WBC, neutrophil, MPV, AST, ALT, INR levels and NLR increased, while lymphocyte, platelet levels and PLR decreased compared with those resulting in death. In addition, the results of the ROC curve analysis showed that some markers (neutrophil, MPV, INR, NLR) could be used to predict prognosis in CCHF patients. Some studies in the literature have investigated laboratory parameters related to disease severity and mortality in CCHF disease. It has been reported that if one of the criteria of leukocyte count >10.000/mm^3, platelet count <20.000/mm^3, AST level >200 U/L, ALT level >150 U/L or aPPT >60 s is met during the first 5 days of the disease, the risk of death will be 90% (29). Ergönül (1) analyzed risk factors in patients with CCHF infection and revised the severity criteria. It was reported that in patients with a mortal course, the mean platelet count was significantly low (20.000/10.600/mL), mean PT (16/27 secs) and mean aPTT (44/73 secs) were longer, and the mean ALT level (331/1125 IU/L) and mean AST level (913/3118 IU/L) were higher. High AST (>700 IU/L) and ALT (>900 IU/L) levels were suggested as severity criteria (1). In Cevik et al. (6), surviving and non-surviving cases were compared. The mean ALT (293/1688 IU/L), mean AST (634/3028 IU/L), and mean INR (1.1/1.38) values were determined and were found to be significantly higher in patients with a mortal course. The mean platelet count was calculated as 47.569×10^9/L in nonmortal cases and 12.636×10^9/L in cases with mortality. In severe CCHF, the neutrophil count is higher and the lymphocyte and monocyte counts are lower (9). The lymphocyte and platelet counts start to decrease in the period before bleeding and reach the lowest values in the hemorrhagic period of the disease (1). Hatipoglu et al. (30) examined laboratory data as determinants of mortality in 152 CCHF patients. The WBC values were found to be high and the platelet values were low in patients with mortality. It has been reported that MPV is a prognostic factor for the length of stay in hospital and mortality in CCHF patients (31). In a study by Tekin and Engin (26), the mean WBC, neutrophil, and MPV values were found to be significantly higher and the platelet values were lower in patients who developed mortality. The NLR and PLR are accepted as good markers of systemic infection (32,33). It is thought that mortality increases because of increasing inflammation in the body and impairment in the anti-inflammatory mechanism developing against this. In several studies, NLR or PLR have been accepted as reliable markers showing immune activation, oxidative stress damage, and inflammation (28). Bilek and Deveci (34) concluded that the median NLR value was approximately two-fold higher in CCHF patients who developed mortality compared with survivors. In another study conducted in an intensive care unit, the mean NLR was found to be high and the mean PLR was low in CCHF patients with mortality (28). Our results are similar to those of this study. In the current study, the SII value was found to be significantly high in the non-survived patient group. As a result, the SII level examined at the time of presentation at the ED can predict mortality.

In some of the current study data and in most other studies in literature, data have been used containing a single type or two parameters such as NLR and PLR to predict the prognosis of CCHF disease, but because of the complex interactions in the pathogenesis of CCHF, there is still a need for data containing more parameters to predict the severity of the disease. Therefore, it would seem to be more logical in this respect to use biomarkers that contribute to the calculation of various cell types (platelets, neutrophils, lymphocytes) in inflammation, such as SII. SII is calculated by multiplying platelets by NLR, and just as NLR and PLR, SII has a tendency to be higher in conditions of increased inflammation (35). It has even been suggested that in various clinical scenarios, SII is more useful than NLR and PLR alone in the prediction of the inflammatory status and prognosis (36). In recent years, SII obtained using 3 types of inflammatory cells (platelets, neutrophils, lymphocytes) which are among the hemogram parameters, has predicted mortality in some medical conditions (12-14).

The SII is accepted as a good definitive index that can reflect the local immune response and systemic inflammation in the whole human body (37-39). Moreover, it has been reported that the SII could be more sensitive in the prediction of prognosis in certain cancer patients compared to the existing methods that use only one or two cell subtypes (18). Many studies have confirmed high prognostic values in various tumors such as colorectal cancer, cervical cancer, hepatocellular cancer, lung cancer, esophageal cancer and epithelial ovarian cancer (40). Yang et al. (36) reported that SII showed better predictive value of major cardiovascular events than traditional risk factors in patients with coronary artery disease following coronary intervention. In addition to tumors and acute coronary disease, SII may be associated with negative outcomes for other malignant diseases. In CCHF disease, the virus passes to the epithelium after a tick bite, then reaches endothelial cells and damages the cells (10,19). This damage created in the endothelial cells results in the activation of the immunological and inflammatory pathways either directly with the effect of the virus or indirectly (19-21). SII is a new inflammatory index that comprehensively reflects the immune and inflammatory balance of the host (41). As the immunological and inflammatory pathways are activated in CCHF disease, it is thought that SII could be a predictive tool for mortality in these patients. In a recent study, it was concluded that SII could be used to predict mortality in the hemorrhagic period of patients with severe CCHF (42).

In many studies conducted in previous years, the importance of SII in predicting mortality was emphasized, and this was supported in our study. It was concluded that SII level examined at the admission time in the ED can predict ortality.

Study Limitations

Our study had some limitations. Patients younger than 18 years were excluded from the study. Another limitation of this study is that it was a retrospective design with file review for clinical and history data from a single center. There were patients whose study data could not be accessed. Therefore, some patients were not included in the study. Our current findings may shed light on larger clinical trials in the future.

Conclusion

In conclusion, this is the first study to show the efficacy of SII at the time of presentation at ED in the determination of prognosis in CCHF patients. The study results demonstrated that the SII value was independently related to CCHF. SII is formed from simple, low-cost, and widely used hemogram parameters, which are available in every ED. SII can be a predictive tool for mortality in these patients, but for the confirmation of full validity there is a need for further studies with a greater number of patients. Therefore, further studies should be conducted to confirm the role of SII in the treatment of CCHF patients.

Acknowledgement

The English in this document has been checked by a professional native speaker.

Ethics

Ethics Committee Approval: This study is an observational study and ethics committee approval was obtained from the Sivas University Non-interventional Clinical Research Ethics Committee with the date of 19.10.2022 and the decision number 2022-10/30.

Informed Consent: This study was conducted as a retrospective cross-sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Ç., Concept: Ş.Ç., Design: Ş.Ç., İ.K., Data Collection or Processing: Ş.Ç., İ.K., Analysis or Interpretation: Ş.Ç., Literature Search: Ş.Ç., İ.K., Writing: Ş.Ç., İ.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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