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# Crimean-Congo hemorrhagic fever cases in the eastern Black Sea Region of Turkey: demographic, geographic, climatic, and clinical characteristics

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**Aim:** Crimean–Congo hemorrhagic fever (CCHF) is a disease that is known since 1944 affecting many people across the world and causing a high mortality rate. The aim of this study was to determine the epidemiological and clinical characteristics of the CCHF cases in our region.

**Materials and methods:** The present study was conducted in patients with CCHF who were hospitalized between 2004 and 2006 at Karadeniz Technical University. Demographic, geographic, climatic, and clinical characteristics of all patients were investigated.

**Results:** A total of 102 patients with confirmed CCHF were investigated in this study. All of the patients were from rural areas. Eighty-seven patients (85.2%) were livestock workers. None of the cases was from the region where mountain range faced the sea and all cases were from areas of Harşit, Kelkit, and Çoruh valleys situated at 1100-2265 m above sea level where the mountain ranges ceased to separate the sea and inner regions and streams reached the sea.

**Conclusion:** CCHF case series have been reported from Turkey as well and particularly Middle Anatolia and northeastern regions have been determined as endemic areas recently. Population of those regions mostly earns their life from livestock breeding and agriculture, which increases the risk of exposure to ticks and development of CCHF. Therefore, especially in cases coming from regions categorized as endemic, it has been concluded that mortality can be reduced by carefully taken medical history and practice of rapid medical treatment and replacement therapies in consideration of CCHF pre-diagnosis.

**Key words:** Crimean–Congo hemorrhagic fever, CCHF, viral hemorrhagic fever

## Türkiye'nin Doğu Karadeniz bölgesindeki kırım-kongo kanamalı ateş vakaları: demografik, coğrafik, iklimsel ve klinik özellikler

**Amaç:** Kırım-Kongo Kanamalı Ateşi (KKKA) 1944 yılından beri bilinen, dünyada birçok insanı etkileyen ve mortalite oranı yüksek olan bir hastalıktır. Bu çalışmanın amacı bölgemizdeki KKKA olgularının epidemiyolojik ve klinik özelliklerini belirlemekti.

**Yöntem ve gereç:** Sunulan çalışma Karadeniz Teknik Üniversitesinde 2004-2006 yılları arasında hastanede yatırılan KKKA'lı hastalarda yapıldı. Hastaların demografik, coğrafik, iklimsel ve klinik özellikleri incelendi.

**Bulgular:** Bu çalışmada KKKA'li toplam 102 hasta incelendi. Hastaların hepsi kırsal kesimde yaşıyor ve %85.2'si hayvancılık yapıyordu. Hiçbir vaka sıradağların denize bakan yüzeyindeki bölgeden olmayıp, vakaların deniz ile iç bölgeleri ayıran sıradağların kesildiği ve akarsuların denize ulaştığı Harşit, Kelkit ve Çoruh Vadileri'ndeki denizden yükseklikleri 1100-2265 m arasındaki yerleşim alanlarından geldiği tespit edildi.

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**Sonuç:** Son yıllarda Türkiye'den de KKKA vaka serileri bildirilmeye başlanmış olup, özellikle ülkemizin Orta Anadolu ve Kuzeydoğu bölgeleri hastalık açısından endemik bölgeler olarak belirlenmiştir. Bu bölgelerde halkımız geçimini genel olarak tarım ve hayvancılıkla sağlamakta olup, bu durum kene ile temas riskini artırarak KKKA gelişimine neden olabilmektedir. Bu nedenle özellikle endemik olarak kabul ettiğimiz bölgelerden başvuran hastalarımızın epidemiyolojik hikayelerinin dikkatlice sorgulanması, KKKA ön tanısının düşünülerek yapılacak hızlı tıbbi müdahale ve replasman tedavileri ile mortalitenin düşürüleceği kanısına varılmıştır.

**Anahtar sözcükler:** Kırım-kongo kanamalı ateşi, KKKA, viral kanamalı ateş

## Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a disease caused by Crimean-Congo Hemorrhagic Fever Virus (CCHFV) belonging to the Nairovirus genus of Bunyaviridae family. The disease has been reported in Asia, Europe, Africa, and the Middle East (1,2). As encountered in countries neighboring Turkey, such as Russia, Iran, Yugoslavia, and Bulgaria, it has also been reported in Turkey recently (3-11).

Eastern Black Sea Region of Turkey is split into 2 as north and south by mountains spanning parallel to the sea with heights varying between 1500 and 3700 m. Harşit stream, Çoruh stream, and Kelkit stream, situated in the southern aspect of those mountains, flow northwards from 3 different points and reach the sea. Those valleys in the southern part of Eastern Black Sea mountains are separated from Middle Anatolian Region by mountains situated again in the south with heights varying between 1700 and 3800 m. The reported case series in our country occur in this closed basin localized in the northeastern part of Turkey and in the habitats of this valley extending towards east and west (7-11).

The main transmission route of the virus to humans is known to be tick bite. Moreover, contact with patients at the viremic phase of the disease or exposure to tissue or blood of an infected animal can lead to the disease (1,2). The disease affects multiple organ systems and generally is characterized with fever, weakness, myalgia, or hepatic dysfunction (1,2). Furthermore, the patients may exhibit a reduction in plasma volume due to permeability increase or display hemorrhages because of defects in the coagulation system.

In the present study, demographic, geographic, climatic, and clinical characteristics of the CCHF cases in our region followed up for 3 years were analyzed and risk factors were evaluated. Moreover, the altitude and climatic conditions of the geography of the cases were assessed, as well.

## Methods

The present study was conducted in patients with CCHF who were hospitalized between 2004 and 2006 in the Department of Infectious Disease and Clinical Microbiology, Medical Faculty, Karadeniz Technical University. Patients whose CCHF diagnoses were confirmed through detection of IgM and IgG by ELISA and/or genomic segment of the virus by RT-PCR in Refik Saydam Hygiene Central were included in the study. Patients in whom infectious (hepatitis A, B, and C viruses [HAV, HBV, HCV], herpes viruses, HIV, malaria, brucella, and leptospira) and noninfectious diseases (hematologic diseases) were eliminated by routine tests.

Demographic, geographic, climatic, and clinical characteristics, occupation, tick exposure history, incubation time, symptoms, duration between onset of symptoms and admission, and laboratory tests (white blood cell count [WBC], platelet count [PLT], hemoglobin [Hb], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], creatine phosphokinase [CK], myoglobin [Mb], blood-urea-nitrogen [BUN] and plasma creatinine [Cr], prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR]) of all patients were recorded.

## Results

In this study, 102 patients with confirmed CCHF were investigated. Sixty-nine (67.6%) of the patients were female, and 33 of them (32.4%) were male. The mean age of the patients was 48.5 ± 18.4 (range: 7–77) years. Eighty-seven patients (85.2%) were livestock

workers. Seventy-five patients (73.5%) were farmers. Sixty-nine patients (67.6%) had a history of tick contact. All of the patients were from rural areas (Table 1). During the hospitalization, tick removal was applied to 3 patients.

Malaise, fever, myalgia, nausea, vomiting, diarrhea, abdominal pain, fatigue, and hemorrhage were the most common presenting complaints (Table 2). Hemorrhagic manifestations were observed in 29 patients (28.4%), including vaginal hemorrhage in 10 patients, hematemesis in 9 patients, melena in 4 patients, epistaxis in 3 patients, and gingival hemorrhage in 3 patients. Six patients had ecchymosis during hospitalization. Tache noir was observed in 10 patients (9.8%) at the site of the tick bite. The most commonly encountered signs were fever (≥38 °C), bleeding, and petechia.

Complete blood counts showed thrombocytopenia in 92 patients ($67 \times 10^3 \pm 49.7 \times 10^3$) and leukopenia in 95 ($2.6 \times 10^3 \pm 1.6 \times 10^3$) patients. While serum AST levels were elevated in 96 patients (424 ± 1051 U/L), ALT levels were increased in 84 patients (180 ± 299 U/L), LDH levels showed a rise in 99 patients (median: 1119 ± 1328 U/L), and CPK levels were elevated in 78 patients (710 ± 1050 U/L). AST values were higher than ALT values in all patients. Coagulation tests showed prolonged PT in 32 patients (14.7 ± 5.4 s), and aPTT in 19 patients (33.2 ± 7.7 s).

The leukopenia and thrombocytopenia of the patients showed improvement at 5.5 ± 2.8 (range: 1–12) and 6.6 ± 3.4 (range: 1–15) days respectively, whereas elevated ALT, AST, CPK, and LDH values dropped to normal levels at 5.8 ± 3.0 (range: 1–11), 6.3 ± 2.8 (range: 1–10), 3.4 ± 2.3 (range: 1–12), and 5.5 ± 3.3 (range: 1–13) days, respectively.

Table 1. Demographic characteristics of 102 patients with CCHF.

| Characteristic | Value |
|---|---|
| Age | 48.5 ± 18.4 |
| Sex | |
| Male | 33 (32.4%) |
| Female | 69 (67.6%) |
| Tending livestock | 87 (85.2%) |
| History of tick contact | 69 (67.6%) |
| Farming | 75 (73.5%) |
| Duration of hospitalization | 6.6 ± 3.4 |

Table 2. Symptoms and signs of the 102 patients with CCHF.

| Characteristics | n = 102 | % |
|---|---|---|
| Symptoms | | |
| Malaise | 99 | 97.0 |
| Fever | 87 | 85.2 |
| Nausea | 60 | 58.8 |
| Vomiting | 55 | 53.9 |
| Myalgia | 51 | 50.0 |
| Diarrhea | 27 | 26.4 |
| Abdominal pain | 20 | 19.6 |
| Fatigue | 12 | 11.7 |
| Hematemesis | 11 | 10.7 |
| Vaginal hemorrhage | 10 | 9.8 |
| Melena | 4 | 3.9 |
| Epistaxis | 3 | 2.9 |
| Gingival hemorrhage | 3 | 2.9 |
| Signs | | |
| Fever | 50 | 49.0 |
| Bleeding | 36 | 35.2 |
| Petechia | 26 | 25.4 |
| Abdominal tenderness | 17 | 16.6 |
| Hepatomegaly | 17 | 16.6 |
| Site of the tick bite | 10 | 9.8 |
| Lymphadenopathy | 7 | 6.8 |

**Geographic and Climatic Characteristics**

Eighty-four of these patients (82.3%) were from Gümüşhane, and the others were from nearby provinces, such as Giresun (n = 6), Artvin (n = 9), Trabzon (n = 1), Tunceli (n = 1), and Erzincan (n = 1); 64.7% of the cases were living in the valley of Harsit stream, whereas 25.4% were living in Kelkit valley, and 9.8% were living in the valley of Çoruh river. None of the patients was from the region where mountain range faced the sea and all cases were from areas of Harşit, Kelkit, and Çoruh valleys situated at 1100-2265 m above sea level where the mountain ranges ceased to separate the sea and inner regions, and streams reached the sea (Figure 1). All patients admitted in the spring and summer months when air temperatures rise above 20 °C. The largest number of patients (43.1%) was admitted in June (Figure 2).

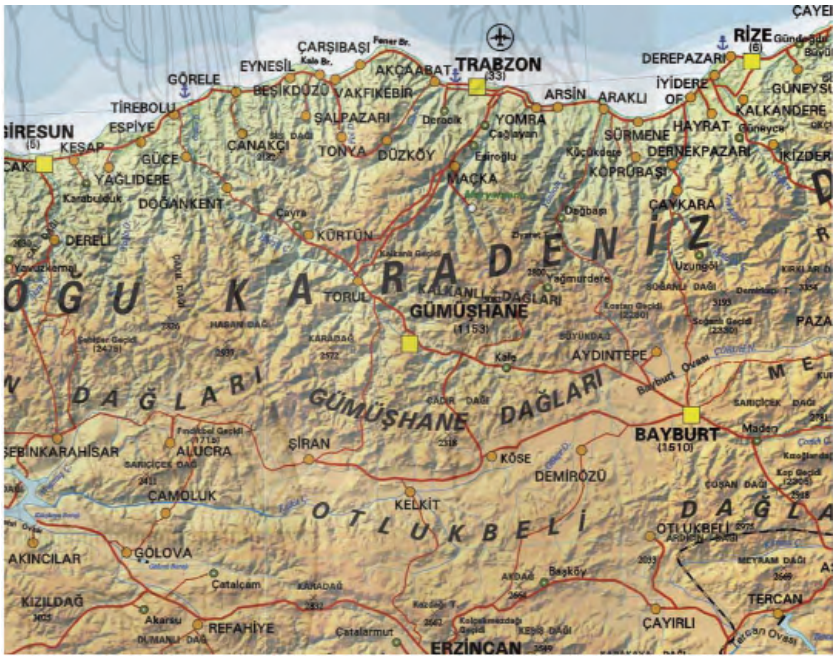


Figure 1. Physical map of the eastern Black Sea region (Harşit, Kelkit, and Çoruh valleys).

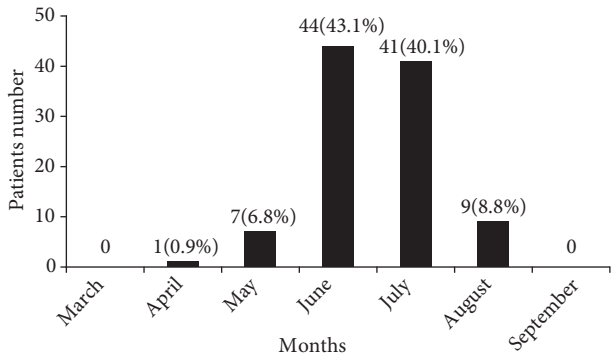


Figure 2. Distribution of the CCHF cases by months.

Based on the analysis of temperatures in the region, it was determined that at an altitude of 1100 m, temperatures rise above 20 °C from April on, but at an altitude of 1700 m they rise above 20 °C starting in June. Patients applied in July-August, in parallel to temperatures at 1700 meters and above.

## Discussion

CCHF was first described in Crimea in 1944. By 1969, the pathogen behind the disease was recognized to be the one responsible for febrile illnesses identified in the Congo. Since then, many human cases have been reported from different countries (1,2). Recently, many human cases have been reported across the world including Turkey (7-11). CCHF was found to be endemic in the middle, northern, and eastern Turkey (11).

The virus can be transmitted to humans by tick bites or by contact with blood or tissue of CCHF patients or infected livestock. Hence, farmers, slaughterhouse workers, veterinarians, people living in rural areas and handling livestock, and healthy personnel in epidemic areas have been described as the risk groups for CCHF (2,12). In our series, all of the patients were living in rural areas and in most of the cases they were livestock workers. Our region is located around Harşit and Kelkit Valleys. These valleys are probably highly suitable for tick activation. In the present study, female patients were dominant (67.6%). In our region, women work in all types of farming tasks and tend livestock in rural areas. Therefore, exposure of women may be as high as men.

Tick bite is the transmission route of the disease and crushing ticks during removal is hazardous (1).

There was a history of ticks in 69 (67.6%) patients, and tick bite was determined to be the risk factor for CCHF in our study. In other studies on this issue, having a history of tick bite, physical contact with ticks, and contact with livestock have been found to be the risk factors for CCHF (8,9).

CCHF patients may present with a spectrum of conditions varying from mild to severe clinical profile. The initial symptoms are generally nonspecific and patients frequently complain about fever, fatigue, generalized pain, muscle pain, nausea, and vomiting. In severe cases, hemorrhage may be one of the presenting symptoms. The hemorrhages observed in patients may be in the form of epistaxis, hematemesis, melena, hematuria, gingival bleeding, vaginal bleeding, petechia or ecchymosis as well as occult hemorrhage without any significant signs, which is reflected by symptoms such as hemorrhage-related abdominal pain (1,2,13). The most commonly reported presenting symptoms of our patients were fatigue, fever, nausea, vomiting, myalgia, diarrhea, and abdominal pain. While 85.2% of our patients presented fever, which was one of the most common presenting symptoms, the physical examinations carried out during admittance revealed 49% fever rate. Hemorrhage, petechia, abdominal tenderness, hepatomegaly, tick bite, and lymphadenopathy were the other common symptoms following fever in an incidence. The results and symptoms of patients in the case series reported in the literature showed consistence with the results and symptoms observed in our study (4,7-9,12,14-16).

Routine laboratory analyses carried out on admittance revealed leukopenia and thrombocytopenia in most of the patients, and indicated high ALT, AST, CPK, LDH, and myoglobin levels. Those laboratory findings were remarkable for the patients that exhibited risk factors of CCHF in their epidemiological history and came from a region endemic for CCHF who presented to our hospital with symptoms such as fever, myalgia, generalized pain, and fatigue. Particularly elevated CPK is found to be remarkable because it reflects the common symptoms of fatigue and myalgia. Karti et al., who worked in our hospital as well, conducted a study on CCHF series and reported elevated CPK levels in 14 (75%) cases verified for the CCHF, which was thought to be associated with myositis (7). Similar to the results of our study, Ergönül et al. performed a study on a CCHF case series and reported that all the patients had leukopenia and thrombocytopenia along with high levels of ALT, AST, CPK, and LDH as they underscored the fact that 86% of their cases had more severe results (8). Ozkurt et al. determined that 90% of their patients had leukopenia while 98.3% had thrombocytopenia as they found high levels of ALT and AST in all cases and elevated CPK in 90% of the patients (9).

As 32 (31.3%) patients demonstrated high PT, 10 patients exhibited elevated aPTT and these high values were remarkable due to their value in determining the damage caused in liver by the CCHFV. The vascular endothelial damage, accompanying thrombocytopenia, and elevated PT and aPTT levels caused by CCHFV associated with the pathogenesis of the disease, lead to hemorrhages and widespread ecchymosis (2).

The CCHF cases in the present study were not observed in the northern faces of the Eastern Black Sea mountains, all the cases were determined in habitats situated at 1100-2265 m above sea level. Even if no case of CCHF was encountered in our region below altitudes of 1100 m and at sea level, it must not be forgotten that infected ticks may pass through these areas during the trading and transportation of animals and animal feeds. The fact that temperatures rise above 20 °C at altitudes of 1700 m and above toward the end of June and that patients in the region apply in July-August confirms the correlation with CCHF. Hence, climate and geography are thought to be important factors in infected ticks and CCHF. The basin created by Kelkit stream extends westwards and joins Yeşilırmak river basin within the borders of Tokat province before reaching Black Sea in Samsun. Similar to our study, the studies of Ergonul, Bakir, and Ozkurt included cases living in those regions (8-10).

In conclusion, CCHF is a disease that is known since 1944 affecting many people across the world and causing a high mortality rate when not treated early. Recently, case series have been started to be reported from Turkey as well and particularly Middle Anatolia and Northeastern regions have been determined as endemic areas. As patients included in both our and other investigators' studies were living in the inner

areas separated from the sea by mountain ranges of 1100-2265 m and because patients present during April-August when temperature rises above 20 °C, it may be concluded that CCHFV requires specific conditions for living and infecting. People of those regions mostly earn their life by livestock breeding and agriculture, which increases the risk of exposure to ticks and thus the development of CCHF. Therefore, especially in cases coming from regions categorized as endemic, it is concluded that mortality can be reduced by carefully taken medical history and practice of rapid medical treatment and replacement therapies in consideration of CCHF pre-diagnosis.

## References


1. Ergonul O. Crimean-Congo Hemorrhagic Fever. Lancet Infect Dis 2006; 6: 203-14.
2. Whitehouse CA. Crimean-Congo haemorrhagic fever. Antiviral Res 2004; 64:145-60.
3. Papa A, Bino S, Llagami A, Brahimaj B, Papadimitriou E, Pavlidou V et al. Crimean-Congo Haemorrhagic Fever in Albania, 2001. Eur J Microbiol Infect Dis 2002; 21:603-6.
4. Mardani M, Jahromi MK, Naieni KH, Zeinali M. The Efficacy of Oral Ribavirin in the Treatment of Crimean-Congo Haemorrhagic Fever in Iran. Clin Infect Dis 2003; 36:1613-8.
5. Papa A, Bozovic B, Pavlidou V, Papadimitrou E, Pelemis M, Antoniadis A. Genetic detection and isolation of Crimean-Congo Hemorrhagic fever virus, Kosovo, Yugoslavia. Emerg Infect Dis 2002; 8:852-4.
6. Papa A, Christova I, Papadimitrou E, Antoniadis A. Crimean-Congo Hemorrhagic fever in Bulgaria. Emerg Infect Dis 2004; 10:1465-7.
7. Kartı SS, Odabaşı Z, Korten V, Yilmaz M, Sonmez M, Caylan R, et al. Crimean-Congo Haemorrhagic Fever in Turkey. Emerg Infect Dis 2004; 10:1379-84.
8. Ergönül Ö, Çelikbaş A, Dokuzoğuz B, Eren Ş, Baykam N, Esener H. Characreristics of patients with Crimean-Congo Haemorrhagic Fever in a Recent Outbreak in Turkey and Impact of Oral Ribavirin Therapy. Clin Infect Dis 2004; 39:284-7.
9. Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. J Infect 2005; 52:207-15.
10. Bakır M, Uğurlu M, Dokuzoğuz B, Bodur H, Taşyaran MA, Vahaboğlu H; Turkish CCHF Study Group. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures. J Med Microbiol 2005; 54:385-9.
11. Gunes T, Engin A, Poyraz O, Elaldi N, Kaya S, Dokmetas I, et al. Crimean-Congo hemorrhagic fever virus in high-risk population, Turkey. *Emerg Infect Dis* 2009; 15:461-4.
12. Jamil B, Hasan RS, Sarwari AR, Burton J, Hewson R, Clegg C. Crimean-Congo hemorrhagic fever: experience at a tertiary care hospital in Karachi, Pakistan. Trop Med Hyg 2005; 99:577-84.
13. Çelikbaş A, Ergönül Ö, Dokuzoğuz B, Eren Ş, Baykam N, Polat-Düzgün A. crimean-Congo hemorrhagic fever infection simulating acute appendicitis. J Infect 2005; 50:363-5.
14. Athar M, Baqai HZ, Ahmad M, Khalid MA, Bashir N, Ahmad AM, et al. Short Report: Crimean-Congo Haemorrhagic Fever Outbreak in Rawalpindi, Pakistan, February 2002. Am J Trop Med Hyg 2003; 69:284-7.
15. Sheikh AS, Sheikh AA, Sheikh NS, Shan RU, Asif M, Afridi F, Malik MT. Bi-annual surge of Crimean-Congo hemorrhagic fever (CCHF): a five-year experience. International J Infect Dis 2005; 9:37-42.
16. Altaf A, Luby S, Ahmed AJ, Zaidi N, Khan AJ, Mirza S, et al. Outbreak of Crimean-Congo haemorrhagic fever in Quetta, Pakistan: contact tracing and risk assessment. Trop Med Int Health 1998; 3:878-82.