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Review

# Prognostic factors, pathophysiology and novel biomarkers in Crimean-Congo hemorrhagic fever

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is a geographically widespread tick-borne zoonosis. The clinical spectrum of the illness varies from mild infection to severe disease and death. In severe cases, hemorrhagic manifestations develop, with fatality rates of 4–20%, depending on the geographic region and quality of the health care. Although vast majority of the CCHF cases were reported from Turkey, mortality rate is lower than the other regions, which is 5% on average. Prediction of the clinical course of the disease enables appropriate management planning by the physician and prompt transportation, if needed, of the patient to a tertiary care hospital for an intensive therapy. Thus, predicting the outcome of the disease may avert potential mortality. There are numerous studies investigating the prognostic factors of CCHF in the literature. Majority of them were reported from Turkey and included investigations on clinical and biochemical parameters, severity scoring systems and some novel biomarkers. Somnolence, bleeding, thrombocytopenia, elevated liver enzymes and prolonged bleeding times are the most frequently reported prognostic factors to predict the clinical course of the disease earlier. High viral load seems to be the strongest predictor to make a clinical decision about the patient outcome. The severity scoring systems based on clinically important mortality-related parameters are especially useful for clinicians working in the field to predict the course of the disease and to decide which patient should be referred to a tertiary care hospital for intensive care. In the light of the pathophysiological characteristics of CCHF, some new biomarkers of prognosis including cytokines, soluble adhesion molecules, genetic polymorphisms and coagulopathy parameters were also investigated. However most of these tests are not available to clinicians and they were obtained mostly for research purposes. In spite of the various studies about prognostic factors, they have several inherent limitations, including large variability in the results and confusing data that are not useful for clinicians in routine practice. In this paper, the results of diverse studies of the prediction of the prognosis in CCHF based on epidemiological, clinical and laboratory findings of the disease were summarized and suggestions for future studies are provided.


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## 1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a geographically widespread zoonotic disease, ranging from South Africa over Eastern Europe to the Middle East and Asia (Leblebicioglu, 2010; Vorou et al., 2007; Yilmaz et al., 2009). The vast majority of reported cases have been in Turkey. The causative agent is the CCHF virus (CCHFV), which belongs to the *Nairovirus* genus of the *Bunyaviridae* family (Bente et al., 2013). The major transmission route of the virus is contact with blood or tissues of viraemic hosts via skin or mucous membranes or the bite of with *Hyalomma* ticks (Vorou et al., 2007). Humans are the only known host to develop disease after exposure to the CCHFV. The clinical spectrum of the illness varies from asymptomatic or mild infections to severe disease and death. In endemic regions, most of the patients, with a rate of 88%, have subclinical infection (Bodur et al., 2012). The main laboratory features are thrombocytopenia, leukopenia, prolonged bleeding times and elevated liver enzymes (Leblebicioglu, UpToDate, 2015). In severe cases, hemorrhagic manifestations develop 3–6 days after the onset of symptoms (Vorou et al., 2007). Reported fatality rates range from 4 to 20%, depending on the geographic region and quality of health care (Leblebicioglu et al., 2016a). It also tends to vary inversely with the number of patients and may be high for small anectodal reports or low for large studies. In Turkey, mortality rate was reported as 4.8% on average (Leblebicioglu et al., 2016b). Currently, there is no effective antiviral therapy approved for CCHF (Ascioglu et al., 2011; Bodur et al., 2011; Ceylan et al., 2013; Elaldi et al., 2009; Koksal et al., 2010). Supportive therapy is the main approach for managing the disease (Leblebicioglu et al., 2012). Although there is no evidence-based guideline defining discharge protocols, discharge of the patient who prone to bleeding must be avoided (Leblebicioglu et al., 2016c).

The investigations by now presented that several factors can influence the course and outcome of CCHF, such as the viral load, host immune response and host genetic factors. However, we have limited data about the relationship between genotypes of the virus and the severity of the disease. Although CCHFV presents a high genetic diversity, there is no obvious correlation between viral genetic diversity and pathogenicity for humans (Burt and Swanepoel, 2005; Deyde et al., 2006). On the other hand, adaptation of the virus to hosts living in different regions may lead to variations in pathogenicity of the virus. For example, while AP92 strains were previously detected in asymptomatic or mild infections in Greece and Turkey (Antoniadis A and Casals, 1982; Midilli et al., 2009; Elevli et al., 2010; Ozkaya et al., 2010), a recent case report presented the first fatal case of CCHF due to AP92 like strain in Iran (Salehi-Vaziri et al., 2016). Additionally, there are some data considering a relationship between M segment reassortment and increased severity of CCHF infection (Burt et al., 2009).

The prediction of the clinical course of the disease enables the physician to plan appropriate management of the patient. One of the most important reason to attempt to identify reliable prognostic markers is to help doctors decide which patients can safely be admitted to a local hospital and which patients should be transferred to tertiary medical centres, where they can receive intensive supportive care. Numerous studies have reported prognostic factors in CCHF. These studies examined clinical data and laboratory findings to detect the risk factors that determine the severity of the disease. However, large variability in the data means that the findings are not useful for clinicians in routine practice. The aim of the current review is to summarise the results of diverse studies of the prediction of the prognosis in CCHF based on epidemiological, clinical and laboratory findings of the disease and make some suggestions for the further investigations.

The literature search was conducted of peer-reviewed publications from January 1, 1957 to April 25, 2016, in PubMEd, Scopus and Science Citation Index (SCI)-Expanded databases using the following keywords: “hemorrhagic fever, Crimean” [MeSH terms] OR “hemorrhagic” [All Fields] AND “fever” [All Fields] AND “Crimean” [All Fields]) OR “Crimean hemorrhagic fever” [All Fields] OR “Crimean” [All Fields] AND “Congo” [All Fields] AND “haemorrhagic” [All Fields] AND “fever” [All Fields]) OR “Crimean Congo hemorrhagic fever” [All Fields] OR “Crimean Congo hemorrhagic fever” [All Fields] combined with the terms “incidence” *OR* “follow-up studies” *OR* “mortality” *OR* “prognosis*” *OR* “predict*” *OR* “course”. Comparative studies that had performed a statistical analysis on the prognosis of the disease and that were written in English were included. Short reports, studies written in languages other than English or those that included paediatric patients were excluded. Two authors (E.A. and H.B.) independently selected the studies. The PubMed search identified 1202 studies with terms related to CCHF, **295** of which included terms related to the prognosis. Among these, 60 studies met the inclusion criteria. In this review, all these studies were evaluated and recommendations for future studies are provided.

## 2. Prognostic factors to aid clinical decision making

### *2.1. Clinical findings and routine biochemical tests early in the disease course*

Early prediction of the clinical course of the disease may be lifesaving. It’s important for clinicians to be aware of clinical and laboratory features of CCHF patients that make it possible to predict the future course of illness, to plan appropriate management and transport the patient to a tertiary care hospital on time for intensive care. It was suggested that for optimal management of the patients, the prognosis should be established during the first 5 days of the illness (Swanepoel et al., 1989).

Swanepoel et al. (1989) reported the first study on prognostic factors of CCHF in 1989. In this study clinical characteristics of 15 fatal and 35 nonfatal CCHF cases in South Africa were evaluated. The authors reported that changes in abnormal clinical pathological values were more marked in fatal than in nonfatal cases. Thrombocyte counts were extremely low from the early stage of the disease in fatal patients, and early onset of thrombocytopenia was reported as indicative of a poor prognosis. While leukopenia was recorded in the early stage of the disease in survivors, initial total leukocyte counts were within normal ranges or elevated