MAJOR ARTICLE

Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavirin and Corticosteroids on Fatality

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Background. Patients infected with Crimean-Congo hemorrhagic fever (CCHF) virus present with a wide clinical spectrum. In observational studies, the effects of therapeutic agents are confounded by severity. We describe use of a clinical severity scoring index (SSI) for CCHF patients and assess the effect of ribavirin and corticosteroid therapy on the case-fatality rate, stratified by SSI.

Methods. The study group included hospitalized patients who received a diagnosis of CCHF at the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Education and Research Hospital between 2004 and 2011. The SSI included platelet count, bleeding, fibrinogen level, activated partial thromboplastin time, and somnolence. The effects of ribavirin and corticosteroid on the case-fatality rate were studied by univariate and multivariate analysis, stratified by SSI.

Results. Two hundred eighty-one confirmed cases of CCHF were included in the study. Of 281 patients, 23 (8%) died. The mean age (±SD) of the patients was 47 ± 16 years. Forty-nine percent were female. The mean duration of stay at our clinic after onset of symptoms was 4.4 days, with a range of 1–14 days. In multivariate analysis of factors for the prediction of death, the SSI (odds ratio [OR], 3.27; 95% confidence interval [CI], 2.09–5.13) and ribavirin use (OR, 0.04; 95% CI, .004–.48) were found to be statistically significant factors.

Conclusion. The SSI is an accurate predictor of death and will therefore be a useful tool for case management and for drug-assessment studies. After stratification of cases by SSI, ribavirin was found to be effective in reducing the case-fatality rate, especially among moderately ill patients, whereas steroids were found to be beneficial particularly among patients with severe disease.

Keywords. Crimean-Congo hemorrhagic fever; severity scoring index; ribavirin; corticosteroids.

Crimean-Congo hemorrhagic fever (CCHF) is a fatal viral infection described in parts of Africa, Asia, Eastern Europe, and Middle East [1]. The virus belongs to the genus *Nairovirus* in the *Bunyaviridae* family and causes severe diseases in humans, with a reported mortality rate of 5%–30% [1]. The CCHF virus infection has been one of the most important public health issues in Turkey since 2002, because of its high case-fatality rate. In the past decade, about 8000 cases were reported to Ministry of Health of Turkey, and patients died in 400 (5%).

The clinical characteristics of the patients with CCHF virus infection present with a wide spectrum of disease severity, from mild to fatal outcomes [2]. So far, ribavirin is the only antiviral agent used in treatment of CCHF virus infections. Because of the wide clinical spectrum of CCHF, outcome studies assessing the benefit of ribavirin were usually biased by the propensity of the disease. Usually, initiation of ribavirin therapy

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is confounded by indication. In mild infections, usually no drug was given, but in severe infections ribavirin was not found to be beneficial [3]. Therefore, for case management, a scoring index was needed that could predict death and guide the clinician's choice of therapy. The predictors of death were defined by Swanepoel [4] in 1989, and since then, revisions have been made by our group [2, 5]. In this study, we used our clinical experience in parallel with an increased sample size of patients with CCHF to revisit our severity criteria [2] and suggest a clinical severity scoring index (SSI) for the prognosis and therapy of CCHF. By using this index, we also assessed the effect of ribavirin and supportive corticosteroid therapy.

METHODS

The study group included patients who were hospitalized in the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Education and Research Hospital between 2004 and 2011 with a diagnosis of CCHF. Acute-phase serum specimens obtained at admission to the hospital and convalescent-phase serum specimens obtained 2 weeks after admission were sent to Refik Saydam Hygiene Center, the national reference laboratory of Turkey. The diagnosis of CCHF was confirmed by enzyme-linked immunosorbent assay detected of immunoglobulin M and/or positive results of polymerase chain reaction for CCHF virus in blood. Complete blood counts and biochemical laboratory parameters were measured daily after admission to the hospital.

The SSI included the following 5 parameters: platelet count (0–3 points), activated partial thromboplastin time (aPTT, 0–3 points), fibrinogen (0–3 points), bleeding (0–3 points), and somnolence (0 or 1 points; Table 1). The SSI was calculated daily as the sum of the scores for the 5 parameters. The patients were categorized according to their SSI on admission. The analysis was performed prospectively for patients admitted during and after 2010 and retrospectively for patients admitted before 2010.

All patients who had onset of symptoms <7 days of diagnosis and had no contraindications against ribavirin received oral ribavirin at the dosage recommended by the World Health Organization (4 g daily for 4 days, followed by 2.4 g daily for 6 days). Written consent to participate in the study was obtained from each patient or a member of their family. Patients were given erythrocytes, fresh frozen plasma, and total blood preparations, depending on their hemostasis needs. Patients whose condition deteriorated rapidly in terms of clinical and laboratory parameters despite receipt of ribavirin were given corticosteroid treatment formulated as 10 mg/m^2 dexamethasone.

Mean comparisons for continuous variables were done using independent groups *t* tests. Proportion comparisons for categorical variables were done using χ^2 tests, although the Fisher exact test was used when data were sparse. A multivariate analysis was performed to detect the effect of ribavirin and corticosteroid therapy on progression to death. In addition to the use of ribavirin and steroid therapy, the SSI was included in the model to adjust for confounding. Variance inflation factors for independent variables were calculated for diagnosis of collinearity. The variance inflation factors for each of these independent variables were calculated as <1.5, and variables were found to be uncorrelated with the other predictor variables in the model. Significance was set as a P value of < .05, using 2-sided comparisons. Stata, version 11 (Stata; College Station, TX), was used in the analysis.

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

SSI Parameter	Score
Platelet count, ×10^3 platelets/mm^3	
>150	0
150–50	1
49–20	2
<20	3
aPTT, sec	
≤34	0
35–45	1
46–59	2
>60	3
Fibrinogen level, mg/dL	
≥180	0
179–160	1
159–120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1

Abbreviation: aPTT, activated partial thromboplastin time; SSI, severity scoring index.

RESULTS

Two hundred eighty-one patients with confirmed CCHF who were admitted to our clinic were included to the study. Out these, 23 (8%) died. The mean age (±SD) of the patients was 47 ± 16 years (range, 16–86 years). Nearly half (49%) were female. The mean duration of symptoms (±SD) before admission to our clinic was 4 ± 2 days, with a range 1–14 days.

The minimum and maximum severity scores were 0 and 13, respectively. The severity scores and outcomes for the 281 patients are presented in Figure 1. On daily assessment of severity

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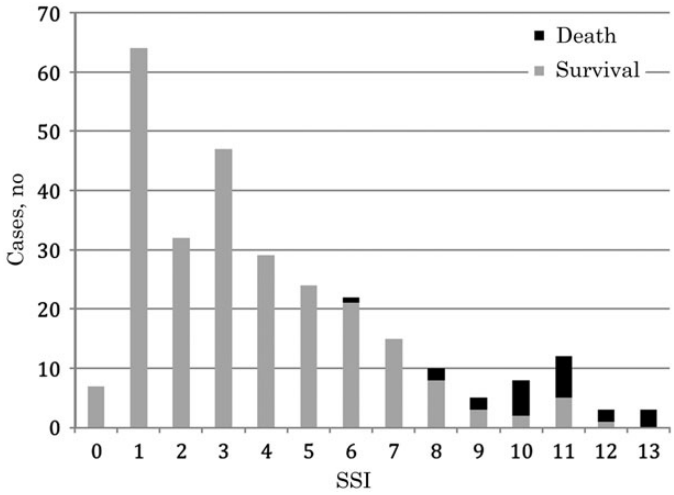


Figure 1. Distribution of outcomes among patients with Crimean-Congo hemorrhagic fever, stratified by severity scoring index (SSI).

scores, patients with mild and moderate SSIs did not progress to more severe groups. The median SSIs overall and among patients who survived were 3. Accordingly, diseases associated with an SSI of < 3 was defined as mild. The boundary between moderate and severe cases was set as 10, because if the score was >10, the CFR was >50%. The SSI predicted death with a sensitivity 100% (95% confidence interval [CI], 29%–100%), a specificity of 93% (95% CI, 89%–95.6%), a positive predictive value of 13% (95% CI, 2.7%–33.6%), a negative predictive value of 100% (95% CI, 98.6%–100%), and the area under the receiver operating characteristic curve was 96.4% (95% CI, 94.9%–97.9%).

The effect of ribavirin and corticosteroid therapy on the CFR was analyzed among mild, moderate, and severe SSI strata (Table 2). Among 47 patients who received steroid therapy, 44 also received ribavirin. Only 3 patients could not receive ribavirin. In 1 patient, ribavirin therapy was stopped because of elevated amylase levels. In 2 patients, oral ribavirin therapy was not given because of gastrointestinal bleeding. Among mild cases, there were no fatalities and no corticosteroid use. Among moderately ill patients, ribavirin was found to have a significant effect on reducing the CFR. Among ribavirin recipients, the CFR was 1.49%, whereas among those who did not receive ribavirin, the CFR was 17% ($P = .001$). For assessment of the additive value of corticosteroids, the patients who did not receive ribavirin were excluded. Among moderately ill patients, 28 received additional corticosteroid therapy, with 1 fatality, and 106 patients did not receive corticosteroid therapy, with 1 fatality ($P = .308$; Table 2). On the other hand, among severely ill patients, 16 received additional corticosteroid therapy, and 8 died (CFR, 50%), whereas 8 did not receive additional corticosteroid therapy, and all died (CFR, 100%; $P = .014$; Table 2). The effect of ribavirin use was not found to have significant effect on the CFR among severely ill patients ($P = .326$; Table 2).

In a multivariate analysis that included all patients, after stratification by SSI, ribavirin use was found to be significant in reducing the CFR (OR, 0.04; 95% CI, .004–.48; $P = .010$). Steroid use also had a reducing effect, although it was not statistically significant (Table 3).

DISCUSSION

CCHF is a fatal disease, with a variable range of clinical severity. To this point, clinicians have tended to try existing therapeutic options for the treatment of CCHF [6–8]. Some of these studies

Table 2. Effects of RBV and Additional Therapy on CFRs Among Patients With Crimean-Congo Hemorrhagic Fever, Stratified by SSI

	CFR, % (Proportion of Patients), by RBV Status			CFR, % (Proportion of Patients), by CS Status		
SSI, Disease Severity	RBV	No RBV	*P* Value	CS	No CS	*P* Value
0–2, mild	0 (0/77)	0 (0/26)		0	0 (0/103)	
3–9, moderate	1.49 (2/134)	17 (3/18)	.001	4 (1/28)	1 (1/106)	.308
10–13, severe	67 (16/24)	100 (2/2)	.326	50 (8/16)	100 (8/8)	.014

Abbreviations: CFR, case-fatality rate; CS, corticosteroid; RBV, Ribavirin; SSI, severity scoring index.

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Table 3. Univariate and Adjusted Analysis for Prediction of Death

	Univariate Analysis		Adjusted Analysis	
Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
SSI	2.49 (1.82–3.41)	<.001	3.27 (2.09–5.13)	<.001
Ribavirin use	0.68 (.23–1.93)	.470	0.04 (.004–.48)	.01
Corticosteroid use	5.65 (2.31–13.77)	<.001	0.22 (.039–1.27)	.092

Abbreviations: CI, confidence interval; OR, odds ratio; SSI, severity scoring index.

reported controversial conclusions of the effect of ribavirin [3]. One of the most important biases in previous reports involved not stratifying patients according to CCHF severity, resulting in a lack of control for the critical confounding parameter. In this study, we defined an SSI and reevaluated the effects of the leading therapeutic options on disease outcome by using this index.

Severity criteria for CCHF were first defined by Swanopoel et al in 1989 [4]. These criteria included platelet count (<20 000 platelets/mm^3), aPTT (>60 seconds), leukocyte count (≥10 000 leukocytes/mm^3), fibrinogen level (<110 mg/dL), and elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. In 2006, we suggested revisions by adding some clinical parameters such as somnolence, gastrointestinal bleeding, and we also suggested higher threshold levels for AST and ALT [2]. Both studies defined criteria for the fatality effectively, but found to be unsatisfactory to categorize the clinical stages of the disease. Based on our clinical experience of a growing number of patients, we improved some of the parameters by grading. We excluded some parameters, which were observed to be not contributory for clinical practice. In this context, the levels of platelet count, aPTT, fibrinogen, and bleeding were graded. Based on our observations, the AST and ALT levels were not found to have additional benefit, and not included in the SSI. The negative predictive value of SSI on admission (100%; CI, 98.6%–100%) was high. We can conclude that, if the patients were mildly diseased on admission, they would not progress to death.

Grouping of the patients as mild, moderate, and severe could be a useful tool in case management, and drug assessment studies. The ribavirin is the drug of choice as an antiviral agent for viral hemorrhagic fevers including CCHF [9, 10]. However, the use of ribavirin is still controversial. The effect of ribavirin use was not evidenced by randomized clinical trials, since the ethical constraints do not allow for randomized placebo controlled study design [11]. Ribavirin use was more common as the SSI increased. About one-third (37%) of cases were in the mild group. Ribavirin was significantly less frequently used for mild cases (75% vs 89%; $P = .001$), and there were no deaths (Table 2). The largest group of patients (54%) had moderate illness, and 89% of patients in this group received ribavirin. The CFR among patients who received ribavirin was significantly lower than that among those who did not receive ribavirin (1.49% vs 17%; $P = .001$; Table 2). Only 9.25% of patients had severe disease, of whom 92% received ribavirin. In the severe group, ribavirin was found to be ineffective for reducing the CFR ($P = .326$), but this could be related to the decreased statistical power of the analysis of this group. Among severely ill patients, use of corticosteroid therapy was beneficial ($P = .014$). In multivariate analysis adjusted by SSI, ribavirin but not corticosteroid therapy was found to be effective in reducing the CFR (Table 3).

The beneficial effect of corticosteroid therapy on reducing the CFR could be explained by the pathogenic mechanism of the disease, which is characterized by an intense immune reaction in some of patients. Production of high amounts of proinflammatory cytokines [5] and hemophagocytosis were described in previous reports [12]. Our findings support the hypothesis described elsewhere on the beneficial role of ribavirin therapy during the earlier, viremic phase of the disease course [10]. In later phases of the disease, corticosteroids could be effective in severely ill patients, in whom enormous amounts of cytokines have been released [10]. The SSI evaluated in this study appears to be useful tool for determining the appropriate therapy for CCHF.

In conclusion, grouping of patients on the basis of an SSI is necessary for case management and also for observational drug-assessment studies. After stratifying patients on the basis of the SSI described here, ribavirin was found to be effective in reducing the CFR among moderately ill patients, whereas steroids were found to be beneficial among patients with more-severe disease.

Notes

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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