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# Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited

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## ABSTRACT

The aim of this study was to determine the predictors of mortality among patients infected with Crimean-Congo haemorrhagic fever (CCHF) virus. Among patients with acute febrile syndrome, characterised by malaise, bleeding, leukopenia and thrombocytopenia, who were admitted to hospital during the spring and summer of 2002–2004, 54 had positive IgM and/or PCR results for CCHF virus in blood or tissue. The overall case fatality rate was 7.4%. Among the fatalities, haematemesis (p 0.009), melaena (p 0.001) and somnolence (p 0.022) were more common, the median platelet count was significantly lower (10 600/mL vs. 20 000/mL; p 0.038), the mean prothrombin time (27 s vs. 16 s; p 0.002) and mean activated partial thromboplastin time (73 s vs. 44 s; $p < 0.001$) were longer, and the mean alanine transferase (ALT) level (1125 vs. 331; $p < 0.001$), the mean aspartate transferase (AST) level (3118 vs. 913; p 0.004) and the mean fibrinogen level (119 vs. 340; p 0.012) were higher. Serum IgM and IgG against CCHF virus was detected in 25% and 0%, respectively, of fatal cases, compared with 94% and 62%, respectively, of cases with favourable outcomes. Oral ribavirin was prescribed to 22 (41%) patients. Of the four fatal cases, it was the intention to prescribe ribavirin to three patients, but this was not possible because of haematemesis and melaena. Higher levels of AST (≥ 700 U/L) and ALT (≥ 900 U/L) are suggested for use as severity criteria. Oral ribavirin was not effective for patients with haematemesis, and intravenous ribavirin is necessary for treatment of CCHF.

**Keywords** Crimean-Congo haemorrhagic fever virus, diagnosis, ribavarin, risk-factors, severity criteria

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## INTRODUCTION

Crimean-Congo haemorrhagic fever (CCHF) is a fatal viral infection described in parts of Africa, Asia, Eastern Europe and the Middle East [1]. The virus belongs to the genus *Nairovirus* in the Bunyaviridae family, and causes severe disease in humans, with a reported mortality rate of 15–30% [2]. Humans become infected through the bites of ticks, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viraemic livestock [3].

Cases infected with CCHF virus (CCHFV) were first reported in Turkey in 2002 [4–6], although epidemics were reported before 2003 in neighbouring countries. CCHFV infection is an important public health issue in Turkey because of its high case fatality rate. Since 2002, 399 cases of CCHF have been reported to the Ministry of Health of Turkey, and 19 (4.7%) of these cases died. The present study analysed the risk-factors of 54 CCHF patients, based on epidemiological, clinical and laboratory findings. Based on this analysis, the predictors of fatality criteria, defined previously by Swanepoel *et al.* [7] in 1989, were reassessed.

## MATERIALS AND METHODS

Patients with acute febrile syndrome, characterised by malaise, bleeding, leukopenia and thrombocytopenia, during the spring and summer of 2002, 2003 and 2004 were admitted to the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Education and Research Hospital. Patients with positive IgM and/or PCR results for CCHFV in blood or

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tissue were included in the study. Recent or current CCHFV infection was confirmed by demonstrating seroconversion, or at least a four-fold increase in antibody titre in paired serum samples, or IgM antibodies with ELISA in a single sample [8]. ELISA methods are quite specific and much more sensitive than immunofluorescence and neutralisation tests [9]. RT-PCR is the method of choice for rapid laboratory diagnosis of CCHFV infection [10].

The presence of antibodies to *Leptospira*, Lyme disease, *Salmonella*, rickettsiae, *Brucella*, *Coxiella burnetii*, *Toxoplasma*, rubella virus, cytomegalovirus, herpes virus and hepatitis A, B and C viruses was investigated by serology. Acute and convalescent sera from all the acute cases were sent to the Refik Saydam Hygiene Center of Ankara, Turkey for ELISA and PCR tests [8,10]. Laboratory parameters were measured on a daily basis following hospital admission.

The patients were given erythrocytes, fresh frozen plasma and total blood preparations, depending on the state of their haemostasis. The patient characteristics were assessed according to the 90% fatality outcome criteria described by Swanepoel *et al.* [7]. According to these criteria, patients were defined as 'severe' when they had white blood cell (WBC) counts $\geq 10\ 000/mm^3$, platelet counts (PLT) $\leq 20\ 000/mm^3$, aspartate transferase (AST) levels $\geq 200$ U/L, alanine transferase (ALT) levels $\geq 150$ U/L, activated partial thromboplastin times (aPTT) $\geq 60$ s, or fibrinogen levels $\leq 110$ mg/dL during the first 5 days of illness. Various threshold levels were investigated with the aim of achieving higher sensitivity, specificity, positive and negative predictive values.

Mean comparisons for continuous variables were performed using independent group *t*-tests. Proportion comparisons for categorical variables were performed using chi-square tests, with Fisher's exact test being used when data were sparse. A multivariate analysis was performed for the prediction of fatality. Physical findings, haematemesis, melaena, somnolence, and the laboratory tests (AST, ALT, PLT, WBC count, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), prothrombin (PT), aPTT and fibrinogen) were included in the model as independent variables. Significance was set at $p < 0.05$ using two-sided comparisons. The STATA v.8.0 software package (Stata Corp., College Station, TX, USA) was used for the analyses.

Results of diagnostic tests were not available for up to 4 weeks; therefore, all ribavirin therapy was initiated before laboratory evidence of CCHF infection. Oral ribavirin was administered, within a mean 5.5 days following the onset of symptoms, at the dosage recommended by the WHO (4 g four times daily for 4 days; 2.4 g four times daily for 6 days) [11]. The intravenous form of ribavirin was not available in Turkey at this time. Written consent was obtained from the patients or their family members.

## RESULTS

Fifty-four patients were admitted from various regions of north-eastern Anatolia and the southern parts of the Black Sea region; all of these patients were involved in animal husbandry. Four (7.4%) cases were fatal with massive haemorrhage. The age, gender and number of days from the appearance of symptoms to admission were similar between favourable and fatal cases ($p > 0.05$). Fever lasted for an average 4.3 (± 2.5) days. Among the clinical findings, haematemesis (p 0.009), melaena (p 0.001) and somnolence (p 0.022) were more common among fatal cases (Table 1).

Forty-eight (89%) of the 54 patients were IgM-positive, 31 (57%) were IgG-positive during the acute or convalescent phase, and 22 (41%) patients were PCR-positive (Table 2).

All the patients had leukopenia, thrombocytopenia, and elevated AST, ALT, LDH and CPK levels (Table 3). On admission, 31 patients had thrombocytopenia of $\leq 20\ 000/mm^3$, 45 patients had AST levels $\geq 200$ U/L, 40 patients had ALT levels $\geq 150$ U/L, 16 patients had aPTT of $> 60$ s. The fibrinogen level of one patient was $\leq 110$ mg/dL. None of the patients had leukocytosis, with the exception of one fatal case whose leukocyte count increased to $12\ 000/mm^3$ on the final day (day 10 since the onset of disease). Among the fatal cases, the median PLT was significantly lower (10 600/mL vs. 20 000/mL; p 0.038), the mean PT (27 s vs. 16 s; p 0.002) and

**Table 1.** Demographic characteristics of 54 patients with Crimean-Congo haemorrhagic fever

| | Favourable cases $n = 50$ (%) | Fatal cases $n = 4$ (%) | p |
|---|---|---|---|
| Number of females | 26 (52) | 2 (50) | 0.939 |
| Mean age (SD), years | 43 (18) | 54 (11) | 0.280 |
| Days from symptoms to admission | 6 | 4 | 0.074 |
| Symptoms | | | |
| Nausea-vomiting | 41 (82) | 4 (100) | 0.471 |
| Myalgia | 31 (62) | 4 (100) | 0.285 |
| Fever | 38 (76) | 4 (100) | 0.576 |
| Headache | 35 (70) | 3 (75) | 0.684 |
| Physical findings | | | |
| Fever (Temperature > 38 °C) | 21 (42) | 2 (50) | 0.755 |
| Bleeding | | | |
| Haematemesis | 13 (26) | 4 (100) | 0.009 |
| Melaena | 7 (14) | 4 (100) | 0.001 |
| Epistaxis | 20 (40) | 3 (75) | 0.301 |
| Haemoptysis | 4 (8) | 1 (25) | 0.341 |
| Haematuria | 8 (16) | 0 (0) | 0.509 |
| Maculopapular rash | 15 (30) | 1 (25) | 0.640 |
| Conjunctival injection | 21 (42) | 1 (25) | 0.638 |
| Somnolence | 17 (34) | 4 (100) | 0.022 |
| Jaundice | 5 (10) | 1 (33) | 0.330 |
| Diarrhoea | 17 (34) | 2 (50) | 0.607 |
| Hepatomegaly | 17 (35) | 0 (0) | 0.293 |

SD, standard deviation.

**Table 2.** Serology and PCR results for 54 patients with Crimean-Congo haemorrhagic fever

| | Favourable cases $n = 50$ (%) | Fatal cases $n = 4$ |
|---|---|---|
| IgM-positive | 47 (94) | 1 (25) |
| IgG-positive | 31 (62) | 0 (0) |
| PCR-positive | 19 (48) | 3 (75) |