Research Article (Araştırma Makalesi)

Evaluation of the Cases With Pre-Diagnosis of Crimean-Congo Hemorrhagic Fever in Two District Hospitals in Tokat Province

Tokat ilinde İki İlçe Hastanesinde Kırım-Kongo Kanamalı Ateşi Ön tanısı ile Takipli Olguların Değerlendirilmesi

Emine TURKKOGLU YILMAZ[1], Duygu CERCIOGLU OZDEMIR[2]

[1] Gaziosmanpasa University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Tokat, Turkey
[2] Ministry of Health Kayseri City Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Kayseri, Turkey

Özet

Amaç: Tokat, Türkiye'de Kırım-Kongo kanamalı ateşinin (KKKA) endemik görüldüğü illerden biridir. KKKA ölümcül ve bulaşıcı olduğu için, hastalar hospitalize edilip izole takip edilmelidir. Bu çalışma ile Tokat ili iki ilçe hastanesinde takip edilen konfirme KKKA vakaları ile KKKA'nın ekarte edildiği olgular arasındaki epidemiyolojik, klinik ve laboratuvar bulgularının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu vaka kontrol çalışmasına, Ocak 2018-Aralık 2019 yılları arasında, Turhal ve Zile Devlet Hastaneleri'nde, KKKA ön tanısı ile takip edilen vakalar dâhil edildi. Hastaların demografik verileri, klinik bulguları, tedavi ve prognoz bulguları kaydedildi. "KKKA ön tanısı" en az iki semptomla birlikte lökopeni ya da trombositopeni varlığı olarak tanımlandı. KKKA antikor pozitifliği ya da polimeraz zincir reaksiyonu pozitifliği saptanan olgular "KKKA-pozitif grup" olarak kabul edilirken, diğerleri "KKKA-negatif grup" olarak belirlendi. Hospitalize edilmeyen ve 18 yaş altı olgular dışlandı. Kategorik değişkenlerin karşılaştırılmasında Pearson ki kare ve Fisher's testleri kullanıldı. İstatistiksel anlamlılık için $p<0.05$ kabul edildi.

Bulgular: KKKA-pozitif grupta, negatif gruba kıyasla, baş ağrısı (20 vs. 18), bulantı-kusma (20 vs. 16), myalji (18 vs. 16) ve ishal (11 vs. 5) semptomları daha sıktı. Ayrıca, lökopeni, trombositopeni, aspartat aminotransaminaz (AST), alanin aminotransaminaz (ALT), laktat dehidrogenaz (LDH) yüksekliği ile protrombin zamanı (PTZ) ve aktive parsiyel tromboplastin zamanında (aPTT) uzama daha sıktı. AST yüksekliği ve PTZ uzaması istatistiksel olarak anlamlıydı (sırasıyla; $p=0.01$ ve $p=0.003$). KKKA-pozitif grupta mortalite hızı %3.8'di.

Sonuç: Endemik bölgede yaşayıp baş ağrısı ve gastrointestinal semptomlarla başvuran olgularda, kene ısırığı öyküsü olmasa bile, lökopeni, trombositopeni, karaciğer enzim yüksekliği (KCFT) ve LDH yüksekliği, PTZ ve aPTT uzaması saptandığında KKKA olasılığı yüksektir. Bu yakınmalar ve laboratuvar bulguları ile başvuran hastalarda KKKA mutlaka akılda tutulmalıdır.

Anahtar kelimeler: Epidemiyoloji, Kırım-Kongo kanamalı ateşi, Lökopeni, Tokat, Trombositopeni

Abstract

Objective: Tokat is one of the cities in Turkey where Crimean–Congo hemorrhagic fever (CCHF) is endemic. Given that CCHF is fatal and contagious, patients should be isolated and hospitalized. This study aimed to compare the epidemiological, clinical, and laboratory findings of CCHF-positive and CCHF-negative cases in two district hospitals in Tokat.

Materials and Methods: Patients applied to Turhal and Zile State Hospitals between January 2018 and December 2019 and had a pre-diagnosis of CCHF were included in this case–control study. The patients' demographic data, symptoms, treatment, and prognosis were recorded. "Pre-diagnosis for CCHF" was defined as the presence of leukopenia or thrombocytopenia, in addition to the presence of at least two symptoms. Cases had antibodies to CCHF virus or CCHF virus-RNA were defined as "CCHF-positive group" and the others were "CCHF-negative group". Pearson's chi-square test and Fisher's test were used to compare the categorical variables. P values that are less than 0.05 were considered statistically significant.

Results: Symptoms of headache (20 vs. 18), nausea and vomiting (20 vs. 16), myalgia (18 vs. 16), and diarrhea (11 vs. 5) were more common in the CCHF-positive group than CCHF-negative group. Leukopenia, thrombocytopenia, elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels, and prolongated prothrombin time (PT) and activated partial thromboplastin time (aPTT) levels were also more common. AST elevation and PT prolongation were statistically significant ($p=0.01$ and $p=0.003$, respectively). The mortality rate in the CCHF-positive group was 3.8%.

Conclusion: Even if there is no history of tick bite in patients living in the endemic region and presenting with headache and gastrointestinal symptoms, CCHF probability is high in the presence of leukopenia, thrombocytopenia, elevated liver enzymes and LDH levels, prolonged PT and aPTT. CCHF should always be considered in patients with these symptoms and laboratory findings.

Keywords: Epidemiology, Crimean-Congo hemorrhagic fever, Leukopenia, Tokat, Thrombocytopenia

Yazışma Adresi: Emine TÜRKKOĞLU YILMAZ, Gaziosmanpaşa Üniversitesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Ana Bilim Dalı, Tokat, Türkiye

Telefon: +905415708820 **e-mail:** eminee43@hotmail.com

ORCID No (Sırasıyla): 0000-0003-4418-4692, 0000-0003-1792-515X

Geliş tarihi: 12.04.2022

Kabul tarihi: 14.06.2022

DOI: 10.17517/ksutfd.1102450

INTRODUCTION

Crimean–Congo hemorrhagic fever (CCHF) was first seen among Soviet soldiers who helped farmers in Crimea in 1944 during World War II. CCHF is among those diseases generally named viral hemorrhagic fever (1). It is endemic in more than 30 countries, especially in Africa, Asia, South East Europe, and Middle East. In Turkey, it was first reported in Tokat province in 2002, and it is endemic in the north regions of Central Anatolia and Central Black Sea and in Eastern Anatolia (2).

CCHF is a zoonotic disease that is transmitted via ticks. Fever and bleeding are the common clinical features of CCHF. The causative microorganism is a RNA virus belonging to the genus *Nairovirus* in the family *Bunyaviridae* (3). Although the virus is transmitted by various ticks, the primary vector is *Hyalomma marginatum marginatum*. The life cycle of the CCHF virus involves vector ticks and wild and domestic vertebrates. Through a tick bite, the virus infects wild and domestic animals, and a tick–vertebrate cycle occurs. The virus is transmitted to humans through tick bites, by crushing ticks with bare hands, or through contact with the blood/tissues of viremic animals. Infections in humans may also result from direct contact with infected blood/tissues and through mother-to-infant vertical transmission (1-3).

This study evaluated cases with suspected CCHF in two district hospitals in Tokat, where CCHF is endemic. This study aimed to compare the epidemiological, clinical, and laboratory findings of the confirmed CCHF cases and the ruled out cases.

MATERIALS AND METHODS

Study Place and Design

This case–control study included patients who presented to the Turhal and Zile State Hospitals between January 2018 and December 2019 and who had a pre-diagnosis of CCHF. The patients were divided into two groups, namely, CCHF-positive group and CCHF-negative group. The socio-demographic characteristics, symptoms, and laboratory findings of the patients were compared.

Patients and Data Collection

This study included 52 patients who presented to the Turhal and Zile State Hospitals with a pre-diagnosis of CCHF and were hospitalized between January 2018 and December 2019. "Pre-diagnosis for CCHF" was defined as having a positive result for at least one of the laboratory parameters, leukopenia or thrombocytopenia, along with the presence of at least two of the following: sudden onset of fever, headache, general body pain, arthralgia, weakness, diarrhea, and bleeding. Leukopenia was described as reduced white blood cell count (<4.000/mm^3), and thrombocytopenia was described as reduced thrombocyte count (<150.000/mm^3).

Serum samples were obtained upon admission and were sent to the Public Health Institution of Turkey, National Virology Reference Laboratory to determine the presence of CCHF immunoglobulin (Ig) M antibodies and CCHF virus ribonucleic acid (RNA). If a positive result was obtained in at least one of these tests, the case was included in CCHF-positive group. If all tests were negative, the case was included in CCHF-negative group.

Information on the demographic characteristics, symptoms, laboratory findings, treatment, and prognosis of the patients were obtained by examining the hospital automation system, files, and epicrisis.

Patients under 18 years of age and patients not hospitalized were excluded from this study.

A hemogram test was performed using a Sysmex XE 2100 analyzer (Sysmex Europe GmbH, Norderstedt, Germany); biochemical measurements were performed using a Beckman Coulter AU680 chemistry analyzer (Beckman Coulter, Inc., California, USA); and coagulation measurements were performed using a Succeeder SF-8100 coagulation analyzer (Beijing Succeeder Technology Development Co., Ltd., Beijing, China). The viral genome (CCHF virus RNA) was obtained using the real-time polymerase chain reaction (RT-PCR) method, and IgM antibody was investigated using the enzyme-linked immunosorbent assay (ELISA) method.

Determination of Sample Size

With the G-power 3.1 program, when the effect size was 0.80, the α error level was 0.05, the power was 0.80, and the degree of freedom (df) was 5. The sample size was calculated as 40, and by adding 5% of the calculated value, the minimum sample size was 42.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22. Data normality was tested using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive statistics are presented as numbers and percentages for categorical variables, as means ± standard deviation (SD) for normally distributed continuous variables, and as median (minimum–maximum) for non-normally distributed continuous variables. Pearson's chi-square test and Fisher's test were used to compare categorical variables. Significance of Difference between Two Means and One-Way Analysis of Variance were used for comparing the means of quantitative variables between groups. P values of less than 0.05 were considered statistically significant.

Ethic Statement

The study was approved by Tokat Gaziosmanpaşa University, Non-Invasive Clinical Research Ethical Board (date: April 26, 2021, No: 2020/04 and Project No: 20-KAEK-063). Study procedures were performed likewise Helsinki Declaration. All participants signed a written informed form.

RESULTS

Fifty two patients who were applied between January 2018 and December 2019 and who were followed up with a pre-diagnosis of CCHF were included in the study. Twenty six (50%) of the patients were diagnosed with CCHF by PCR and/or IgM positivity. There was no difference detected between CCHF positive and negative groups in terms of gender and mean age (p=0.76, p=0.26). A history of interaction with agriculture and livestock was higher in the CCHF positive group and it was statistically significant (p=0.05, p=0.01). History of tick contact was higher in CCHF positive group but it was not statistically significant (p=0.15) (**Table 1**). Symptoms including headache, myalgia, nausea and vomiting, and diarrhea were more common in CCHF-positive group, but these findings were not statistically significant (p=0.53, p=0.56, p=0.22, p=0.07) (**Table 2**). Among laboratory parameters, leukopenia, thrombocytopenia, elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) levels and prolonged prothrombin time (PT) and activated partial thromboplastin (aPTT) levels were higher in CCHF positive group. However, only AST elevation and PT prolongation were statistically significant (p=0.01, p=0.003) (**Table 3**).

It was determined that the most patients applied to hospital in June, but the most CCHF cases were in May (**Figure 1**). Empirical ribavirin was started in 23 (44.2%) of the cases hospitalized with suspicion of CCHF. CCHF was ruled out, and ribavirin was stopped because CCHF antibodies or the presence of CCHFV (confirmed with PCR) was not detected in four of these 23 patients. Ribavirin was started in seven patients who were not initially given ribavirin but whose CCHF test results were positive, although their symptoms lasted no more than four days. Eighteen patients with CCHF positivity were referred to Faculty of Medicine due to complications such as deterioration in their general condition or the need for blood product replacement.

Table 1. Demographic and epidemiological data of the patients

	CCHF positive (n=26)	CCHF negative (n=26)	p-value
Male gender (n, %)	18 (69.2)	19 (73.1)	0.76
Age, mean (SD)	46.11 (16.26)	52±18.89	0.26
Agricultural occupation (n, %)	25 (96.2)	17 (65.4)	0.05
Livestock engagement (n, %)	21 (80.8)	12 (46.2)	0.01
Tick bite (n, %)	19 (73)	14 (53.9)	0.15
Removal the tick at home (n, %)	12 (85.7)	9 (90)	1

CCHF: Crimean–Congo hemorrhagic fever, SD: standard deviation

Table 2. Symptoms of the patients

	CCHF positive (n=26)	CCHF negative (n=26)	p-value
Fever (n, %)	23 (88.5)	24 (92.3)	1
Headache (n, %)	20 (76.9)	18 (69.2)	0.53
Myalgia (n, %)	18 (69.2)	16 (61.5)	0.56
Weakness (n, %)	23 (88.5)	22 (84.6)	1
Abdominal pain (n, %)	5 (19.2)	7 (26.9)	0.51
Nausea-vomiting (n, %)	20 (76.9)	16 (61.5)	0.22
Diarrhea (n, %)	11 (42.3)	5 (19.2)	0.07
Rash (n, %)	-	1 (3.8)	1
Bleeding (n, %)	1 (3.8)	1 (3.8)	1

CCHF: Crimean–Congo hemorrhagic fever

Table 3. Laboratory parameters of the patients

	CCHF positive (n=26)	CCHF negative (n=26)	p-value
Leukopenia (n, %)	14 (53.8)	7 (26.9)	0.06
Anemia (n, %)	3 (11.5)	4 (15.4)	0.7
Thrombocytopaenia (n, %)	23 (88.5)	21 (80.8)	0.64
AST elevation (n, %)	19 (73.1)	10 (38.5)	0.01
ALT elevation (n, %)	17 (65.4)	10 (38.5)	0.06
CK elevation (n, %)	17 (65.4)	17 (65.4)	0.84
LDH elevation (n, %)	17 (65.4)	11 (42.3)	0.12
PT prolongation (n, %)	10 (38.5)	1 (3.8)	0.003
aPTT prolongation (n, %)	4 (15.4)	1 (3.8)	0.35

AST: aspartate aminotransferase, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, CCHF: Crimean–Congo hemorrhagic fever, CK: creatine kinase, LDH: lactate dehydrogenase, PT: prothrombin time

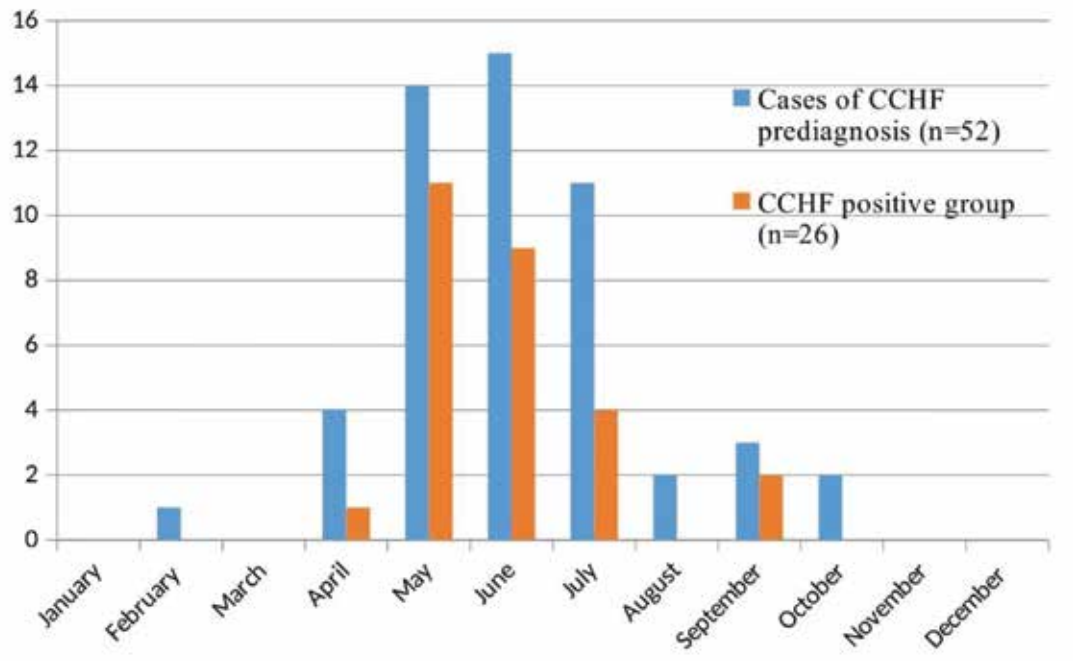

Figure 1. Distribution of patients with CCHF prediagnosis and CCHF positive group by months.

One of the CCHF-positive cases referred to the hospital died; the other 17 cases were discharged as their conditions improved. The remaining eight patients of the original 52 were not referred and were discharged with full recovery. The mortality rate of the sample was 3.8%. The patient who died was one of the patients did not receive ribavirin therapy in the early intervention period.

DISCUSSION

This study found that headache and gastrointestinal symptoms such as nausea, vomiting and diarrhea were most important symptoms for CCHF. The possibility of CCHF is high in people who have leukopenia, thrombocytopenia, elevated liver enzymes and LDH, and prolonged PT and aPTT.

CCHF is endemic in Turkey. Indeed, Turkey has the greatest number of reported CCHF cases worldwide (1). The first case was reported in Tokat Province in 2002; a significant portion of other cases are reported in the 15 provinces that comprise the Kelkit Valley (4). Since the first case in 2002, more than 10,000 cases have been recorded (5).

There are limited studies investigating CCHF positivity rates in patients hospitalized with a pre-diagnosis of CCHF. The literature reports rates varying from 21–57% (4,6-10). The present study derived a rate of 50%.

The most important risk factor for CCHF is living in an endemic area and working in farming and animal husbandry (2). In Bodur et al.'s study, the number of people working in farming was statistically higher among the individuals with CCHF seropositivity compared to the seronegative patients (49.9% and 37.5%, respectively) (11). Yılmaz et al. reported that the majority of their patients (61.7%) had a history of close contact with animals (12). Similar to the literature, in the present study, the number of people working in farming and animal husbandry was higher in the CCHF-positive group compared to the CCHF-negative group and was statistically significant.

Approximately 60% of patients with a diagnosis of CCHF have a history of tick bites (2). In two separate studies, Gözdaş and Günaydın et al. reported that 67.6% and 74.2% of patients had known tick bites, respectively (6,13). The present study is consistent with this –73% of the patients had known tick bites; this percentage was higher in the CCHF-positive group than in the CCHF-negative group.

CCHF cases are mostly seen in spring and summer and are associated with tick movements, with most cases occurring in May, June, and July. During the winter months, the tick population decreases due to cold weather (1,12). In the present study, in accordance with the literature, the greatest number of cases was detected in May and June.

In terms of gender, 69.2% of CCHF-positive patients were male. In a study performed in Afghanistan by Hatami et al. the number of CCHF-positive men was twice that of women (7). This result can be attributed to the fact that men work in farming and animal husbandry more than women. In contrast, multiple studies report that there is no difference in incidence rate between men and women (6).

There are four phases in the typical course of CCHF infection: incubation, the pre-hemorrhagic phase, the hemorrhagic phase, and the convalescent phase. The duration of the incubation phase depends on the route of transmission. It averages 5–6 days and can last up to 13 days (14). In the pre-hemorrhagic period, fever, headache, myalgia, dizziness, diarrhea, nausea and vomiting, rash, and conjunctivitis can be observed (15). The hemorrhagic phase can be characterized by many types of bleeding, from petechiae to extensive ecchymosis to gastrointestinal bleeding (14).

The most common symptoms reported in CCHF are fever, weakness, myalgia, headache, nausea, vomiting, diarrhea, and in severe cases, bleeding (16). In a study by Mourya et al. in India, gastrointestinal symptoms such as nausea and vomiting and diarrhea were more common in the CCHF-positive group (17). In Gözdaş' study, nausea, vomiting, and headache were statistically more common in the CCHF-positive group (6). In the present study, headache, myalgia, nausea and vomiting, and diarrhea were more common in CCHF-positive patients, but these findings were not statistically significant.

Most of the patients in the present study had leukopenia, thrombocytopenia, and elevated AST, ALT, CK, and LDH levels. Prolonged PT and aPTT were the other important laboratory findings in CCHF (3). In Hatami et al.'s study, thrombocytopenia was the most important laboratory finding; leukopenia also supported a diagnosis of CCHF (7). In the present study, leukopenia; thrombocytopenia; increased AST, ALT, LDH; and PT and aPTT prolongation were higher in CCHF-positive patients. However, only AST elevation and PT prolongation were statistically significant ($p=0.01$, $p=0.003$).

Currently, there is no specific antiviral therapy approved for the treatment of CCHF. Yet, ribavirin, as a broad-spectrum antiviral, has been shown to inhibit the replication of the CCHF virus. In fact, the World Health Organization (WHO) has stated that ribavirin is effective in terms of the treatment of CCHF. Moreover, a number of studies have shown ribavirin to have a positive effect on the prognosis of those with CCHF and also to reduce the mortality rate associated with the virus. It is most effective when used during the early stages of the disease (3,15). Indeed, if ribavirin is started within the first four days of the onset of CCHF, the mortality rate is only 5%; however, if patients are not treated with ribavirin within the same period, the mortality rate is 27% (18). In the present study, in accordance with the findings presented in the literature, ribavirin was administered to all patients with a confirmed diagnosis of CCHF. Importantly, empirical treatment was not initiated for all suspected CCHF patients due to the difficulty of obtaining the necessary drugs. After the CCHF diagnosis was confirmed in seven patients, ribavirin could be obtained and started during a later stage of the virus.

CCHF can prove fatal. More specifically, the fatality rate reported in the prior literature varies from 5–80% worldwide, while studies conducted among Turkish populations have shown it to range from 3–9% (1,4,5). Furthermore, according to data provided by the Public Health Institution of Turkey, the fatality rate of CCHF ranges between 4% and 5% (16). In this study, the fatality rate was determined to be 3.8%, which is below the Turkish average. This difference may be related to the relatively small number of patients included in the present study.

The limitations of this study include the fact that it was conducted retrospectively and included only a small number of patients. Additionally, the characteristics of the CCHF patients were only evaluated at the time of admission, meaning that their symptoms and laboratory findings were not evaluated throughout the course of the virus. In light of these limitations, further studies involving larger numbers of patients and including the symptoms and laboratory findings that develop over the course of CCHF are required to verify and extend the present results.

CONCLUSION

According to the results of this study, people living in endemic areas such as Tokat are at high risk of developing CCHF, especially if they have a history of tick bites and/or engage in agriculture or animal husbandry. The presence of headache and gastrointestinal symptoms such as nausea, vomiting, and diarrhea are the most important signs of CCHF. The likelihood of developing CCHF is high in those who have leukopenia, thrombocytopenia, elevated LFT and LDH, and prolonged PT and aPTT. It should be borne in mind that some cases may not have a history of tick bites. Thus, in individuals living in endemic regions, even if there is no history of tick bites, CCHF must be ruled out if there are any related symptoms and/or laboratory findings.

Funding: No funding

Acknowledgments: None

Conflict of Interest: This statement is to certify that all authors have seen and approved the manuscript being submitted. We warrant that there is no conflict of interest to declare.

Ethical Approval: The study was approved by Tokat Gaziosmanpaşa University, Non-Invasive Clinical Research Ethical Board (date: April 26, 2021, No: 2020/04 and Project No: 20-KAEK-063). Study procedures were performed likewise Helsinki Declaration. All participants signed a written informed form.

Author contributions: Idea/Concept: ETY/Design: ETY, DÇÖ/Data collecting: DÇÖ/Analysis: DÇÖ, ETY/Literature review: ETY Writing the article ETY

REFERENCES

1. Blair PW, Kuhn JH, Pecor DB, Apanaskevich DA, Kortepeter MG, Cardile AP et al. An emerging biothreat: Crimean-congo hemorrhagic fever virus in southern and western asia. Am J Trop Med Hyg. 2019;100(1):16–23.
2. Ergonul O, Celikbas A, Dokuzoguz B, Eren S, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. Clin Infect Dis. 2004;39(2):284-287.
3. Eren Gok S. Crimean- Congo hemorrhagic fever. Eur Arc Med Res. 2016;32(Supp): 13-19.
4. Hekimoglu HC, Ates Demirci N. Evaluation of cases with a preliminary diagnosis of Crimean- Congo hemorrhagic fever and comparison of characteristics in patients admitted to a secondary care hospital in Kastamonu, Turkey. Afr Health Sci. 2014;14(4):873-881.
5. Leblebicioglu H, Ozaras R, Irmak H, Sencan I. Crimean-Congo hemorrhagic fever in Turkey: current status and future challenges. Antiviral Res. 2016;126:21–34.
6. Gozdas HT. Evaluation of Crimean-Congo hemorrhagic fever suspected cases admitted to a secondary care hospital in Kastamonu, Turkey between 2014-2017. Afr Health Sci. 2019;19(1):1433-1440.
7. Hatami H, Qaderi S, Omid AM. Investigation of Crimean-Congo hemorrhagic Fever in Patients Admitted in Antani Hospital, Kabul, Afghanistan, 2017–2018. Int J Prev Med. 2019;10:117.
8. Erenler AK, Kulaksiz F, Ulger H, Erdem M, Kocak C, Soylemez F et al. Characteristics of patients admitted to the emergency department due to tick bite. Trop Doct. 2014;44(2):86–88.
9. Mostafavi E, Pourhossein B, Chinikar S. Clinical symptoms and laboratory findings supporting early diagnosis of Crimean-Congo hemorrhagic fever in Iran. J Med Virol. 2014;86(7):1188–1192.
10. Duran A, Kucukbayrak A, Ocak T, Hakyemez NI, Tas T, Karadag M et al. Evaluation of patients with Crimean- Congo hemorrhagic fever in Bolu, Turkey. Afr Health Sci. 2013;13(2):233–242.
11. Bodur H, Akinci E, Ascioglu S, Onguru P, Uyar Y. Subclinical infections with Crimean-Congo hemorrhagic fever virus, Turkey. Emerg Infect Dis.2012;18:640-642.
12. Yilmaz GR, Buzgan T, Irmak H, Safran A, Uzun R, Cevik MA et al. The epidemiology of Crimean-Congo hemorrhagic fever in Turkey, 2002–2007. Int J Infect Dis. 2009;13(3):380–386.
13. Gunaydin NS, Aydin K, Yilmaz G, Caylan R, Koksal I. Crimean-Congo hemorrhagic fever cases in the eastern Black Sea Region of Turkey: Demographic, geographic, climatic, and clinical characteristics. Turk J Med Sci. 2010;40(6):829-834.
14. Shayan S, Bokaean M, Shahrivar MR, Chinikar S. Crimean-Congo Hemorrhagic Fever.Lab Med. 2015;46(3):180-189.
15. Ergonul O. Crimean-Congo Haemorrhagic fever: Treatment and use of Ribavirin. Klimik J. 2016;29(1):2-9.
16. Public Health Institution of Turkey, Department of Zoonotic and Vectorial Diseases. Avaliable 18 April 2021. Avaliable from: https://hsgm.saglik.gov.tr/tr/zoonotikvektorel-kkka.
17. Mourya DT, Viswanathan R, Kumar Jadhav S, Yadav PD, Basu A, Chadha MS. Retrospective analysis of clinical information in Crimean-Congo haemorrhagic fever patients: 2014-2015, India. Indian J Med Res. 2017;145(5):673–678.
18. Tasdelen Fisgin N, Ergonul O, Doganci L, Tulek N. The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: Early use is promising. Eur J Clin Microbiol Infect Dis. 2009;28(8):929-233.