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Association Between Severity Grading Score And Acute Phase Reactants In Patients With Crimean Congo Hemorrhagic Fever

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ABSTRACT

As the COVID-19 pandemic continues, countries still have to struggle with their endemic diseases such as Crimean-Congo hemorrhagic fever (CCHF). Severity grading score (SGS) is a practical approach and may shed light on the course of the CCHF, whose pathogenesis is not clearly understood, and have no effective treatments. It is aimed to assess the association between SGS and acute phase reactants (APR). Laboratory-confirmed patients were categorized by severity scores, and the relationship between APR and SGS was evaluated. A significant correlation between SGS and C-reactive protein (CRP) was found ($p < 0.001$). High SGS was associated with mortality and high CRP levels were used to predict the mortality at the beginning of the hospital admission. To predict the outcome of the disease and for appropriate patient management, SGS and APR can be used simultaneously.

KEYWORDS

Crimean-Congo hemorrhagic fever; hemorrhagic fever; acute phase reactants; C-reactive protein; severity criteria

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a fatal zoonotic disease, which is endemic in Asia, Africa and southeast Europe [1]. Turkey is one of the endemic countries, and the case fatality rate is 4.8% [2]. The pathogenesis of the disease has not been entirely understood; hence, recently improved scores have been started to use to estimate the outcome of the disease [2,3]. Severity grading score (SGS) includes parameters that are found to be closely related to mortality; therefore, some authors have suggested its use in the prediction of prognosis of the illness and clinical management in the initial period of the infection [3]. Almost, all the reference centers in Turkey are capable of performing laboratory tests for SGS, so it is a convenient method for daily use. This practical method has also been found beneficial to predict the need for blood products, triage of the patients and associated health-care cost [3,4]. The other laboratory test investigated to determine the severity of illness is acute phase reactants (APR). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used biomarkers in the presence of infections. We aimed to assess the association between SGS and APR. According to our knowledge, this is the first study that investigates the association between SGS and APR.

Material and methods

This retrospective study was conducted between 2011 and 2016 in Ondokuz Mayis University hospital, which is one of the reference centers in Turkey. Laboratory-confirmed patients were enrolled in this study. They were categorized by severity scores. SGS includes clinical and laboratory findings that are demonstrated in Table 1. According to the SGS, patients were classified into three groups: low-risk (≤4), intermediate-risk (5–8) and high-risk (≥9). CRP was measured by nephelometry using a nephelometer (Siemens device). ESR was measured by the Westergren method (Eventus Vacuplus ESR100). While the serum samples for CRP and ESR were obtained within the first 2 days of the hospitalization, control serum samples were obtained during the recovery period before discharge. Recovery period was defined as the presence of improvement in the laboratory findings (platelet ≥20,000 cells/µl without transfusion, normal international normalized ratio value, at least half fold change in liver function tests and absence of fever and hemorrhage).

The data were analyzed by IBM SPSS V23. The normal distribution was investigated by Shapiro–Wilk test. The data that were not normally distributed were compared by Mann–Whitney *U* test. Spearman correlation was used to determine the association between APR and SGS. The association between SGS groups and mortality was investigated by Chi-square test. Binary logistic regression analysis was performed to determine the association between SGS and CRP. Results were presented as mean ± standard deviation and median (min-max). A value of $P < 0.05$ was considered as statistically significant.

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Table 1. Components of severity grade score (SGS) for CCHF (from Bakir et al. [3]).

Items	Classification	SGS points
Aspartate transaminase	<5× ULNV	0
	≥5× ULNV	1
Alanine transaminase	<ULNV	0
	≥ULNV	1
Lactate dehydrogenase	<3× ULNV	0
	≥3× ULNV	1
White blood cells	<10,000 cells/μL	0
	≥10,000 cells/μL	1
Hepatomegaly	No	0
	Yes	1
Organ failure	No	0
	Yes	1
Bleeding	No	0
	Yes	1
Age	<60 years	0
	≥60 years	1
Platelets	≥100,000 cells/μL	0
	≥50,000, <100,000 cells/μL	1
	<50,000 cells/μL	2
Prolongation of PT	<3 s	0
	≥3 s, <6 s	1
	≥6 s	2
aPTT	<70	0
	≥70	1
INR	<1.6	0
	≥1.6	1

ULNV, upper limit of normal value; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR: international normalized ratio.

Results

A total of 108 patients were included in the study. Fifty-one (47.2%) were female. Patients were classified into three groups according to their SGS results including 50, 41 and 17 patients in the low, intermediate and high SGS, respectively (Table 2).

There was a significant correlation between high scores and elevated CRP and also control CRP and SGS (correlation coefficient: 0.459, $p < 0.001$; correlation coefficient: 0.620, $p < 0.001$). Although no correlation was observed between initial ESR levels and SGS, positive association was identified between control ESR and SGS (correlation coefficient: 0.083, $p = 0.430$; correlation coefficient: 0.553, $p < 0.001$). Twenty-one (19.4%) patients died. Among the fatal cases, 10 were involved in the high and 11 were involved in the intermediate SGS group. High SGS was associated with mortality, and high CRP levels were used to predict the mortality at the beginning of the hospital admission. CRP levels on admission, control CRP and control ESR levels were found considerably high among fatal cases ($p < 0.001$). Ten of 108 (9.2%) patients had concomitant infections which were urinary tract infection ($n = 3$), pneumonia ($n = 4$) and bacteremia ($n = 3$). Three patients developed nosocomial infection. Control CRP levels of the subjects with infection were all declined except three cases with nosocomial infection.

Discussion

Biomarkers such as cytokines, adhesion molecules and APRs have been investigated to evaluate the severity of the disease in the literature [5–7]. The commonly used APRs in clinical practice are ESR and CRP. While some studies have found ESR and CRP useless to demonstrate the course of illness [6], some indicated a significant difference in CRP between fatal and nonfatal cases [7,8]. We found a significant correlation between high SGS and CRP levels on admission. CRP has been found to be a considerably important test for the detection of the severity of the illness [9]. However, in this study, patients have been classified by whether they exhibit hemorrhage or not. In the present study, SGS that includes multiple prognosis-related parameters was used for the classification; hence, it may be more beneficial to determine the association between severity and APRs.

The rarely encountered issue in clinical practice is concomitant bacterial infections with CCHF. However, CRP is not sufficient to make a decision to differentiate viral infection from bacterial infection [10]. Bacterial infection accompanying CCHF on admission cannot be verified by CRP. However, high CRP in the follow-up period after expected duration for recovery of the disease may point out the presence of hospital-acquired infection. Control CRP levels were all decreased except in fatal cases and for three patients with nosocomial infection. Although high CRP levels on admission may not be useful to confirm concomitant infection, in the presence of elevated CRP on the follow-up period, it can be a clue to need close monitoring for the severe prognosis or hospital-acquired infection. CRP has been reported as a prognostic factor in

Table 2. Comparison of SGS and AFR.

Parameter	Low SGS ($n = 50$)	Intermediate SGS ($n = 41$)	High SGS ($n = 17$)	p Value
Sedimentation median (min-max)	10 (3–38)	9 (2–84)	13 (2–56)	0.525
	$n = 37$	$n = 33$	$n = 15$	
Control sedimentation median (min-max)	22.5(7–85)	38(6–102)	97 (27–119)	<0.05
	$n = 16$	n = 23	$n = 9$	
CRP median (min-max)	7 (0–60)	13 (0–170)	59 (10–320)	<0.05
	$n = 43$	$n = 31$	$n = 17$	
Control CRP median (min-max)	0 (0–38)	5 (0–79)	79 (4–205)	<0.05
	$n = 19$	$n = 31$	$n = 9$	

the literature and it has been found higher in the fatal cases [11]. In this study, additional CRP in SGS did not make any change in the sensitivity of the SGS.

Two patients had no change in their initial and control ESR, the rest of the patients showed low level of ESR in the beginning of infection and high levels in recovery period, in the presence of infection and also severe course. ESR looks like a redundant test to determine the severity of the illness [6,8]. However, control ESR levels were significantly high among fatal cases in the present study hence can be beneficial during the course of the infection but not useful on admission.

The main limitations of the study were retrospective design and sample size. We did not check all the patients for APRs on admission and before discharge. The importance of APRs can be obviously demonstrated by enlarging the sample size with further studies. As clinicians in this field need some clues to assess, to manage and to refer the patient properly, SGS parameters and CRP are available in the reference centers and also practical for daily use and both point out the severe clinical outcome.

Disclosure statement

The authors of this paper have no conflict of interest including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials included.

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