

Risk Factors Associated With Poor Prognosis in Children With Crimean-Congo Hemorrhagic Fever

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Background: Crimean-Congo hemorrhagic fever (CCHF) was a rare disease in Iran before 1999. During the last 15 years, it has been reported from different provinces of Iran, mostly from southeastern Iran.

Objectives: This study aimed to evaluate the factors associated with poor outcome in children and adolescents with CCHF.

Patients and Methods: We studied all files of children (age < 19 years old) with CCHF who were admitted to our hospital in Zahedan from September 1999 to October 2012. Evaluated Factors in association with the prognosis included aspartate transaminase (AST), alanine transaminase (ALT), activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count, and hemorrhagic diathesis.

Results: We evaluated 39 children and adolescents (mean age, 12.9 ± 4.2 years) with CCHF. Among them, nine patients (23%) died. The risk factors associated with poor prognosis were platelet count < 50000, PT > 15 seconds, aPTT > 45 seconds, the presence of hemorrhagic diathesis, ALT and AST more than five-time the upper limit of normal, loss of consciousness, and myocarditis.

Conclusions: The most important factor associated with mortality was a platelet count < 50000 at the admission time. More investigations on the efficacy of drugs such as steroid and specific immunoglobulin in treatment of patients with risk factors such as severe thrombocytopenia are needed.

Keywords: Crimean-Congo Hemorrhagic Fever; Mortality; Prognosis; Risk Factors

1. Background

Crimean-Congo hemorrhagic fever (CCHF) is an asymptomatic viral illness in infected animals, but it can be fatal in humans. CCHF is one of the most widely-distributed viral hemorrhagic fevers worldwide. This disease has been reported from many countries in Africa, Asia, and Eastern Europe (1-5). Climatic change, which can lead to tick vectors proliferation, can increase the incidence of disease. *Hyalomma*, a genus of hard tick, is the principal vector (1, 2). Infection in human begins with an acute onset of nonspecific manifestations such as flu-like symptoms, but can progress to a serious and hemorrhagic phase with a high-mortality rate (20%-80%). Although the virus is usually transmitted by infected ticks, animal-to-human and sometimes, human-to-human transmission have been reported too (6, 7). Tick bite, exposure to the infected human secretions or animal tissues, and drinking unpasteurized milk can transmit infection to human. This disease is a serious hazard to livestock holders, veterinarians, husbandry workers, and laboratory as well as hospital staff (4-7). Hospital transmission via aerosol has been reported from Russia, Iran, and Turkey (4, 8, 9). CCHF presents with an acute onset of fever, chills, headache, myalgia, and arthralgia. Gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea

are also common. This first stage of illness, ie, prehemorrhagic phase (1-3), takes several days and in some patients, hemorrhagic phase follows. This stage is often short and lasts for two or three days. A petechial rash can be the first symptom and is followed by petechiae or ecchymoses on the skin and mucous membranes. Epistaxis, hemoptysis, hematemesis, melena, hematuria, and bleeding from venous lines are also common. Bleeding can occur in the brain. In patients who survive, recovery begins ten to 20 days after the onset of disease. The convalescent phase is accompanied by a generalized weakness and can take up to a year (1, 7, 9). Many studies have reported the risk factor associated with mortality in CCHF (10-14). Most of the studied risk factors were lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count, and hemorrhagic diathesis (9-12). Although Sistan-and-Baluchistan Province is an endemic area for CCHF, there was no study concerning its risk factors from this area.

2. Objectives

This study was conducted to evaluate the factors associated with poor outcome in children and adolescents with CCHF.

Table 1. Risk Factors Associated With Death in Children

Risk Factors	Platelet < 50000	Myocarditis (One Case)	Decreased Level of Consciousness (One Case)	Abnormal PT and aPTT	Hemorrhagic Diathesis
Dead	6	1	1	7	9
Alive	1	0	0	5	6

3. Patients and Methods

This study was a cross-sectional descriptive study. We studied all files of children and adolescence (age < 19 years old) with CCHF who were admitted to our university hospitals in Zahedan from September 1999 to October 2012. The evaluated Risk factors were ALT and AST levels, platelet count, PT, aPTT, level of consciousness at the admission time, and hemorrhagic diathesis. Data analysis was performed using SPSS (v. 14, SPSS Inc., Chicago, IL, USA) and a P value < 0.05 was considered as statistically significant for all analyses.

4. Results

Among 39 children and adolescents with the mean age of 12.9 ± 4.2 years who were diagnosed with CCHF, 30 cases (77%) survived and 9 (23%) died. The most important risk factors associated with mortality were consecutively severe thrombocytopenia at the admission time (< 50000), PT > 15 seconds, aPTT > 45 seconds, present of hemorrhagic diathesis, ALT and AST of more than five-time the upper limit of normal (ULN), and loss of consciousness. There was a significant association between mortality rate and platelet count < 50000 ($P < 0.05$). In addition, there was a significant association between mortality rate and PT > 15 seconds. Although the level of AST and ALT > 5-time the ULN and aPTT > 45 seconds had some associations with mortality, they were insignificant. One patient died due to myocarditis and another case was a patient with a loss of consciousness who died three days after admission (Table 1).

5. Discussion

CCHF is a viral hemorrhagic infection due to a virus in the Nairoviruses family. It is widely distributed in wild and domestic animals such as goats, cattle, hares, sheep, and ticks throughout many countries in Asia, especially in the Middle East, Eastern Europe, and Africa (1, 3-5). Although the first human cases of CCHF in Iran were identified in the west of Iran, since 1999, numbers of patients with CCHF have been increased in several provinces with an increasing morbidity rate and approximately high mortality (up to 30%). Between 1999 and 2004, health authorities faced with a large number of patients with CCHF (165 confirmed cases) with about 22% case fatality rate in Sistan-and-Baluchistan Province, in the Southeast of Iran. During 2005 to 2007, among 32 patients with

CCHF, 3% died (7, 15-18). At the onset of the recent epidemic in southeastern Iran, we had not enough information on epidemiology of disease and treatment of patients; however, during the last decade, ribavirin was available in hospitals and many reports have shown its effect on disease. On the other hand, there was a close collaboration between physicians and health authorities for early recognition of the disease and more importantly, treating the patients at early stage. Both of these factors had significant positive effects on survival of the patients (7). Between 1999 to 2004 (in the first study) in Sistan-and-Baluchistan, we had 165 confirmed patients with a mortality rate of 22%, but this rate was decreased in the recent years (3%-19%) (8, 18, 19).

During the last 13 years, nearly three-fourths of all cases of CCHF in Iran have been reported from Sistan-and-Baluchistan and among the patients who died due to CCHF, severe thrombocytopenia at the admission time (< 50000) was the most important factor followed by the present of hemorrhagic diathesis and increased PT (5-9). Tasdelen et al. also reported the mortality-associated risk factors in patients with CCHF. Their results were similar to ours. They found that the level of ALT and AST were significantly higher in those who passed away. Moreover, the LDH levels were high, and PT and aPTT were prolonged in fatal cases. There was also a significant difference in median age between two groups. Old age, late admission, low platelet count, increased AST, ALT, CPK, and LDH levels, and prolonged PT and aPTT might be an early indicator of poor prognosis in patients with CCHF (13). Another study by Oflaz et al. showed that platelet count < 80000, aPTT > 42 seconds, and a high level of LDH were independent risk factors for severe disease (12). Most studies recommend that when the physicians are faced with a patient with CCHF and aforementioned risk factors, they should promptly begin treatment with ribavirin and perform other interventions to increase the rate of improvement and cure in such patients.

To put in a nutshell, severe thrombocytopenia, prolonged PT or aPTT, hemorrhagic diathesis, increased level of ALT and AST, and a decreased level of consciousness are the major risk factors associated with death and severity of disease in patients with CCHF.

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Authors' Contributions

Seyed Mohammad Hashemi-Shahri, Batool Sharifi-Mood, and Maliheh Metanat designed the study, collected the data, searched the literature, and wrote the manuscript.

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