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Evaluation of epidemiological, clinical, and laboratory characteristics and mortality rate of patients with Crimean-Congo hemorrhagic fever in the northeast region of Turkey

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ABSTRACT

Background & objectives: Crimean-Congo hemorrhagic fever (CCHF), an illness characterized by fever and hemorrhage, is caused by a CCHF virus (CCHFV). It is an important public health problem in Turkey. The objective of this study was to evaluate the demographic, clinical, and laboratory characteristics and mortality rates of CCHF patients in the northeast region of Turkey.

Methods: A total of 206 patients, diagnosed with CCHF, from northeast region of Turkey were included and evaluated between 2011 and 2017. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence (IFA) methods were used for the diagnoses.

Results: Of the patients included in the study, 77.2% were farmers/livestockers, while 22.8% had other occupations. The incidence of tick bite or tick contact with bare hands was 52.9%. About 94.2% of the patients were living in rural areas and 5.8% in city centers. However, all the patients living in city centers had a history of visit to rural areas. The disease was more common in May, June, and July months. The most common symptoms at the time of admission included fatigue, fever, and widespread body pain, while laboratory findings were thrombocytopenia, leukopenia, and anemia. Bleeding, tachycardia, and rash were the most common findings on physical examination. Of all the patients, 95.6% were identified by RT-PCR and 4.4% by IFA methods. Severe cases constituted 22.3% (46) of the included patients. Throughout the course of this study, 7 (3.4%) patients died, and the remaining 96.6% (199) patients were discharged with a full recovery. Disease severity was significantly correlated with mortality rate and duration of hospitalization (p <0.001 and p = 0.013).

Interpretation & conclusion: In this study, the mortality rate observed was lower than that reported in the literature because of accessibility of early supportive therapy. It would be beneficial in CCHF treatment to recognize the disease at an early stage, begin supportive treatment quickly, and educate the people living in high-risk areas as well as health care personnel working in these areas.

Keywords Clinical; Crimean-Congo hemorrhagic fever; epidemiology; laboratory; tick; treatment; Turkey

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is an illness characterized by fever and hemorrhage and is caused by the CCHF virus (CCHFV; Family Bunyaviridae, Genus *Nairovirus*)[1]. CCHF is a fatal disease that has a severe course in humans. This infection is caused by CCHFV and has been reported in Asia, Europe, Africa, and the Middle East[2]. The virus is carried by ticks in the *Hyalomma* genus, especially *H. marginatum*[3]. Humans become infected after being bitten by infected ticks or through contact with tissue or blood of human or viraemic animals that are in the acute phase of the disease[4].

While the clinical spectrum of the disease varies from mild to moderate or severe infection, some cases result in death[5]. CCHF is initially characterized by non-specific symptoms and clinical features such as fatigue, widespread muscle/joint pain, headache, nausea, vomiting, diarrhoea, and fever[6]. However, patients with a severe course develop hepatosplenomegaly, vascular disorders, and bleeding. Laboratory findings mainly include thrombocytopenia, leukopenia, elevated liver enzyme levels, and a prolongation of hemorrhagic markers. Mortality rates are between 4–20% depending on the geographical region and the quality of health care services[5, 7].

CCHF is an important public health problem in

Turkey due to its high mortality rate[8]. In Turkey, the first CCHF cases were reported in the Kelkit Valley, but cases are now encountered yearly, resulting in numerous mortalities in several regions, including Erzincan[9]. The objective of this study was to evaluate the demographic, clinical, and laboratory characteristics along with the mortality rates of CCHF confirmed patients in the northeast region of Turkey followed up for seven years.

MATERIAL & METHODS

Study area

The study was performed in an area of 13,564 km^2 between 40° 6' 15.26'' N latitude and 39° 52' 4.73'' E longitude covering Erzincan, Gümüşhane, Bayburt, Bingöl, Giresun, Sivas, and Tunceli provinces (Fig. 1). This region is affected by the climates of both the Black Sea and Eastern Anatolia regions. The study area covered numerous mountains and plateaus and is located in the eastern part of the Kelkit Valley. The Kelkit Valley where agriculture and animal husbandry are common is endemic for tick population.

Study population and scoring system

The study was performed retrospectively by using the database of Mengucek Gazi Training and Research Hospital, Erzincan University, Erzincan. The data of CCHF patients, hospitalized and treated in the Infection Diseases and Clinical Microbiology clinic between 2011 and 2017 were screened. Patients with contagious [hepatitis A, B, and C viruses (HAV, HBV, HCV), herpes viruses, human immunodeficiency virus (HIV), malaria, *Brucella*, and *Leptospira*] and non-contagious (*e.g.* hematological diseases leading to thrombocytopenia) diseases were eliminated; and a total of 206 CCHF patients were included in the study. Patient demographics, such as age, gender, epidemiological history, address, and occupation; date of hospital admission; existing symptoms; physical examination findings; and daily laboratory outcomes were recorded. In addition, the length of the hospitalization and the mortality rate were calculated. The patients were defined as mild to moderate or severe cases based on the severity grading score system defined by Bakir *et al*[10–11].

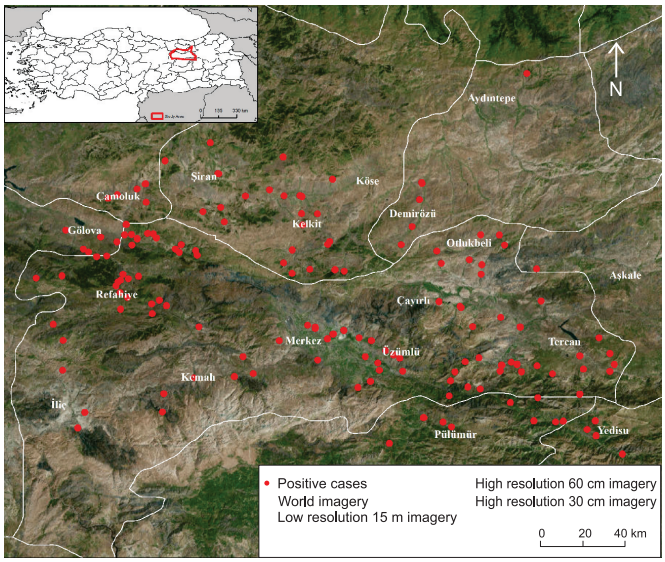

Fig. 1: Distiribution of CCHF positive cases in the Kelkit Valley, Turkey.

Laboratory testing

Patients' diagnoses were confirmed in the Turkish Public Health Authority, Department of Microbiology Reference Laboratories, National Virology Reference Center Laboratory, Ankara, Turkey (THSK-MRLDB). Real-time reverse transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence (IFA) methods were used for the CCHF diagnosis. For this purpose, viral RNA was isolated from the patients' blood samples using the High Pure Viral Nucleic Acid Kit (Roche Diagnostics GmbH, Germany). Written consent was obtained from all the participants. The presence of CCHFV RNA was tested using the TaqMan-based single-step RT-PCR as described by Yapar *et al*[12]. This method was run using a combination of reverse transcriptase (MBI Fermentas, Germany) and Hot Start Taq DNA polymerase (Bioron GmbH, Germany) with the Perkin-Elmer 7700 Sequence Detection System (Applied BioSystems, USA). In the IFA method, CCHF virus IgM antibodies (CCHFV Mosaic 2, Euroimmun Labordiagnostika AG, Germany) were studied in accordance with the recommendations of the manufacturer.

Laboratory tests were closely monitored at the time of admission and during daily follow-up examinations. Accordingly, white blood cells, platelet count, hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine phosphokinase (CK), plasma creatinine, prothrombin time, aPTT, and international normalized rate (INR) were recorded.

Mapping

The study used ArcMap 10.3.1 software (ESRI, Redlands, CA, USA) and the Google Earth Pro program (Google, Mountain View, CA, United States of America) to draw and analyze maps (Fig. 2). We started our analysis by first drawing the Kelkit Valley. Locations of the cases were identified in the Google Earth Pro program and transferred to the ArcGIS software and then baseline data were created using the ArcGIS Basemap Open Street Map service. For spatial analysis, distance analyses were

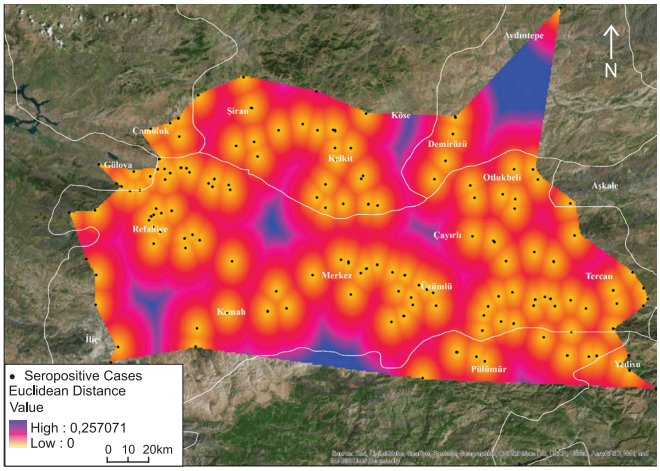

Fig. 2: Mapping of CCHF positive cases using Euclidean distance analysis in the study area.

performed to determine the intensity of the cases in the study area[13]. Euclidean distance is defined as the distance of a straight line between two points on a plane[14], and by means of this analysis, the distance of each pixel to other pixel was measured on the raster map[15]. Euclidean distance analysis enabled us to determine where positive cases were concentrated (Fig. 2).

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, Windows version 21.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable (gender, age group, occupation, unprotected contact, place of living, symptoms, physical examination findings and laboratory findings) were determined. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Median and minimum-maximum values were used for variables without normal distribution. Statistical significant differences between the groups were determined by Chi-square test for categorical variables (disease severity and sex, anaemia, occupation). Non-parametric statistics (Mann-Whitney U) were used for continuous variables. A statistically significant difference was considered when the p-value ≤ 0.05.

RESULTS

In the study, 104 (50.5%) of the 206 adult patients diagnosed with CCHF were male and 102 (49.5%) were female, with a median age of 53 (Range: 17–87) years. No statistically significant difference was observed in the incidence of the disease between the genders. Of the patients included in this study, 159 (77.2%) were farmers/livestockers, while 47 (22.8%) were from the other occupations. Tick bite/tick contact with bare hands was detected in 109 (52.9%) patients. Of these, 104 (50.5%) had a history of tick bite and 5 (2.4%) had a history of contact with ticks without biting or gripping/crushing the ticks stuck to animals with their bare hands. Unprotected direct contact with blood/tissue and other body fluids of animals was found in 109 (52.9%) patients, and direct contact with blood and body fluids of infected patients was detected in 3 (1.5%) patients. Of all patients, 194 (94.2%) were living in rural areas and 12 (5.8%) in city centers. All the 12 patients who lived in city centers had a history of temporary visit to rural areas (Table 1). Although, the disease was observed in all areas where the study was conducted, the patients were more commonly from Refahiye, Tercan, and Kelkit counties and central villages of Erzincan province (Figs. 1 and 2). The disease was observed only between March and September every year, but it was more common in May, June, and July months (Fig. 3).

Patients' duration of referral to the hospital after the onset of complaints compatible with CCHF varied from 1 to 9 (median: 3) days. The most common symptoms seen in patients at the time of admission included fatigue, fever, widespread body pain, headache, nausea/vomiting, and abdominal pain. Physical examinations revealed tachycardia in 23 (11%), rash in 14 (6.8%), hypotension in 11 (5.3%), and mental fog in 7 (3.4%) patients. Bleeding was seen in 25 (12.1%) patients and was most com-

Table 1. Demographics and epidemiological characteristics of 206 patients

Characteristics	No. of patients
Gender	
Male	104 (50.5)
Female	102 (49.5)
Age group (yr)	
10–19	9 (4.4)
20–29	23 (11.2)
30–39	25 (12.1)
40–49	29 (14.1)
50–59	45 (21.8)
60–69	45 (21.8)
70–79	26 (12.6)
80–89	4 (1.9)
Occupation	
Farming/Husbandry	159 (77.2)
Other	47 (22.8)
Unprotected contact	
Tick bite/Tick contact with bare hands	109 (52.9)
Contact with animal blood/tissue and other body fluids	109 (52.9)
Contact with blood/body fluids of infected people	3 (1.5)
Place of living	
City center*	12 (5.8)
Rural area**	194 (94.2)

*All the 12 patients living in city centers had a history of temporary visits to rural areas; **Counties, towns, and villages; Figures in parentheses indicate percentages.

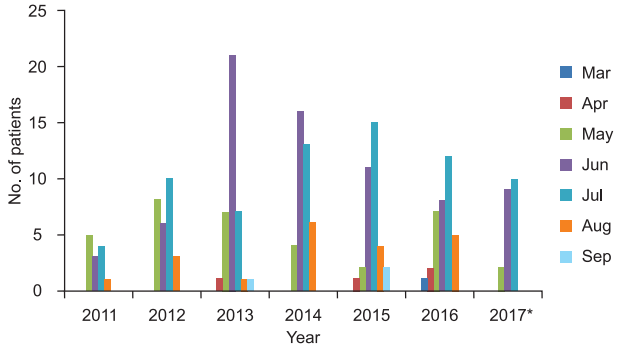

Fig. 3: Distribution of patients by years and months. The incidence of CCHF was generally found to be higher and statistically significant in May, June, and July compared to the other months every year. *In 2017, the patients followed up until the end of July were included in the study.

monly found as ecchymosis in the skin in 5 (2.4%) and as epistaxis in 5 (2.4%) patients. In addition, petechia was detected in 4 (1.9%), vaginal bleeding in 4 (1.9%), gum bleeding in 3 (1.4%), bloody diarrhoea in 3 (1.4%), and hematuria in 3 (1.4%) patients.

Laboratory findings at the time of admission included leukopenia in 188 (91.2%), thrombocytopenia in 198 (96.1%), and anaemia in 29 (14%) patients. All the eight patients without thrombocytopenia at admission developed thrombocytopenia during the subsequent follow-up period. Elevated AST and ALT was found in 170 (82.5%), elevated LDH in 173 (84%), elevated CK in 152 (73.8%), and elevated INR in 38 (18.4%) patients. All patients' symptoms, physical examinations, and laboratory findings detected at the time of admission are shown in Table 2 in order of frequency.

Table 2. Symptoms, physical examinations, and laboratory findings of 206 patients

Characteristics	No. of patients
Symptoms	
Fatigue	201 (97.5)
Fever	185 (89.8)
Widespread body pain	190 (92.2)
Headache	186 (90.3)
Nausea/Vomiting	128 (62.1)
Diarrhoea	58 (28.1)
Physical examination findings	
Tachycardia	23 (11.1)
Rash	14 (6.8)
Hypotension	11 (5.3)
Mental fog	7 (3.4)
Laboratory findings	
Leucopenia (<4000/mm^3)	188 (91.2)
Thrombocytopenia (<150,000/mm^3)*	198 (96.1)
Anemia (<12.5 gr/dL)	29 (14)
Increased AST/ALT (>40 U/L)	170 (82.5)
Elevated LDH (>450 U/L)	173 (84)
Elevated CK (>240 U/L)	152 (73.8)
Elevated INR (>1.2 sec%)	38 (18.4)

*All the eight patients with normal platelet values at hospitalization developed thrombocytopenia during their follow up; Figures in parentheses indicate percentages.

CCHFV RT-PCR was positive in 197 (95.6%) patients. IgM antibody positivity was detected in all the nine patients who had a negative RT-PCR. Of all the patients, 160 (77.7%) were assessed as mild to moderate cases, and 46 (22.3%) as severe cases. While all the patients received supportive therapy, blood and blood products were given to 41 of 46 (89.1%) severe cases. No ribavirin or other antiviral treatments were used in any of the patients. Patients' hospitalization varied between 1 to 15 (Median: 7) days. Throughout the course of the study, 7 (3.4%) patients died, and the remaining 199 (96.6%) patients were discharged with a full recovery. All the patients who died were in the severe course group. Mortality in the patients occurred within 5 to 19 (Median: 7) days after the onset of clinical symptoms and 3 to 15 (Median: 4) days after the hospitalization.

When the groups were compared according to severity scoring of the disease, disease severity was found to be significantly correlated with mortality rate, and duration of hospitalization (p <0.001 and p = 0.013). The mean duration of hospitalization was 6 (1–14) in patients with mild-to-moderate course, and 7.5 (3–15) days in patients with severe course. No significant correlation was found between disease severity and the parameters of occupation, sex and anaemia (p >0.05).

DISCUSSION

Crimean-Congo hemorrhagic fever is one of the most common tick-borne viral infections worldwide. It is a fatal disease prevalent in Asia, Africa, and Europe[4]. This study evaluated the demographic, clinical, and laboratory characteristics and mortality rates of CCHF patients in the northeast region of Turkey near eastern part of Kelkit Valley. A total of 206 patients who were referred from the seven provinces located in the study area were enrolled in the study between 2011 and 2017. Of all the patients, 194 (94.2%) were living in rural areas and dealing with farming/husbandry, only 12 (5.8%) patients were living in city centers. However, these 12 patients had a history of either travel to rural areas or tick contact/bite. These data demonstrate the importance of questioning the epidemiological and detailed medical history of patients, particularly at the time of first admission to health centers.

CCHF is an endemic disease in Turkey and was first detected in 2002. Thereafter, since 2004, many cases have been reported from various parts of Turkey[16]. According to the Ministry of Health data[17], a total of 10,219 CCHF cases were reported in Turkey between 2002 and 2016.

The disease has been reported from many provinces, especially Tokat, Yozgat, Çorum, Sivas, Gümüşhane, and Bayburt. CCHF is endemic in and around Kelkit Valley, which also includes these provinces and is located in the northeast of Turkey[18].

CCHF disease is usually transmitted to humans during the blood-sucking process by the virus-infected ticks. Another known way of transmission includes contact with blood and body fluids of viremic animals or infected patients[19–20]. In the present study direct transmission from a tick was considered in 109 (52.9%) patients as they had direct tick contact/bite; 97 (47.1%) patients had no history of tick contact/bite. The transmission in them might have occurred earlier through viremic animals or a tick contact/bite, which they were not aware of. This assumption was made because the vast majority of the patients (77.2%) were farmers/livestockers. Three patients (1.4%) had a history of close contact with a patient diagnosed with CCHF within the previous two weeks. CCHF was detected in the spouses of two and in a first-degree relative of one of these three patients. One of the patients thought to be infected from his spouse, died. CCHF shows seasonal characteristics and is more common in the months when the activation of ticks is higher. In general, the disease is typically seen between April and September in the country. The disease is mostly commonly seen in June and July[21–22]. Similarly, most of the cases were found in May, June, and July in this study. The number of cases decreased with the cooling weather again, and no disease was seen after October.

In CCHF, symptoms usually present with an acute onset. High fever, fatigue, headache, weakness, and widespread muscle and joint pain are commonly seen in patients. In severe cases, the patient may become agitated with mental fog. Rash and conjunctival hyperemia in the face, trunk, and extremities have frequently been reported[23–24]. In addition, because of the tendency to bleed, notably subcutaneous hemorrhages and nasal and gum bleeding, findings such as hematuria, hematemesis, vaginal bleeding, and bleeding into the viscera have been commonly reported[25–26]. Similar to other studies, mostly fever, headache, fatigue, and widespread muscle and joint pain were detected in patients during admission. Nausea, vomiting, diarrhoea, and rash were less commonly identified. A common feature of bleeding patients was that they were in the severe case group and there was a rapid decrease in their platelet counts. Therefore, blood and blood products were provided to these patients in addition to the supportive therapy. In this study, 23 of the 29 patients detected with anemia were in the mild-to-moderate group, and none of these patients had bleeding. The rate of anemia was higher than reported in the literature. Those patients might have suffered from anemia independent from CCHF. In CCHF, supportive therapy is the basis of treatment. Many studies have claimed that ribavirin treatment should or should not be given. In some of these studies, ribavirin has been reported to be effective *in vitro* against the CCHF virus, in reducing the mortality, and it should be used especially in the early stage of the disease[27–28]. Alternatively, the use of ribavirin has not been recommended by several studies[29–32]. In the present study, all patients were treated with supportive therapy. In addition to supportive therapy, fresh frozen plasma (FFP) was given to the patients with bleeding, aPTT > 60 sec, and INR > 1.5. Furthermore, platelet suspension was given to the patients with a platelet count < 20,000/mm^3, and an erythrocyte suspension was given to those who developed anemia, and complete blood when necessary. Accordingly, a total of 51 (24.7%) patients received blood and blood products, and none of patients was given ribavirin treatment. In our opinion, ribavirin is not required for mild CCHF patients.

The mean mortality rate from CCHF is around 5% in Turkey[33]. This mortality rate in Turkey is lower than the rates reported by other countries. The main reasons for these are more common occurrence of mild to moderate cases, a good surveillance system, and relatively good treatment facilities across the country. In addition, the CCHFV strain identified in the country was significantly homologous with the strain identified in Russia and Kosovo (formerly Yugoslavia)[22], and the mortality rate in the CCHF cases caused by similar strains was lower than that of other regions[31, 34–35.] The mortality rate in this study was 3.4%, which is lower than the rates reported in the literature. Several factors might be playing a role for this low mortality rate. Mainly, in all regions where the disease is endemic in Turkey, yearly educational activities are carried out throughout the year. In line with the recommendations of the Ministry of Health, family physicians and other health care staff are trained every year before the CCHF season begins. As a result of these training activities, awareness in both physicians/health care workers and the public has increased, leading to easier and higher detection of mild to moderate cases as observed in this study. Particularly, mild to moderate events can be easily confused with many diseases, such as a simple upper respiratory tract infection, thus, causing a misdiagnosis.

CONCLUSION

CCHF remains a serious seasonal problem in the study area and in certain endemic regions of Turkey. A worldwide recognized vaccine with proven efficacy to

protect against the disease, or a specific antiviral drug that can be used in treatment, has not yet been developed. Although the use of ribavirin has been recommended in several studies, we believe that patients with mild CCHF do not need ribavirin therapy. Recognition of the disease at an early stage and, especially a rapid initiation of supportive treatment, constitute the most important steps of treatment. Educating the people living in risky areas and the health care personnel working in these areas for raising their awareness about the disease would further help in minimizing its burden.

Conflict of interest

The authors declare that there is no conflict of interest in this study.

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