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A new perspective to determine the severity of cases with Crimean-Congo hemorrhagic fever

Mehmet Bakir[1], Aynur Engin[1], Mustafa Gokhan Gozel[1], Nazif Elaldi[1], Saadettin Kilickap[2] & Ziynet Cinar[3]

[1]*Department of Infectious Diseases and Clinical Microbiology;* [2]*Department of Medical Oncology;* [3]*Department of Biostatistics, Cumhuriyet University School of Medicine, Sivas, Turkey*

ABSTRACT

Background & objectives: We have established a severity grading score (SGS) system for predicting the fatality in Crimean-Congo hemorrhagic fever (CCHF) for the first time.

Methods: This SGS has been set up by using several variables which were assumed to be associated with mortality according to the literature and also were considered to have clinical importance.

Results: In all, 237 patients who had symptoms of CCHF for ≤5 days were included. The patients were grouped into three categories according to the mortality risk by using SGS as follows : low or no risk, intermediate and high risk groups. A SGS ≤5 showed no association with mortality (there were 158 cases in this group and all survived). This group constituted 66.7% of all the patients with CCHF. A SGS 6–10 showed moderate risk of mortality (10%) and seven out of 70 patients in this group died. SGS ≥11 means high risk for mortality (67%) and six out of 9 patients in this group died ($p = 0.001$). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for ≥11 points of SGS were 67, 100, 98, 100, and 98%, respectively.

Conclusions: This scoring system may help the clinicians to decide which patient to refer to a tertiary step hospital which may also decrease the cost and improve the functionality of healthcare staff.

Key words Crimean-Congo hemorrhagic fever; mortality; severity grading score

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic disease with a mortality rate between 3 and 30%. The clinical course and outcome of the CCHF infection differ a lot among the cases. The virus causing CCHF belongs to the *Nairovirus* genus of the Bunyaviridae family. CCHF was first described in 1940s in the Crimean peninsula of former Soviet Union, whereas it is now endemic in about 30 countries in Africa, Asia, Europe and Middle East[1]. Up to 2009, 4448 confirmed CCHF cases have been reported in Turkey[2].

Up to date, several studies have evaluated the effect of several clinical data and laboratory findings on the mortality of CCHF. However, for a clinician, it is not easy to decide the severity of the disease every time, therefore, we composed a new disease severity grading score (SGS) for CCHF. According to severity of grading score of patients, we aimed to determine which patients are available for a follow-up in a primary care hospital or which patients should be sent to a secondary or a tertiary care hospital for intensive care units or for platelet apheresis.

MATERIAL & METHODS

Study design and patients

This prospective study was conducted in Cumhuriyet University Hospital, between 1 June 2009 and 30 September 2010. Our hospital is located at high endemic region for CCHF and together with surrounding cities it has been serving a population of nearly three million as a tertiary care reference hospital.

A total of 387 patients were referred to our hospital between 1 June 2009 and 30 September 2010 with a suspicion of CCHF disease according to the clinical and laboratory findings. All referred patients were hospitalized and followed-up at the infectious diseases and clinical microbiology ward, until the definitive diagnosis of CCHF. Diagnosis of CCHF was confirmed in 275 patients. The cases which were referred to our hospital in a very late stage of the disease course were excluded and in all 237 patients who had symptoms for only 5 or less days were included in the study. All the patients with a diagnosis of CCHF were followed-up until death or complete recovery. The study protocol was approved by the Human Ethics Com-

mittee of the Cumhuriyet University School of Medicine.

Diagnosis of CCHF

Acute and convalescent phase serum samples were sent to the Virology Laboratory of Refik Saydam Hygiene Center in Ankara, Turkey for serological and virological analyses. All the serum specimens were stored at –70 ºC until testing. Definitive diagnosis of CCHF infection was based upon typical clinical and epidemiological findings; by detection of CCHF virus-specific IgM by enzyme-linked immunosorbent assay (ELISA); and/or by detection of genomic segments of the CCHF virus revealed by reverse transcription-polymerase chain reaction (RT-PCR) either in the acute and convalescent phase of the disease.

Severity grading score system

A new SGS system was established by the variables which were assumed to be associated with mortality according to the literature and were considered to have clinical importance as: advanced age, hepatomegaly, bleeding, organ failure, elevated level of aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), lactate dehydrogenase (LDH), increased number of white blood cells (WBC) and disseminated intravascular coagulation (DIC) score. The variables that were analyzed as risk factors are summarized in Table 1. Organ failure was considered as impairment of two or more organ systems in an acutely ill patient where homeostasis cannot be maintained without therapeutic intervention. The parameters such as organ failure, hepatomegaly and bleeding were recorded as present or not. For each parameter, one point was added to the severity score as shown in Table 2. We categorized the patients to determine the cut off levels for AST ALT lactate dehydrogenase and white blood cell. AST values were measured at the first hospitalization day of the patients. AST was categorized into four groups as: normal AST; AST increased 1 to 3 times of the upper limit; 3 to 5 times the upper limit; and >5 times the upper limit. After

Table 1. The variables associated with mortality for CCHF patients

Patients		No. survived	No. died	*p*-value
Age (yr)	< 60	165 (97.6)	4 (2.4)	0.001
	≥60	59 (86.8)	9 (13.2)	
Bleeding	No	167 (97.7)	4 (2.3)	0.001
	Yes	57 (86.4)	9 (13.6)	
Hepatomegaly	No	218 (95.6)	10 (4.4)	≤0.001
	Yes	6 (66.7)	3 (33.3)	
Organ failure	No	224 (95.7)	10 (4.3)	≤0.001
	Yes	0 (0)	3 (100)	
Aspartate aminotransaminase	<5 × ULNV	167 (98.2)	3 (1.8)	≤0.001
	≥5 × ULNV	57 (85.1)	10 (14.9)	
Alanine aminotransaminase	N	125 (99.2)	1 (0.8)	0.001
	≥ULNV	99 (89.2)	12 (10.8)	
Lactate dehydrogenase	< 3 × ULNV	188 (97.9)	4 (2.1)	≤0.001
	≥3 × ULNV	36 (80)	9 (20)	
Leucocyte (cells/µl)	< 10,000	220 (95.7)	10 (4.3)	≤0.001
	≥10,000	4 (57.1)	3 (42.9)	
Prolongation of PT	< 3 sec	197 (97)	6 (3)	≤0.001
	≥3 sec, < 6 sec	20 (95.2)	1 (4.8)	
	≥6	7 (53.8)	6 (46.2)	
Fibrinogen (mg/dl)	≥100	224 (94.5)	13 (5.5)	–
	< 100	0	0	
D-dimer	N	7 (100)	0 (0)	≤0.001
	≥ULNV, < 10 × ULNV	163 (100)	0 (0)	
	≥10 × ULNV	54 (80.6)	13 (19.4)	
Platelet (cells/µl)	≥100,000	90 (100)	0 (0)	0.003
	≥50,000, < 100,000	75 (94)	5 (6)	
	< 50,000	56 (87.5)	8 (12.5)	

ULNV—Upper limit normal value; and PT—Prothrombin time; Figures in parentheses indicate percentage.

Table 2. The variables of severity grading score system

Items	Classification	SGS points
Aspartate amino-transaminase	<5 × ULNV	0
	≥5 × ULNV	1
Alanine amino-transaminase	<ULNV	0
	≥ULNV	1
Lactate dehydrogenase	< 3 × ULNV	0
	≥3 × ULNV	1
White blood cell	< 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 (yr)	< 60	0
	≥ 60	1
DIC score		
Platelet	≥100,000 cells/μl	0
	≥50,000, <100,000 cells/μl	1
	<50,000 cells/μl	2
Prolongation of PT	< 3 sec	0
	≥3, and <6 sec	1
	≥6 sec	2
Fibrinogen	≥100 mg/dl	0
	< 100 mg/dl	1
D-dimer	Normal	0
	> ULNV and < 10 × ULNV	2
	≥10 × ULNV	3

ULNV—Upper limit normal value; DIC—Disseminated intravascular coagulation; PT—Prothrombin time.

the statistical analysis, AST elevated >5 times the upper limit was found to be associated with mortality, and therefore the cut-off point for AST was determined to be 200 IU/l (normal: 15–40 IU/l). Similarly, the cut-off point for ALT was determined as 50 IU/l (normal: 15–50 IU/l) and for LDH it was 750 IU/l (normal: 98–250 IU/l). The cut-off point for WBC was determined to be over 10,000 cells/μl because the previously published trials reported increased mortality for patients with leucocytosis (normal limits: 4000–10,000 cells/μl)[3]. Then, by using these cut-off levels, levels over the cut-off point were scored as 1 and the other lower than the cut-off as 0 (Table 2). On the other hand DIC was scored by the International Society on Thrombosis and Haemostasis scoring system[4]. DIC score included the platelet count, a prolonged protrombine time, the fibrinogen level and an elevated fibrin related marker (D-dimer was used). DIC score was determined at the first and third days of hospitalization (Table 2).

The SGS was established by the above mentioned parameters. Maximum SGS obtained in this study was 13 points. According to points of SGS at the hospital admission, the patients were divided into three risk groups for mortality: low (0–5 points); intermediate (6–10 points); and high risk (11–16 points). In addition, points of SGS were evaluated again at the third day of hospital admission and compared with the first day of outcomes.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 14 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The non-parametric data were expressed as median (min–max) and categorical data as percentages. SGS for each patient was analyzed using Mann Whitney U-test in fatal and non-fatal patients. Proportions for categorical variables were compared using the chi-square test. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for SGS were calculated. A p-value of <0.05 was considered significant in all analyses.

RESULTS

In total, 237 patients were evaluated in this study. Of all, 142 were males and 95 were females with a median age 52 yr (range 17–82) with a median follow-up time of 7 days (range 1–19). Where 13 patients died and 224 patients were discharged. Only RT-PCR was positive in 72 patients (30.4%), only CCHF virus specific IgM was positive in 38 patients (16%), and both RT-PCR and CCHF virus specific IgM were positive in 127 patients (53.6%).

Table 1 shows the prognostic effects of each parameter in the SGS system. The median of SGS at hospital admission for all the patients was 4 (0–13) and was higher for the patients who have died during the follow-up period, 10 (6–13). On the other hand, the score for the patients who have survived was 4 (0–11) (p <0.001). A SGS ≤5 showed no association with mortality [there were 158 (66.7%) cases in this group and all survived]. A SGS between 6 and 10 points, was equal to a moderate risk of mortality (10%) and totally 7 out of 70 patients in this group died while SGS ≥11 means high risk for mortality (67%) and 6 out of 9 patients in this group died (p=0·001) (Table 3). Nearly half of (6 of 13) the deaths occurred at the first 72 h of admission. The SGS was calculated again for the remaining 220 patients (6 patients died and 11 patients were discharged within the first 72 h) after 3 days of hospitalization. The sensitivity, specificity, accuracy, PPV, and NPV for ≥11 points of SGS at the admission were 67,

Table 3. Number of survived and died patients according to SGS at first day

Patients	SGS at first day		
	0–5	6–10	≥11
Survived (n=224)	158 (100)	63 (90)	3 (33)
Died (n=13)	0 (0)	7 (10)	6 (67)
Total (n=237)	158	70	9

SGS—Severity grading score; Figures in parentheses indicate percentages.

Table 4. Number of survived and died patients according to SGS at third day

Patients	SGS at third day		
	0–5	6–10	≥11
Survived (n=213)	142 (100)	71 (95)	0 (0)
Died (n=7)	0 (0)	4 (5)	3 (100)
Total (n=220)	142	75	3

SGS—Severity grading score; Figures in parentheses indicate percentages.

Table 5. Comparison of patients according to SGS at first and third day

		SGS at third day		
		0–5	6–10	≥11
SGS first day	0–5 (n)* No risk—Group 1	124	26	0
	6–10 (n) Moderate mortality risk—Group 2	17	47	1
	≥11 (n) High mortality risk—Group 3	0	3	2

*According to the second evaluation which was done at third day, 124 patients remained in the same group, 26 patients shifted to the second group, however, no patient shifted to the third group in the second evaluation. As can be seen from Table 5, none of group 1 patients shifted to the high risk group and none of group 3 patients shifted to the no risk group.

100, 98, 100 and 98%, respectively.

SGS's at the third day were similar with the beginning scores. There was no mortality risk in the first group (all survived); a low mortality risk (5%) in the second group (4 of 75 patients died); and a high mortality risk (100%) in the third group (3 of 3 patients died) (Table 4). Although a few patients in group 1 shifted to group 2 on the second evaluation, none of these patients died (Table 5).

DISCUSSION

The CCHF is a fatal hemorrhagic disease that is endemic in the central, northern and eastern regions of Turkey. Although CCHF is an acute and generally self-limiting disease, it can cause disease-related mortality. Several studies have reported the prognostic factors for CCHF from various parts of the world. In the previous studies, several clinical and laboratory data such as hemorrhage, diarrhea, melena, confusion, platelet (PLT) count, hemoglobin (Hb), prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), AST, ALT, LDH, creatine kinase (CK) and C-reactive protein (CRP) were reported to be the prognostic criteria[1,3]. However, previously defined parameters do not help to predict the disease course. Therefore, we evaluated the patients who reported to our center with the clinical and laboratory data at the first day of hospital admission to predict the disease course by a more reliable method and we composed a disease severity grading score.

There are some studies investigating the clinical and laboratory parameters associated with mortality in the literature. Tasdelen Fisgin *et al*[5] reported advanced age as the early indicator of poor prognosis in patients with CCHF. Swanepoel *et al*[3] reported that if one of the following is present; leukocyte count ≥10,000/mm^3, a platelet count ≤20,000/mm^3, an AST level ≥200 U/l, an ALT level ≥150 U/l, an activated partial thromboplastin time ≥60 sec, and/or a fibrinogen level ≤110 mg/dl during the first 5 days after the onset of illness, the fatality risk will be 90%. Ergonul *et al*[6] analyzed the risk factors among patients with CCHF infection and revised the severity criteria. They reported that among the fatalities, haematemesis, melaena and somnolence were more common, the median platelet count was significantly lower (10,600/ml *vs* 20,000/ml), the mean PT (27 sec *vs* 16 sec) and mean aPTT (73 sec *vs* 44 sec) were longer, and the mean ALT level (1125 *vs* 331 IU/l), the mean AST level (3118 *vs* 913 IU/l) and the mean fibrinogen level (119 *vs* 340 IU/l) were higher. Higher levels of AST (≥700 IU/l) and ALT (≥900 IU/l) were suggested to be the severity criteria by Ergonul *et al*[6]. In a study of Cevik *et al*[7], among the fatal cases versus non-fatal cases, the mean ALT (1688 *vs* 293 IU/l), mean AST (3028 *vs* 634 IU/l), mean LDH (4245 *vs* 1141 IU/l), mean creatine phosphokinase (CPK) (3016 *vs* 851 IU/l) levels and the mean INR (1.38 *vs* 1.1) were higher, and the mean PT (18.4 sec *vs* 13.4 sec) and

the mean aPTT (69.4 sec *vs* 42.7 sec) were longer. They calculated the mean platelet count as 47,569 × 10^9/l in non-fatal and 12,636 × 10^9/l in fatal cases. They also reported ecchymosis, hematemesis, melena, somnolence, and gingival bleeding to be more common among fatal cases. They emphasized that thrombocytopenia of ≤20 × 10^9/l [hazard rate (HR) 9.67]; a prolonged aPTT ≥60 sec (HR 11.62); existence of melena (HR 6.39); and somnolence (HR 6.30) were independently associated with mortality. Bakir *et al*[8] reported that the INR, AST, LDH and CPK levels were higher in patients with a fatal outcome. Onguru *et al*[9] reported that platelet count, PT, aPTT, INR, and fibrinogen were prognostic factors associated with mortality in CCHF.

In our study, the cut-off points for AST, ALT, LDH and WBC for the fatal patients were determined 200 (5 × ULNV), 50 (1 × ULNV), 750 (3 × ULNV) and 10,000, respectively. Yilmaz *et al*[10] reported that optimum diagnostic cut-off points for specific laboratory parameters in the severe group were: PLT 90,000, Hb 13.5 g/dl, PT 13.1 sec, aPTT 34 sec, INR 1, AST 117 IU/l, ALT 7 IU/l, AST/ALT 1.62, LDH 508 IU/l, CK 267 IU/l and CRP 0.59 mg/dl. In that study, the risk for a severe clinical course in CCHF patients increased 2.59 and 3.93 times in the presence of platelet count and Hb below cut-off values, whereas the same risk increased 2.95, 2.92 and 3.47 times when the results for INR, AST and CRP, respectively, were above the predetermined cut-off values. Hatipoglu *et al*[11] found that the rates of hemorrhage, diarrhea and confusion were higher in fatal cases compared with non-fatal cases and AST, ALT, alkaline phosphatase, LDH, and CRP levels were higher in fatal cases; the INR and aPTT were longer and mean platelet counts were lower. They also determined that diarrhoea, melena, hematemesis, hematuria, elevated ALT and LDH, and prolongation of aPTT were independent clinical and laboratory predictors associated with fatality. Ozkurt *et al*[12] compared the clinical features and laboratory results of the surviving and the patients who died and they found that the rates of fever during hospitalization, confusion, neck stiffness, bleeding from multiple sites and presence of petechia/ecchymosis were higher in the patients who died than in the surviving ones. Additionally, they determined that the mean values of ALT, AST, LHD, CK, PTT, INR, and urea were also higher, mean PLT counts were lower in the patients who died. With regard to one or several of these findings, it is difficult to comment about the severity of the disease and decide to which patients referred to tertiary care hospital. The associations between the clinical or laboratory findings and mortality were investigated in the previous studies. However, disease severity score was not determined in any study. We composed SGS system for predicting the fatality in CCHF patients for the first time. The results of previous studies investigating the fatality risk in CCHF patients and our clinical observations were used to determine the parameters within SGS. Development of DIC is seen in significant proportion of patients with severe CCHF. Because of this reason, DIC score was also added to SGS.

In our study, according to statistical analysis of the calculated SGS, we divided the CCHF patients into three groups. In the first group, consisting of patients who had the SGS ≤5, there was no fatal case. This group constituted 66.7% of all the patients with CCHF (Table 3). These patients may be monitored in the primary care hospitals. If these first group patients are not referred to secondary or tertiary care hospitals, it will reduce the intensity of secondary or tertiary care hospitals and their costs. The patients who had the SGS between 6 and 10 points were classified as the second group. The risk of death is moderate for this group. Of 70 patients in the second group, 7 died at the follow-up. Second group constituted 29.5% of all the patients with CCHF (Table 3). These patients in the second group could be monitored in secondary care hospitals which have intensive care and blood centre units which can perform platelet aphaeresis. In the third group consisting of patients who had the SGS ≥11, the risk of mortality was higher. Although the third group constituted 3.8% of all the patients with CCHF, six of 9 cases who had the SGS ≥11 died at the follow-up (Table 3). Third group of patients should be monitored in the tertiary care hospitals having intensive care conditions. To identify the serious cases with CCHF, the sensitivity, specificity, accuracy, PPV, and NPV of cut-off value for 11 and more points in our study were higher. Because patients with CCHF who have higher mortality risk should be followed up at the experienced and central hospitals, which have intensive care units. It is very important to detect these group of patients. In our study, the specificity and accuracy for cut-off value of SGS ≥11 points were considerably higher (100 and 98%, respectively).

There are several benefits of risk stratification of patients according to SGS. Firstly, patients who have mild disease might be followed-up in primary care hospitals. However, patients with more severe disease may be referred to secondary or tertiary care hospitals which have intensive care and blood centre units which can perform platelet aphaeresis. Hence, superfluous referral of patients to secondary or tertiary care hospitals might be prevented via SGS-based triage. This approach might also provide decreased cost and improved functionality of healthcare staff. In addition, early identification of patients who have

higher risk of death could be achieved. Furthermore, we think that SGS might be useful in therapeutic decision making process, and hence, recommended treatment options (ribavirin, steroid, plasma exchange, *etc.*) might be administered as early as possible. However, we think we need further trials to investigate the potential benefit of surrogacy of SGS. To the best of our knowledge, this is the first study which provided a SGS stratifying patients with CCHF according to risk of mortality.

There are some limitations of this study. First, this manuscript presents only a single centre experience which has an endemic region for CCHF. Second, the cut-off levels for ALT, AST, and PLT might be different in a more heterogeneous cohort. Third, we have not performed multivariate regression analysis for SGS because the number of cases who developed organ failure predicting mortality are limited.

In conclusion, up to now, studies have evaluated the effect of several clinical signs and laboratory findings on the mortality. However, for a physician working in the primary or secondary or tertiary care hospital, it is not easy to decide the severity of diseases every time according to these findings. In this study, we evaluated the patients on the first day of hospitalization. We composed SGS according to clinical and laboratory findings and we aimed to make a comment about prediction of mortality using SGS. According to the statistical analysis of the SGS, we divided the CCHF patients into three groups in terms of the risk of mortality. The first group of patients without any mortality constituted 66.7% of all the patients with CCHF. The first group of patients composed more than half of all patients. These patients could be monitored in the primary care hospital. We believe that if the physicians apply SGS-based triage for patients, it will reduce the intensity of secondary or tertiary care hospitals. This approach might also provide decreased cost. As a result, we believe that the new SGS can be useful in clinical practice.

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Correspondence to: Dr Aynur Engin, Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University School of Medicine, 58140 Sivas, Turkey.
E-mail: aynurum2000@yahoo.com

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