European Review for Medical and Pharmacological Sciences 2015; 19: 3811-3816

Predictors of Crimean-Congo hemorrhagic fever in the Emergency Department

A.K. ERENLER, F. KULAKSIZ, H. ÜLGER, M. ÇAPRAZ[1], L. TOMAK[2], A. BAYDIN[3]

Emergency Department, Hitit University Çorum Education and Research Hospital, Çorum, Turkey
[1]Department of Internal Medicine, Amasya Sabuncuoglu Serefettin Education and Research Hospital, Amasya, Turkey
[2]Department of Statistics, Ondokuz Mayis University, Faculty of Medicine, Turkey
[3]Department of Emergency, Ondokuz Mayis University, Faculty of Medicine, Samsun, Turkey

Abstract. – OBJECTIVE: Crimean-Congo hemorrhagic fever (CCHF) is an acute illness affecting multiple organ systems characterized by thrombocytopenia, and/or leukopenia, elevated levels of alanine aminotranferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and creatine kinase (CK) and it has a case-fatality of 8% to 80%. In this article, we aimed to determine the clinical and laboratory findings that predicts the disease on admission.

PATIENTS AND METHODS: We retrospectively analyzed the medical data of the patients admitted to our emergency department (ED) due to tick bite. These patients were divided into two groups according to their transcriptase-polymerase chain reaction (RT-PCR) test results. Findings of PCR (+) (Group 1) and PCR (-) (Group 2) patients were compared.

RESULTS: Epistaxis was found to be statistically significant clinical finding in Group 1. Also, while aspartate transaminase (AST) levels and potassium (K) level were significantly higher, platelet count and white blood count (WBC) were significantly lower in Group 1 when compared to Group 2.

CONCLUSIONS: Predictors of CCHF in the ED are epistaxis, leukopenia, thrombocytopenia and elevated K and AST levels. In our study, the fatality rate of CCHF was found to be 21.6%.

Key Words:
Emergency Department, Tick bite, Laboratory findings, Fatality rate.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a serious disease caused by the CCHF virus of the Bunyaviridae family[1]. The virus is transmitted to humans through tick bites or exposure to blood and tissues of infected animals. Different domestic and wild animals have been identified as a reservoir for this virus, including cattle, sheep, goats, hedgehogs and hares[2,3]. Numerous species of ticks can carry the virus; however, very few of them have been implicated as vectors. The most important tick vector is the *Hyalomma spp*., as the virus was isolated from it and its geographic distribution coincides with that of the disease[4]. Another transmission route of the virus in humans is through contact with the blood of an infected person during the acute phase of the disease[5].

In the pathogenesis of the disease, it is well-known that microvascular damage and deterioration of hemostasis play important roles. In the recent years, it is also shown that elevated serum levels of matrix metalloproteinases and increased activity of the alternative pathway of the complement system also have roles in the pathogenesis[6,7].

Crimean-Congo hemorrhagic fever is an acute illness affecting multiple organ systems and characterized by extensive ecchymosis, visceral bleeding, and hepatic dysfunction; and it has a case-fatality of 8% to 80%[8]. Although there are studies in the literature suggesting early ribavirin administration, the main method of treatment of CCHF is conservative and supportive[7,8]. The disease has been reported in 30 countries in Africa, Asia, Eastern Europe, and the Middle East. It has been present in Turkey since 2002[11].

Although serological evidence of CCHFV was detected years ago, clinical CCHFV infection was first recognized in 2002, and outbreaks have occurred in Turkey in subsequent years[12]. The majority of patients in our country were from 15 cities in Kelkit Canyon and its environs, particularly the cities of Tokat, Sivas, Yozgat, Çorum, and Erzurum from which two thirds of cases were reported (Figure 1)[11]. Even though Çorum is one of the cities that CCHF is commonly seen,

Corresponding Author: Ahmet Baydin, MD; e-mail: abaydin@omu.edu.tr

Figure 1. Kelkit valley region in Turkey where most of the cases of Crimean-Congo haemorrhagic fever are seen (With permission of Gül Ruhsar Yilmaz.

studies about the epidemiological situation of the disease in the literature are limited. In this study, we investigated the clinical and laboratory findings of the patients hospitalized with the suspicion of CCHF. We also determined the patients with definite CCHF diagnosis whose blood samples were sent to Ankara for transcriptase-polymerase chain reaction (RT-PCR) test and aimed to reveal their characteristics that differ from the PCR (-) patients.

Patients and Methods

We retrospectively collected the medical data of the patients hospitalized in Hitit University Çorum Research and Education Hospital with suspected CCHF. A total of 240 (female/male: 89/151) patients of any age hospitalized with the suspicion of CCHF between January 1st 2010 and December 31st 2012 were involved into the study. Blood samples of the patients were sent to an advanced center for RT-PCR test. CCHF virus RNA in the blood samples through RT-PCR evaluation were considered confirmed CCHF cases.

Patients were divided into two groups as PCR (+) (group 1) and PCR (-) (group 2) according to the test results. Demographical features, complaints on admission, vital signs (temperature, blood pressure, pulse rate) and physical examination findings (according to the systems) of the patients were investigated. Besides, laboratory findings of the patients such as complete blood count (CBC), blood biochemistry test, and coagulation panel were investigated and compared according to the groups. Two patient groups were compared according to these variables.

Statistical Analysis

Statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation (SD). The Shapiro-Wilk test was used to analyze normal distribution assumption of the quantitative outcomes. To compare two groups, Student *t* test was used for normally distributed data and Mann-Whitney U test was used for non-normal data. $p < 0.05$ was accepted as statistically significant in comparisons.

Results

In 3-year period, 15429 patients were admitted to our ED due to tick bite. When seasonal distribution was investigated, it was observed that majority of the cases was admitted in the summertime [between April and September (96.1%)], particularly in June and July (47.4%). Of these patients, blood samples of 240 were sent to an advanced center for PCR test. Ninety-seven of them were determined to be PCR (+). Of these patients with definite CCHF diagnosis, 21 have died. Fatality rate of the disease was found to be 21.6%. When demographical findings of the two

patient groups were evaluated, it was determined that, in both groups, the most of the patients were living in the city center and fever was the most common finding on admission. Any statistical significance could not be determined in 2 groups according to vital signs on admission. It was also determined that there was not a significant difference according to sex and vital signs of the patients. Ticks were commonly removed by ED doctors in both groups. Self-removal rate was higher in group 1 but a significant difference could not be determined. While 5.3% of the patients in group 1 were evaluated as in "poor general condition" by the ED doctors, there were not any patients in group 2 who match this definition. This difference was found to be statistically significant. Physical examination findings were classified according to the systems and it was found that the prevalance of epistaxis was 29.9% and 16.7% in group 1 and 2, respectively. This difference was also found to be statistically significant. When laboratory findings of both groups were evaluated, it was determined in our study that, while aspartate aminotransferase (AST) levels and potassium (K) level were elevated, platelet count and white blood count (WBC) were lower in Group 1 when compared to Group 2, and differences were statistically significant. Basic characteristics of both groups are summarized in the Table I.

Discussion

At present, CCHF is a public health problem in many regions of the world including Asia, Eastern Europe, Africa, and Russia[13]. Since 2002, outbreaks have occurred in Turkey in subsequent years[14,15]. Çorum, with a population of approximately 530000, is located in the Kelkit canyon in mid-Anatolian region and because of its climate and plant cover characteristics, it is one of the five cities where CCHF disease due to tick bites is most prevalent. When considered that 15429 patients were admitted to our ED with a complaint of tick bite, about 0.3% of all population faces the risk of CCHF.

Most of the cases are seen in the summer months, i.e. April to September, with a peak incidence in June and July[11]. The disease has a seasonal pattern correlated to the peak activity period of ticks, between spring and early autumn[16]. In Turkey, the disease occurs between the months of March and October with peak levels in June and July. Nearly 70% of the cases were reported in the months of June and July, which corresponds with the tick season[11]. The climate of this middle Anatolian region is hot, dry summers with cold and moderately rainy winters, the optimum conditions for survival of the Hyalomma tick population. It has been demonstrated that climatic factors have played an important role in the emergence of vector-borne diseases[17].

Similarly, in our study, we determined that number of patients admitted to our ED due to tick bite peaked in June and July. Our findings are compatible with the literature that the disease has a climatic distribution. In winter months, when ticks are inactive, almost no patient had admitted to our ED due to tick bite. In the literature, there is no evidence that tick bites have a significant preference for patient characteristics such as age, gender or race. We also could not determine statistical significance among these features.

Humans commonly become infected by a bite from or contact with infected ticks or by contact with blood or tissues of infected livestock. Most humans who become infected live or work in close contact with livestock (sheep, goats, cattle, or ostriches) in areas where CCHF virus is endemic[18]. Interestingly, majority of the patients in our study were living in the city centre. People in Çorum spend most of their spare time gardening and plant growing in their summerhouses. So, exposure to ticks is possible when their lifestyle is considered. The most common clinical signs of CCHF are known to be fever, nausea, headache, diarrhea, myalgia, petechial rash, and bleeding[19]. Accordingly, in our study, fever was most common finding on admission for patients with CCHF.

In a study, it was reported that the patients showed hemorrhagic signs including epistaxis (26.1%), petechiae (20.3%), ecchymosis (17.4%), melena (17.4%), gingival bleeding (15.9%), hematemesis (13.0%), hematuria (5.8%), and hematoma (2.9%)[13]. There are several studies in the literature correlated with the finding that the most common hemorrhagic finding in CCHF is epistaxis[20,21]. Our results also revealed that the most common hemorrhagic finding was epistaxis and rate of epistaxis was significantly higher in the patients with definite CCHF diagnosis than in the non-CCHF patients. This finding is thought to be related to depth and persistence of thrombocytopenia in CCHF patients and fragility of vessels supplying the nose.

Table I. Comparison of 2 groups according to the basic characteristics.

	Group 1	Group 2
Demographical features		
Gender (n) (M/F)	42/55	47/96
Age (mean)	36	41
Location (n)		
City center	33	52
Village	41	56
Town	2	6
Another city	21	30
Vital signs (mean)		
Temperature (°C)	37.2	36.8
Systolic blood pressure (mmHg)	112	113
Diastolic blood pressure (mmHg)	70	70
Pulse (beats/minute)	83	83
Laboratory findings		
WBC (μL)*	4400	5500
RBC (million/uL)	4700	4600
PLT (thousand/uL)*	99000	119000
Hb (g/dL)	13.3	13.1
PT (second)	16.3	15.8
INR	1.5	1.3
aPTT (second)	29.6	28.5
BUN (mg/dL)	24.1	16.6
Glucose (mg/dL)	108.8	112.5
Creatinine (mg/dL)	0.9	0.9
AST (U/L)*	140	75
ALT (U/L)	78	63
Total Bilirubine (U/L)	0.7	3.6
Conjugate bilirubine (U/L)	0.3	0.3
CK (U/L)	173	142.4
CK-MB (U/L)	27	24
Calcium (mg/dL)	8.2	8.7
Sodium (mEq/L)	137	134
Potassium (mEq)*	8.5	3.9
Chlorine (mEq/L)	99.1	100.2
Amylase		
Signs and symptoms (%)		
Fever	39.4	47.2
Fatigue	31.9	50
Nausea	2.1	1.4
Diarrhea	22.3	12
Epistaxis*	3.2	0
Tick removal (%)		
At hospital	10.3	19.5
Self removal	42.5	31.7
Suspected bite	47.1	48.8

*Statistically significant difference between groups ($p < 0.05$).

Laboratory findings of the disease are well-defined in the literature. Primary laboratory findings in patients diagnosed with CCHF are known to be thrombocytopenia, leukopenia, and increased levels of aminotransferases[20,22-25]. In a study, laboratory findings of the disease were reported as thrombocytopenia (platelet < 150,000/mm^3) and/or leukopenia (WBC < 4000/mm^3), elevated levels of alanine aminotransferase (ALT), AST, lactate dehydrogenase (LDH) and creatine phosphokinase (CK)[26]. In another study, it was reported that almost all of the patients with definite CCHF diagnosis had leukopenia, thrombocytopenia, and elevated AST, ALT, LDH, and CPK levels at the time of admission[13]. Similarly, we determined that patients with CCHF has elevated AST, ALT levels, thrombocytopenia and/or leukopenia. Varying degrees of cytopenia deter-

mined in patients with CCHF may be related to hemophagocytosis seen in similar viral diseases[27].

Besides well-defined laboratory findings of the disease, we also determined that patients with definite CCHF diagnosis has hyperkalemia. Hyperkalemia is a potentially life-threatening condition in which serum potassium exceeds 5.5 mmol/l. It can be caused by reduced renal excretion, excessive intake or leakage of potassium from the intracellular space[28]. The cause of hyperkalemia determined in our study may be due to acidosis or acute cell-tissue breakdown due to hemolysis. However, further investigations are needed to clarify the definite cause of hyperkalemia in patients with CCHF.

Case-fatality of CCHF varies between 8% and 80%[29]. In a study, It was reported that CCHF case-fatality is approximately 30%, with most deaths occurring 5 to 14 days after onset of illness[30]. However, in another study covering 5 years (2002-2007) in Turkey, the fatality rate of the disease in Turkey was found to be 5%. The lower fatality rate in Turkey when compared to the higher rates reported from other parts of the world was linked to better surveillance system, which facilitates the detection of cases with mild to moderate clinical findings, and the relatively better treatment facilities[9]. In another study, case-fatality rate of the disease was found to be 15.9% and this lower rate was linked to a better institution and availability of blood products[13]. In our study, fatality rate of CCHF was found to be 21.6%. The higher rate we determined may be related to insufficiency of the facilities in Çorum and delay in initiating treatment during transport of the patients with definite diagnosis. It is also possible that the fatality of the disease is increasing independently over the years.

Conclusions

Crimean-Congo haemorrhagic fever (CCHF) is a disease caused by a virus belonging to Bunyaviridae family. CCHF virus isolation and/or disease have been reported from more than 30 countries in Africa, Asia, south-eastern Europe, and the Middle East[24]. Common laboratory findings of the disease are known to be thrombocytopenia, and/or leukopenia, elevated levels of ALT, AST, LDH and CK. Clinical symptoms are characterized by fever, hemorrhage, headache of acute onset, myalgia/arthralgia, lethargy, nausea/vomiting, or abdominal pain/diarrhea[26]. In our study, we determined that predictors of CCHF are epistaxis and elevated K^+, WBC and AST levels. Early diagnosis and appropriate supportive therapy may help reduce the mortality rate of the disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Soares-Weiser K, Thomas S, Thomson G, Garner P. Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. BMC Infect Dis 2010; 10: 207.
2) Causey OR, Kemp GE, Madbouly MH, David-West TS. Congo virus from domestic livestock, African hedgehogs, and arthropods in Nigeria. Am J Trop Med Hyg 1970; 19: 846-850.
3) Shepherd AJ, Swanepoel R, Leman PA, Shepherd SP. Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans R Soc Trop Med Hyg 1987; 81: 1004-1007.
4) Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol 1979; 15: 307-417.
5) Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, Gill DE. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg 1987; 36: 120-132.
6) Williams RJ, Al-Busaidy S, Mehta FR, Maupin GO, Wagoner KD, Al-Awaidy S, Suleiman AJ, Khan AS, Peters CJ, Ksiazek TG. Crimean-Congo haemorrhagic fever: a seroepidemiological and tick survey in the Sultanate of Oman. Trop Med Int Health 2000; 5: 99-106.
7) Aydin H, Guven FMK, Yildiz G, Bakir M, Celik C, Korkmaz I. Role of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases-1 in Crimean-Congo hemorrhagic fever disease. Eur Rev Med Pharmacol Sci 2014; 18: 861-868.
8) Williams RJ, Al-Busaidy S, Mehta FR, Maupin GO, Wagoner KD, Al-Awaidy S, Suleiman AJ, Khan AS, Peters CJ, Ksiazek TG. Crimean-Congo haemorrhagic fever: a seroepidemiological and tick survey in the Sultanate of Oman. Trop Med Int Health 2000; 5: 99-106.
9) Sheikh AS, Sheikh AA, Sheikh NS, Tariq M. Ribavirin: an effective treatment of crimean-congo haemorrhagic fever. Pak J Med Sci 2004; 20: 201-206.
10) Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. Clin Infect Dis 2003; 36: 1613-1618.

11) Yilmaz GR, Buzgan T, Irmak H, Safran A, Uzun R, Cevik MA, Torunoglu MA. The epidemiology of Crimean-Congo hemorrhagic fever in Turkey, 2002-2007. Int J Infect Dis 2009; 13: 380-386.

12) Tonbak S, Aktas M, Altay K, Azkur AK, Kalkan A, Bolat Y, Dumanli N, Ozdarendeli A. Crimean-Congo hemorrhagic fever virus: genetic analysis and tick survey in Turkey. J Clin Microbiol 2006; 44: 4120-4124.

13) Cevik MA, Erbay A, Bodur H, Gülderen E, Ba tug A, Kubar A, Akinci E. Clinical and laboratory features of Crimean-Congo hemorrhagic fever: predictors of fatality. Int J Infect Dis 2008; 12: 374-379.

14) Gözalan A, Akin L, Rolain JM, Tapar FS, Oncül O, Yoshikura H, Zeller H, Raoult D, Esen B. Epidemiological evaluation of a possible outbreak in and nearby Tokat province. Microbiyol Bul 2004; 38: 33-34.

15) Karti SS, Odabasi Z, Korten V, Yilmaz M, Sonmez M, Caylan R, Akdogan E, Eren N, Koksal I, Ovali E, Erickson BR, Vincent MJ, Nichol ST, Comer JA, Rollin PE, Ksiazek TG. Crimean-Congo hemorrhagic fever in Turkey. Emerg Infect Dis 2004; 10: 1379-1384.

16) Vorou RM. Crimean-Congo hemorrhagic fever in southeastern Europe. Int J Infect Dis 2009; 13: 659-662.

17) Subak S. Effects of climate on variability in Lyme disease incidence in the northeastern United States. Am J Epidemiol 2003; 157: 531-538.

18) Sanchez AJ, Vincent MJ, Nichol ST. Characterization of the glycoproteins of Crimean-Congo hemorrhagic fever virus. J Virol 2002; 76: 7263-7275.

19) Charrel RN, Attoui H, Butenko AM, Clegg JC, Deubel V, Frolova TV, Gould EA, Gritsun TS, Heinz FX, Labuda M, Lashkevich VA, Loktev V, Lundkvist A, Lvov DV, Mandl CW, Niedrig M, Papa A, Petrov VS, Plyusnin A, Randolph S, Süss J, Zlobin VI, de Lamballerie X. Tick-borne virus diseases of human interest in Europe. Clin Microbiol Infect 2004; 10: 1040-1055.

20) Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, Tasyaran MA, Vahaboglu H; Turkish CCHF Study Group. 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: 385-389.

21) Ergönül O, Celikba 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: 284-287.

22) Papa A, Christova I, Papadimitriou E, Antoniadis A. Crimean-Congo hemorrhagic fever in Bulgaria. Emerg Infect Dis 2004; 10: 1465-1467.

23) Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, Gundogdu M, Tasyaran MA. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. J Infect 2006; 52: 207-215.

24) Whitehouse CA. Crimean-Congo hemorrhagic fever. Antivir Res. 2004; 64: 145-160.

25) Schwarz TF, Nsanze A, Ameen AM. Clinical features of Crimean-Congo haemorrhagic fever in the United Arab Emirates. Infection 1997; 40: 364-367.

26) Yilmaz GR, Buzgan T, Torunoglu MA, Safran A, Irmak H, Com S, Uyar Y, Carhan A, Ozkaya E, Ertek M. A preliminary report on Crimean-Congo haemorrhagic fever in Turkey, March-June 2008. Euro Surveill 2008; 13: pii. 18953.

27) Karti SS1, Odabasi Z, Korten V, Yilmaz M, Sonmez M, Caylan R, Akdogan E, Eren N, Koksal I, Ovali E, Erickson BR, Vincent MJ, Nichol ST, Comer JA, Rollin PE, Ksiazek TG. Crimean-Congo hemorrhagic fever in Turkey. Emerg Infect Dis 2004; 10: 1379-1384.

28) Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. Pediatr Nephrol 2011; 26: 377-384.

29) Al-Tikriti SK, Al-Ani F, Jurji FJ, Tantawi H, Al-Moslih M, Al-Janabi N, Mahmud MI, Al-Bana A, Habib H, Al-Munthri H, Al-Janabi S, Al-Jawahry K, Yonan M, Hassan F, Simpson DI. Congo/Crimean haemorrhagic fever in Iraq. Bull World Health Organ 1981; 59: 85-90.

30) Swanepoel R. Crimean-Congo haemorrhagic fever, p. 723-729. In: JAW Coetzer, GR Thomson, and RC Tustin (ed.), Infectious diseases of livestock, with special reference to Southern Africa. Oxford University Press, Cape Town, South Africa, 1994.