Clinical severity in forecasting platelet to lymphocyte ratio in Crimean–Congo hemorrhagic fever patients

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Crimean–Congo hemorrhagic fever (CCHF) is a life-threatening disease that develops as a result of infection by a member of the Nairovirus genus of the Bunyaviridae family, and its initial symptoms are not specific. In patients with severe clinical progression, in particular, the neutrophil rate is high, whereas lymphocyte and monocyte levels are low. A total of 149 patients, in whom the diagnosis was confirmed with reverse transcriptase PCR, were included in the study. In order to compare patient clinical progression severity, we divided the patients into two groups. For group 1, Çevik's severity score was used. The patients who had a platelet/lymphocyte ratio (PLR) <41 constituted group 2. Of 149 patients, 20 (13.4 %) were determined as group 1 (Çevik's classification) and 38 (25.5 %) were determined as group 2 (PLR <41). Of 11 deaths, 4 (36.4 %) patients were from group 1 and 7 (63.6 %) were from group 2. This is the first study to our knowledge to analyse the relationship between severity and PLR in patients with CCHF. PLR is a simple laboratory test that can aid in determining the prognosis of individuals with this disease.

INTRODUCTION

The Crimean–Congo hemorrhagic fever (CCHF) virus is a member of the genus Nairovirus of the Bunyaviridae family (Vorou et al., 2007). Although the disease is endemic in Africa, the Middle East and Asia, its pathophysiology is not well known (Akncı et al., 2013). The incubation period of the virus ranges from several days to a week; initial symptoms are non-specific and manifest as fever, malaise, myalgia, headache, nausea and vomiting. The clinical spectrum is variable, ranging from asymptomatic to mild or severe, and the disease can progress to death (Bodur et al., 2012).

CCHF patients with fatal clinical progression have particularly high neutrophil and low lymphocyte/monocyte counts. The increase in neutrophils leads to excessive cytokine release, while the decrease in lymphocytes and monocytes results in immunity and humoral antibody response depletion (Bastug et al., 2015). This irregular and excessive secretion of cytokines has toxic effects on the activation of endothelial cells and vascular permeability, which brings about hypotension and multiple-organ dysfunction syndrome that can lead to shock and death (Akncı et al., 2013).

Thrombocytopenia is one of the main laboratory parameters of CCHF disease (Vorou et al., 2007). Lymphocyte levels vary according to the host’s immune response (Bastug et al., 2015), and a number of studies have stated that platelet to lymphocyte ratio (PLR) is prognostic of systemic inflammatory response (Li et al., 2007; Yamanaka et al., 2007). We examined the effect of PLR on the hospitalization time, blood transfusion requirement and survival rate of individuals with severe CCHF.

METHODS

This is a retrospective study in patients with CCHF disease who were admitted to our emergency department between 1 April 2014 and 1 October 2015 and were diagnosed and treated in the infectious diseases department, according to detection of viral RNA by reverse transcriptase PCR. Biochemical and haematological laboratory parameter analyses were performed using Mindray BC 6800 were retrospectively analysed. The blood products used for transfusion were recorded.

The patients were divided into two groups. The first group consisted of those patients whom Çevik et al. (2008) defined as serious according to their characteristic symptoms, bleeding form, platelet transfusion therapy and thrombocytopenia (<20×10⁹), prolonged activated partial thromboplastin time (aPTT, ≥60 s), melena and somnolence. The
second group was defined by us as patients with PLR <41, as calculated using receiver operating characteristic (ROC) analyses.

Erythrocyte transfusion was performed in patients with clinical symptoms due to haematocrit decrease. Thrombocyte apheresis transfusion was carried out in patients with melaena and thrombocytopenia (<50,000 µl), in patients with thrombocytopenia (<10,000 µl) without haemorrhage and fever or in patients with thrombocytopenia (<20,000 µl) and fever. The patients received fresh frozen plasma with a prothrombin time above the upper limit of 3 s (Leblebicioğlu et al., 2012). Patients who were receiving antiviral treatment were excluded from the study, as this treatment can affect laboratory values.

Statistical analyses. The suitability of continuous variables for normal distribution was assessed using the Kolmogorov–Smirnov test. Although none of the variables was distributed normally, descriptive statistics were shown as median (25–75%). The Mann–Whitney U test was used to compare the groups, and ROC analysis was used to determine the cut-off value. Kaplan–Meier analysis was used to calculate the life cycle. Both risk scores were compared using the McNemar test, and the level of statistical significance was set at \( P<0.05 \).

RESULTS

A total of 149 patients were enrolled, with disease confirmed by PCR. The average patient age was 65±16.3 years. Of 149 patients, 64 (43.0 %) were female. All patients had non-specific complaints such as joint pain, fatigue and malaise, and the majority had been admitted to the emergency department on day 5 (3.0–6.0) of their complaints. The mean duration of hospitalization time was 7.0 (5.0–9.0) days. Of the 149 patients, 17 received an erythrocyte infusion (37 U), 41 received platelet apheresis (195 U) and 43 received fresh frozen plasma (274 U). A total of 11 (7.4 %) patients died, and 138 (92.6 %) were discharged (Table 1). The laboratory results are shown in Table 2, while the demographic and clinical results and transfusion rates of the two groups (patients in the severe group according to Çevik’s criteria and those with PLR <41.0) are shown in Table 1.

Table 1. Demographic and clinical results and transfusion rates of groups 1 and 2 and all patients with CCHF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n=20)</th>
<th>Group 2 (n=38)</th>
<th>All patients (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (±16.32)</td>
<td>56 (±16.21)</td>
<td>65 (±16.30)</td>
</tr>
<tr>
<td>Female sex</td>
<td>9 (45 %)</td>
<td>20 (52.6 %)</td>
<td>64 (43.0 %)</td>
</tr>
<tr>
<td>Complaint duration</td>
<td>5.0 (5.0–7.0)</td>
<td>1.0 (1.0–1.0)</td>
<td>5.0 (3.0–6.0)</td>
</tr>
<tr>
<td>Hospitalization time</td>
<td>6.5 (5.0–9.5)</td>
<td>6.0 (5.0–8.0)</td>
<td>7.0 (5.0–9.0)</td>
</tr>
<tr>
<td>Exit</td>
<td>4 (20 %)</td>
<td>7 (18.4 %)</td>
<td>11 (7.4 %)</td>
</tr>
<tr>
<td>Melaena</td>
<td>2 (10.0 %)</td>
<td>3 (7.8 %)</td>
<td>8 (5.4 %)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>1 (5.0 %)</td>
<td>1 (2.6 %)</td>
<td>3 (2.0 %)</td>
</tr>
<tr>
<td>Haematoma</td>
<td>1 (5.0 %)</td>
<td>1 (2.6 %)</td>
<td>3 (2.0 %)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>–</td>
<td>2 (5.3 %)</td>
<td>2 (1.3 %)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (20 %)</td>
<td>4 (10.5 %)</td>
<td>5 (3.4 %)</td>
</tr>
</tbody>
</table>

The bleeding diathesis observed in 21 patients was as follows: melaena in eight (5.4 %), epistaxis in five (3.4 %), haematuria in three (2.0 %), haematoma in three (2.0 %) and haemoptysis in two patients (1.3 %), as shown in Table 1. The laboratory results are shown in Table 2, while the demographic and clinical results and transfusion rates of the two groups (patients in the severe group according to Çevik’s criteria and those with PLR <41.0) are shown in Table 1.

To determine the severity of CCHF, we conducted an ROC analysis on each patient’s admission date, with PLR, and the specificity and sensitivity observed were 95 % and 86.3 %, respectively.

In the study conducted by Çevik et al. (2008), the duration of patients’ hospitalization time was 17.1 days [95 % confidence interval (CI), 16.5–17.8] for those in the mild group and 11.0 days (95% CI, 9.3–12.8) for those in the severe group, and this difference was statistically significant \( (P=0.016) \).

In our study, the duration of hospitalization was 17.2 days (95 % CI, 16.5–17.8) for patients in the mild group (PLR ≥41) and 11.7 days (95% CI, 10.6–12.8) for those with severe clinical symptoms (PLR <41). Our results were also statistically significant \( (P=0.072) \) (Fig. 1).

DISCUSSION

CCHF is a fatal tick-borne viral disease that is characterized by fever and haemorrhage, and CCHF virus is a member of the Nairovirus genus of the Bunyaviridae family. The immune status of the host is known to be influential in the pathogenesis of the virus (Vorou et al., 2007; Bodur et al., 2012; Akinci et al., 2013). Although medical care and therapeutic applications are highly advanced nowadays, these infections can still be fatal. They are endemic in tropical
and subtropical regions and can spread to other parts of the world as people travel to and from these areas (Schwarz et al., 1996; Drosten et al., 2002).

A variety of diagnostic parameters for the diagnosis of CCHF have been introduced, and studies related to the disease continue. We aimed to provide a risk score and correct orientation parameters for physicians by using only complete blood count results.

Numerous studies have been conducted to assess possible reasons for the poor outcome in CCHF disease, and it has been stated that a decrease in fibrinogen and thrombocyte levels, as well as an increase in soluble urokinase plasminogen activators, white blood cell counts, aspartate aminotransferase, alanine aminotransferase, creatine kinase, lactate dehydrogenase rates and prolonged aPTT, is associated with poor outcomes (Swanepoel et al., 1989; Schnittler & Feldmann, 2003; Ergonul et al., 2006; Çevik et al., 2008; Yilmaz et al., 2011). Vascular dysfunction, haemorrhage, disseminated intravascular coagulation and shock are commonly observed in the severe form of the disease (Swanepoel et al., 1989; Joubert et al., 2005).

Çevik et al. (2008) observed bleeding events in 58% of the patients they studied. Epistaxis (26.1%) was the most common event, followed by petechiae (20.3%), ecchymosis (17.4%), melaena (17.4%), gingival bleeding (15.9%), haematemesis (13.0%), haematuria (5.8%) and haematoma (2.9%). We found similar results in our study.

The average mortality rate shown in some studies conducted worldwide is 5.4% (Bakir et al., 2005; Ergonul et al., 2006; Ozkurt et al., 2006); however, Çevik et al. (2008) observed a significantly higher rate of 15.9%. The authors stated that this was due to the number of more seriously ill patients who were admitted to their hospital. In our study, the average mortality rate was 18.4% in the severe group and 7.3% in mild cases. These rates are slightly higher than the average in Turkey. The higher mortality rate decreased hospitalization time in our severe group (Fig. 1). Our clinical and laboratory results are consistent with those previously reported with regard to CCHF disease (Bakir et al., 2005; Ergonul et al., 2006; Ozkurt et al., 2006; Çevik et al., 2008).

Studies regarding the prognosis of CCHF disease with subgroups of complete blood count were conducted by Bastug et al. (2015). They found a poor outcome between the decrease in monocyte and lymphocyte counts and the increase in neutrophil counts. In particular, cut-off values for alanine transaminase, aspartate transaminase, lactate dehydrogenase, creatine phosphokinase, aPTT and prothrombin time were accepted as important laboratory

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Group 1 (n=20)</th>
<th>Group 2 (n=38)</th>
<th>All patients (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (×10³ µl⁻¹)</td>
<td>2.3 (2.0–3.9)</td>
<td>2.7 (2.0–4.0)</td>
<td>2.65 (2.0–3.5)</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>1.5 (0.8–3.1)</td>
<td>1.4 (0.8–2.2)</td>
<td>1.6 (1.1–2.7)</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>0.9 (0.6–1.4)</td>
<td>1.2 (0.8–1.5)</td>
<td>0.6 (0.4–1.0)</td>
</tr>
<tr>
<td>Haemoglobin (g dL⁻¹)</td>
<td>14.1 (12.9–16.2)</td>
<td>14.1 (12.9–15.2)</td>
<td>14.3 (12.9–15.2)</td>
</tr>
<tr>
<td>Platelet (×10⁹ µl⁻¹)</td>
<td>14.0 (10.0–19.0)</td>
<td>22.0 (13.7–48.0)</td>
<td>86.0 (44.5–115.09)</td>
</tr>
<tr>
<td>Mean platelet volume (fl)</td>
<td>10.0 (9.4–10.3)</td>
<td>10.0 (9.4–10.5)</td>
<td>10.2 (9.5–11.1)</td>
</tr>
<tr>
<td>Platelet lymphocyte rate</td>
<td>15.5 (8.2–29.7)</td>
<td>18.8 (9.1–33.2)</td>
<td>122.8 (41.6–267.2)</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>47.3 (40.4–67.2)</td>
<td>41.8 (36.5–51.9)</td>
<td>35.3 (31.2–41.8)</td>
</tr>
<tr>
<td>ALT (U l⁻¹)</td>
<td>262.0 (78.7–371.2)</td>
<td>208.0 (72.2–347.2)</td>
<td>57.5 (30.0–116.7)</td>
</tr>
<tr>
<td>AST (U l⁻¹)</td>
<td>686.0 (254.2–1081.5)</td>
<td>510.0 (154.2–957.7)</td>
<td>103.5 (45.0–290.0)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell.

**Fig. 1.** Hospitalization time according to PLR.
values in determining the severity of CCHF disease (Bastug et al., 2015). The predicted sensitivity and specificity for determining the severity group with PLR <41 were 86.3% and 95%, respectively.

In recent years, the number of studies assessing the efficacy of PLR in the diagnosis and prognosis of various diseases has continued to increase. Cho et al. (2015) analysed the PLR and neutrophil/lymphocyte ratio (NLR) in patients who had undergone percutaneous coronary intervention with a drug-eluting stent and found that high pre-intervention PLR and NLR, especially when combined, were independent predictors of long-term adverse clinical outcomes among those with coronary artery disease. In addition, Aldemir et al. (2015) determined that NLR and PLR are prognostic factors in advanced gastric cancer, while Wu et al. (2015) found that PLR is an independent prognostic factor in non-small cell lung cancer. Atan et al. (2015) compared the PLR of patients with Bell’s palsy and control groups and revealed that the rate was higher among the former. We found no previously published studies related to PLR in CCHF disease.

According to Çevik’s classification, 129 of 149 patients were determined as being in the good or moderate group, and 20 were in the severe group. Only 4 (36.4%) of the 11 patients who died were included in the severe group. In our scoring system, 111 patients were determined in the good or moderate group, and 38 patients were determined as being in the severe group. Of 11 deaths, 7 (63.6%) were in the severe group (Table 3).

When the transfusion needs of patients were evaluated in terms of scales, Çevik’s scoring system predicted 17 patients (29.3%) whereas our scoring system (PLR <41) predicted 25 patients (43.1%) (Table 3).

According to Çevik et al. (2008), the sensitivity and specificity, respectively, were 36 and 29% for mortality and 88 and 96% for transfusion need. We showed that the mortality rate had 63% sensitivity and 43% specificity, and the transfusion requirement had 77% sensitivity and 85% specificity.

In conclusion, the severity scoring systems described in the literature are generally useful in patients who are hospitalized. However, PLR is a simple scoring system that can predict the mortality rate and need for blood product transfusion, with high sensitivity and specificity, especially in emergency clinic patients. This scoring system may be useful in deciding whether patients should be referred to tertiary-level hospitals. Also, it can be used as a prognosis indicator for patients who are in intensive care units.

**ACKNOWLEDGEMENTS**

There are no conflicts of interest or funding source to declare. The study was performed in accordance with the Declaration of Helsinki for Human Research and was approved by the institutional ethics committee.

**REFERENCES**


