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Original Article CLINICAL MICROBIOLOGY

Evaluation of epidemiological, clinical, laboratory and treatment characteristics of Crimen Congo hemorrhagic fever patients: Results of a 10-year analysis

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ABSTRACT

OBJECTIVE: Crimean-Congo hemorrhagic fever (CCHF) is a viral zoonosis transmitted by ticks and may have an acute and severe course with fever, bleeding, muscle aches, headache, diarrhea, weakness, and similar non-specific symptoms. This study aimed to determine the distribution of CCHF cases in Amasya province, which is endemic for this disease, according to districts, epidemiological, clinical, laboratory, and treatment characteristics.

METHODS: The characteristics of 88 CCHF cases over 18 who were admitted to our clinic and treated between January 2013 and January 2023 were evaluated retrospectively. Demographic data such as age, gender, occupation, district of residence, history of tick contact, the incubation period of the disease, period of development of the disease (months, years), length of hospital stay, symptoms, physical examination and laboratory findings, blood product replacement therapies applied, recovery and mortality status of the patients were reached by scanning the patient files.

RESULTS: The mean age (±standard deviation) of 88 cases was 48±18 years, and 53 (60.2%) were male. Of the patients, 68 (77.3%) were engaged in farming and animal husbandry, and 79 (89.7%) lived in villages and hamlets. Tasova district had the highest frequency of cases, with 29 (32.9%) patients. June was the most common month for the disease, with 31 (35.2%) cases. The most common symptom on admission was fatigue, with a rate of 93%. Other symptoms included myalgia and arthralgia (83.2%), fever (65%), headache (64.4%), nausea-vomiting (43.5%), conjunctival hyperemia (35.2%), and diarrhea (21.7%). In clinical follow-up, bleeding was missed in 15 (17.04%) patients. On admission to the hospital, there were elevated levels of thrombocytopenia (92%), leukopenia (84.1%), aspartate aminotransferase and alanine aminotransferase (86.3%), creatinine phosphokinase (71.6%), and lactate dehydrogenase (76.1%). None of the patients were given ribavirin treatment. Our mortality rate was 3.40% with three patients.

CONCLUSION: Amasya is an endemic area for CCHF with all its districts. In our province's spring and summer months, tick contact history and the farming-livestock profession should be questioned in patients with fever complaints in clinic admissions, especially emergency services. In the case of the detection of thrombocytopenia in these patients, CCHF should be kept in mind.

Keywords: Amasya; Crimean Congo hemorrhagic fever; mortality rate.

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Crimean Congo hemorrhagic fever (CCHF) is a tick-borne virus and is one of the leading causes of severe viral hemorrhagic fever in humans. The disease is seen in more than 30 countries in Asia, Africa, Southeastern Europe, and the Middle East, and the mortality rate is reported to be up to 30% [1]. The virus can be transmitted to humans by the bite of infected ticks of the Hyalomma genus or by direct contact with tissue, blood, and body fluids taken from infected animals and humans [2]. Within the tick's life cycle, the human becomes an intermediate host [3]. The disease was first seen in our country in 2002 in and around the province of Tokat, was diagnosed in 2003, and is still seen in a wide geographical area between the north of the Central and Eastern Anatolia Regions and the southern parts of the Black Sea Region [4]. According to the latest statistical data published by the Ministry of Health, the disease is most commonly seen in June and July in our country. While the number of cases increased yearly between 2002 and 2008, it decreased between 2008 and 2017. In 2017, 343 cases of CCHF were reported, and the crude mortality rate calculated between 2002 and 2018 was 4.78%.

In our country, where deaths due to CCHF continue to be seen, the disease still maintains its importance. Among the provinces where CCHF cases are most common are Tokat, Sivas, Corum, Yozgat, Amasya, Gumushane, Kastamonu, Karabuk, Erzurum, Samsun, Cankiri and Giresun [4, 5]. As a result of the increasing activity in animal trade, especially during the Eid al-Adha period, sporadic case reports are made from provinces other than these [6, 7].

Highlight key points

- The Crimean-Congo hemorrhagic fever (CCHF) virus is a tick-borne virus. It is one of the leading causes of severe viral hemorrhagic fever.
- The disease was first seen in our country in 2002, especially in the province of Tokat and its surroundings.
- It was placed in the year 2000 and is still in the north of the Central and Eastern Anatolian Regions and the Black Sea Region. It is seen in a wide geographical area between the southern parts.
- CCHF should be considered in patients living in the endemic region, who present with complaints of fever, fatigue, muscle-joint pain, and headache, and who have thrombocytopenia, leukopenia, elevated ALT, AST, LDH, and CK in laboratory tests.

MATERIALS AND METHODS

In this study, 88 CCHF cases over 18 who were hospitalized and treated in our institution between January 2013 and January 2023 were accessed by retrospective scanning of patient files. The data were analyzed by the Statistical Package for the Social Sciences (IBM SPSS 26, Armonk, New York, United States). The study has been approved by the Amasya University Clinical Research Ethics Committee (date: 06.04.2023, number: 2023/26).

Serum samples of the patients were tested in the Microbiology Reference Laboratory of the General Directorate of Public Health of the Ministry of Health, and the diagnosis was made by detecting the ribonucleic acid (RNA) positivity of the CCHF virus by "real-time" reverse transcriptase polymerase chain reaction (RT-PCR). Patients with positive serological tests (CCHF, immunoglobulin M, and immunoglobulin G) and negative PCR tests were excluded. Demographic data of patients such as age, gender, occupation, county of residence, period of development of the disease (year, month), history of tick contact, presenting symptoms, physical examination findings, length of hospital stay, the survival time of the patients lost and hemogram, C-reactive protein (CRP), creatine kinase (CK), lactic dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), activated partial thromboplastin time (aPTT), laboratory findings, blood and blood product treatments given to patients with bleeding, recovery and mortality status of patients were obtained from patient files. The study was carried out in accordance with the Helsinki Declaration.

RESULTS

The mean age (±standard deviation) of the 88 patients included in the study was 48±18 years, 53 (60.2%) were male, and 35 (39.8%) were female. The mean age of males was 46±17 years and 51±21 years for females. Of the patients, 68 (77.3%) were engaged in farming and animal husbandry, and 79 (89.7%) lived in villages and hamlets. In 35 (71.4%) patients with a history of tick attachment, the patient or a relative removed the tick before applying it to the health institution. In 14 (28.6) cases, tick removal was performed in the health institution. There were 39 (44.3%) patients with no history of tick attachment. Eight patients had plucked the ticks that had clung to their animals with their bare hands. In a patient with no history of tick contact, there was a history of contact

Table 1. Epidemiological and demographic data of Crimean-Congo hemorrhagic fever in Amasya in the last ten years

	%
Gender (n=88)	
Male	60.2
Female	39.8
Mean Age	48±18
Territory	
Rural (village)	89.7
City	10.3
Farmers and livestock	77.3
Contamination	
Tick attachment history	55.7
The helathcare facility where the tick was removed	28.6
Other than healthcare facility	71.4
Contact with animal blood and body fluids with bare hands	10.2
Touching a tick with bare hands	9.1
Undetermined route of transmission	25
Incubation period	4±2.4 days

Table 2. Clinical and laboratory characteristics of Crimean-Congo fever patients with hemorrhage at admission to hospital

	n	%
Fatique	82	93
Muscle-joint pains	73	83.2
Fire	57	65
Headache	57	64.4
Stomach ache	49	55.7
nausea-vomiting	38	43.5
Diarrhea	19	21.7
somnolence	5	5.7
Conjunctival hyperemia	31	35.2
Thrombocytopenia (<150.000/mm^3)	81	92
Leukopenia (<4000/mm^3)	74	84.1
Normal leukocyte count (4000–11000/mm^3)	8	9.1
Leukocytosis (>11.000/mm^3)	6	6.8
CRP elevation (>5 mg/L)	24	27.3
Anemia (Hemoglobin<12 g/dl)	13	14.7
AST-ALT elevation (>45 U/lt)	76	86.3
LDH height (>450 U/lt)	67	76.1
CK height (>240 U/lt)	63	71.6
PT/aPTT prolongation	46	52.2
INR height	32	27.3

CRP: C Reactive Protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatine kinase; PT: Prothrombin time; aPTT: A partial prothrombin time; INR: International normalized ratio.

with the blood and flesh of sheep slaughtered during the feast of sacrifice, and the case resulted in mortality. The other two cases resulted in mortality and a history of tick attachment. No transmission route could be detected in 22 (25%) patients. Table 1 lists the epidemiological and demographic characteristics of the patients.

The disease was seen in all districts of Amasya province. Tasova district had the highest number of cases, with 29 (32.9%) patients. There were 16 (18.3%) cases in Amasya/Merkez, 12 (13.7%) cases in Gumushacikoy, 11 (12.6%) cases in Goynucek, 8 (9%) cases in Merzifon, 8 (9%) cases in Suluova and 4 (4.5%) cases in Hamamozu (Fig. 1). Notably, 85.22% of the cases were concentrated in the three months covering May, June, and July. Figure 2 shows the distribution of case numbers by month and year.

The mean onset of complaints (incubation period) after ticking attachment in patients with a history of tick attachment was 4±2.4 days. In one patient who had contact with the blood and flesh of the slaughtered animal, the incubation period was six days, and the average duration of admission to the hospital after the onset of symptoms was 3±1.3 days. The most common complaints of patients at the application to the health institution

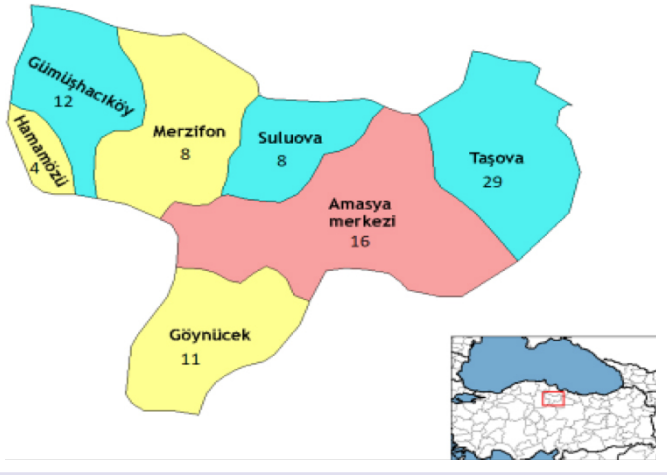

Figure 1. Distribution of Crimean-Congo hemorrhagic fever cases in Amasya in the last ten years by districts.

were; weakness (93%), muscle-joint pain (83.2%), fever (65%), headache (64.4%), abdominal pain (55.7%), nausea-vomiting (43.5%) and diarrhea (21.7%) (Table 2).

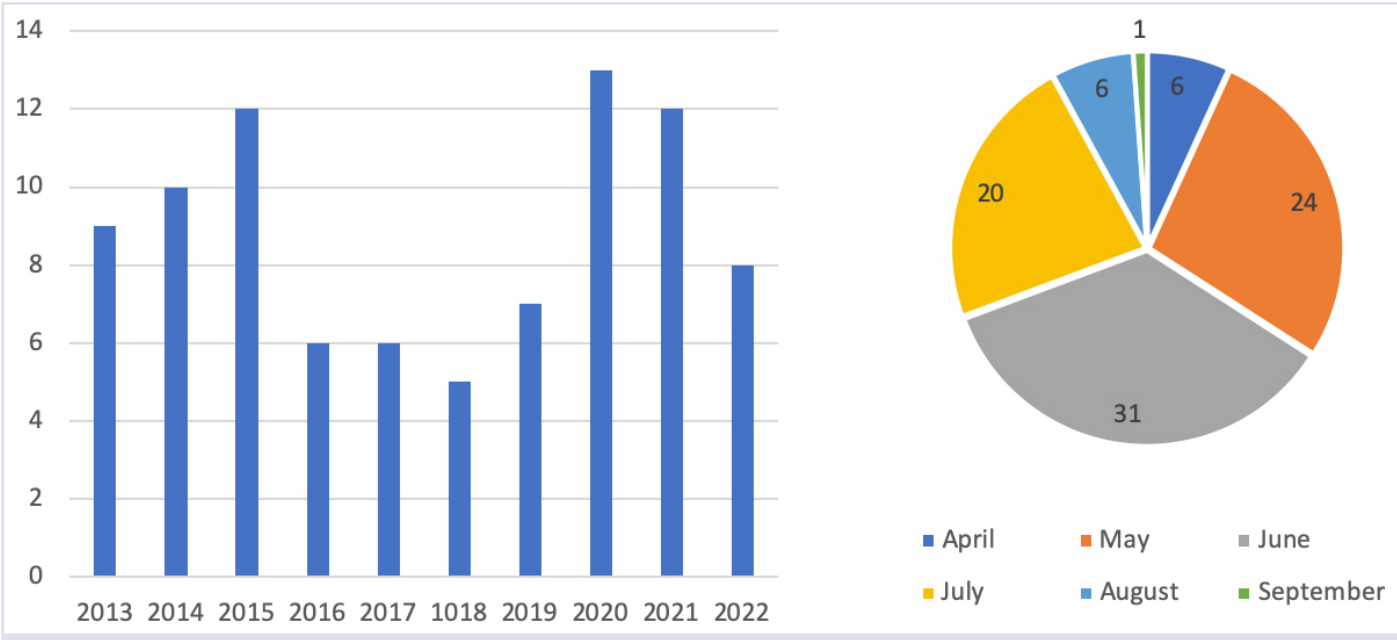

FIGURE 2. Distribution of the number of Crimean-Congo hemorrhagic fever cases in Amasya in the last ten years by months and years.

Of the 31 patients who did not have a fever on admission to the hospital, 17 were found to have a fever in their clinical follow-up. The mean time for the fever to return to normal in patients with fever was 5±1.5 days. The mean length of hospital stay was 8±2.2 days. Bleeding was observed in 15 (17.1%) patients during the follow-up in the clinic. The most common foci of bleeding were hematuria (4.8%), gastrointestinal bleeding (4.2%), epistaxis (3.6%), vaginal bleeding (3.4%), and intra-abdominal free bleeding (1.1%). The mean time between the onset of complaints and the occurrence of ex in three patients with ex was 7.4 days.

When the cases were examined in terms of laboratory findings; at the time of admission to the hospital, thrombocytopenia was 92%, leukopenia was 84.1%, AST-ALT elevation was 86.3%, LDH elevation was 76.1%, CK elevation was 71.6%, PT and aPTT prolongation was 52.2%, and International Normalized Ratio (INR) elevation was 36.4% (Table 2). Thrombocytopenia was not observed in 4 (4.6%) patients at hospital admission, and thrombocytopenia developed in the clinical follow-up. All three (3.4%) patients did not develop thrombocytopenia at hospital admission or during clinical follow-up, and their symptoms were faint. The diagnosis of CCHF was made by RNA detection of the viral genome by RT-PCR in all patients.

Only paracetamol and fluid-electrocute replacement therapies were applied to the patients who did not observe bleeding in the follow-up. Patients with bleeding were additionally treated to replace the missing blood components. Platelet suspension was administered to 7 patients, fresh frozen plasma to 11 patients, and erythrocyte suspension to 4 patients. None were given ribavirin. While 85 (96.6%) of the patients were discharged with healing, 3 of them died. Our mortality rate is 3.4%.

DISCUSSION

Among the viral hemorrhagic fever syndromes, CCHF is the most common disease worldwide [8]. The causative agent of the disease virus was first isolated in our country in 2002 from ticks in the Kelkit Valley countryside. According to the available data from the Ministry of Health, while a significant increase was observed in the notifications of CCHF in the time period between 2002–2008, it is stated that there was a decrease in the number of cases and mortality between 2008–2017 [4, 5]. Our study showed that while the number of cases in our city tended to decrease between 2016–2019, it started to increase again after 2020. It was thought that the reason for this increase could be global warming, which threatens the whole world.

CCHF is a disease frequently seen in middle-aged livestock breeders, rural residents, and slaughterhouse workers, regardless of age and gender. Since working middle-aged people have a higher risk of tick contact, CCHF disease is more common in this age group [8].

In different studies, it is stated that the average age of the patients is 47–51 [4, 9]. In our study, the patient's age range (youngest-oldest) was 18–75 years, and the mean age was 48±18. This age group has a higher labor force and production participation in animal husbandry and farming. It has been reported that 90% of the CCHF cases in our country are of farmers [8, 10]. In our study, 89.7% of the patients lived in rural areas, and 77.3% of them made their living by animal husbandry and farming.

Tick attachment is one of the main ways of transmitting the CCHF virus to humans. In addition, nosocomial transmissions may occur as a result of touching the tick with bare hands, contact with the blood and body fluids of the infected animal, injury to the wig with contaminated needles or cutting tools belonging to the patient and mucosal contact with the patient's blood and body fluids. There is no evidence that the disease is transmitted through the air [10, 11]. In our study, 55.7% of the patients had a history of tick attachment and other ways of transmission; contact with animal blood and body fluids (10.2%), naked and manual contact with the tick (9.1%). No transmission route could be detected in 22 (25%) patients.

In our study, it is seen that the cases were seen between April and September, and 85.2% of them occurred in the three months covering May, June, and July. That is because the heat and humidity suitable for ticks' movement, reproduction, and feeding activities are optimal during these months in the northern hemisphere [8, 12, 13]. It is stated that the number of cases has intensified in these months in many case series reported from our country [14–16]. Although cases seen in the winter months have been reported in our country [7]. A case has not been detected in the winter months in Amasya province.

Our city is known as one of the endemic areas regarding CCHF [8, 17, 18]. Amasya is a province located in the Central Black Sea Region, which has no coast, has seven districts together with the Central District and the people's livelihood is mainly animal husbandry and farming. Its climate is a slightly altered form of the Black Sea climate by continental influences (summers are hotter and drier than the Black Sea climate). Although the disease is seen in all districts, it is seen that the cases are concentrated in the Tasova district (32.9%). This is because animal husbandry and farming are a more common source of livelihood in the Tasova district than in other districts.

The average incubation period of the disease is from 2 to 7 days [19]. Long incubation periods have also been described in the literature. In a series of 312 cases reported from our country, it was stated that the incubation period was considered to be complete 12 days, the incubation period was >12 days in 12 (3.8%) cases, and the longest incubation period was 53 days [20]. In the study of Alkan-Ceviker et al. [4], it was determined that the mean incubation period in patients with a history of tick attachment was 6±2.1 days, and the mean duration of hospital admission after the onset of symptoms was 3±0.97 days. In our study, similarly, the mean incubation period in patients with tick attachment was 4±2.4 (min–max: 1–11) days, and the mean time between the onset of symptoms and hospital admission was 3±1.3 (min–max: 1–11) days. For a patient who had contact with the blood and flesh of the slaughtered animal, the incubation period was six days. A study conducted in Afghanistan stated that the average time between symptom onset and hospital admission was 6.7 days [21]. This situation can be explained by the fact that healthcare access is easier in Turkiye than in Afghanistan.

It is known that the initial symptoms of CCHF are non-specific symptoms such as fever, weakness, muscle-joint pain, abdominal pain, nausea, vomiting, headache [22]. In our cases, the most common symptoms seen at the onset of the disease are; weakness (93%), muscle-joint pain (83.2%), fever (65%), headache (64.4%), abdominal pain (55.7%), nausea-vomiting (43.5%) and diarrhea (21.7%). The presence of fever may not be observed at the patient's initial evaluation. In our cases, fever was not detected in 35% of the patients at the time of initial evaluation, and the presence of fever was observed in 55% of these patients in clinical follow-up. Somnolence was mentioned as a disease severity criterion in the study of Ergonul et al. [23]. The three deceased patients had somnolence, consistent with this literature.

A small proportion of CCHF patients have signs of bleeding. The most common bleeding areas are; the nose, gingival, gastrointestinal, intra-abdominal, and genitourinary system bleeding [8, 24]. In a series of 71 cases reported from our country, it was stated that the rate of bleeding in patients was 22% [4]. Again, a current case series published in our country stated that patients' bleeding rate was 5.7% [25]. In our study, bleeding was observed in 15 (17.1%) patients. The focus of bleeding those missed were hematuria (4.8%), gastrointestinal bleeding (4.2%), epistaxis (3.6%), vaginal bleeding (3.4%), and intra-abdominal free bleeding (1.1%).

The most common laboratory findings of CCHF disease are thrombocytopenia, leukopenia, AST, ALT, LDH, CK elevation, prolonged PT, and aPTT values. Tests that are commonly used to diagnose the disease are based on the demonstration of the presence of the virus in the blood and body fluids by serological or molecular methods [21–24]. In our study, all patients were diagnosed by RT-PCR, which is a molecular method. At the time of admission to the hospital, thrombocytopenia was 92%, leukopenia was 84.1%, AST-ALT elevation was 86.3%, LDH elevation was 76.1%, CK elevation was 71.6%, PT and aPTT prolongation was 52.2%, and International Normalized Ratio (INR) elevation was 36.4%. Three patients who did not have thrombocytopenia in their follow-up were thought to be in the recovery period due to the late admissions. In addition, it was observed that the symptoms were quite faint in these patients.

The basis of the treatment is supportive practices. Hemodynamic parameters should be closely monitored, and appropriate fluid treatments should be given to maintain hemodynamics. Drugs that facilitate bleeding (aspirin) and interventions (intramuscular injection) should be avoided, and if necessary, fresh frozen plasma, platelet, and erythrocyte preparations and replacement therapies should be applied [26]. There is currently no treatment guideline for the treatment of this severe disease. Although the efficacy of ribavirin is controversial, there is data that it is effective during outbreaks. In addition, it is stated that the use of ribavirin in the early period of post-exposure prophylaxis provides a reduction in sickness and death among health workers [27]. However, in the only randomized controlled study conducted by Koksal et al. [28], it was stated that the use of ribavirin did not significantly contribute to the prognosis of CCHF disease. In our study, paracetamol and fluid-electrocute replacement therapies were applied to patients not observed in the blood in all modes. Treatments to replace the missing blood components within the e-indication were applied. Platelet suspension was administered to 12 patients, fresh frozen plasma to 22 patients, and erythrocyte suspension to 6 patients. None of the patients were given ribavirin treatment. While 85 (96.6%) of the patients were discharged with recovery, three died. Our mortality rate was 3.4% with three patients.

Conclusion

As a result, Amasya province is one of our provinces that is endemic for CCHF disease. Although the number of cases decreased between 2016 and 2019, it is noteworthy that they increased again in recent years. In our city, CCHF should be considered in patients who present with fever, weakness, muscle-joint pain, and headache complaints in spring and summer and whose laboratory tests show thrombocytopenia, leukopenia, AST, ALT, LDH, and CK elevations.

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Ethics Committee Approval: The Amasya University Clinical Research Ethics Committee granted approval for this study (date: 06.04.2023, number: 2023/26).

Authorship Contributions: Concept – MA, SC; Design – MA, SC; Supervision – MA, SC; Data collection and/or processing – MA; Analysis and/or interpretation – MA, SC; Literature review – MA, SC; Writing – MA, SC; Critical review – MA, SC.

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