DOI:10.34084/bshr.834435 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Research Article / Araştırma Makalesi

http://dergipark.org.tr/tr/pub/bshr

Epidemiological and Biochemical Evaluation of Patients Under Monitoring with A Diagnosis of Crimean-Congo Hemorrhagic Fever

Kırım Kongo Kanamalı Ateşi Tanısıyla İzlenen Hastaların Epidemiyolojik ve Biyokimyasal Olarak Değerlendirilmesi

Emine Parlak[1], Fatma Kesmez Can[1], Handan Köksal Alay[1], Mehmet Parlak[1], Zülal Özkurt[1], Zahide Koşan[2]

[1] Department of Infectious Diseases and Clinical Microbiology, Atatürk University Faculty of Medicine, Erzurum, Turkey.

[2] Department of Public Health, Atatürk University Faculty of Medicine, Erzurum, Turkey.

ORCID ID: Emine Parlak, https://orcid.org/0000-0001-8912-6360, Fatma Kesmez Can, https://orcid.org/0000-0001-8085-7589, Handan Köksal Alay, https://orcid.org/0000-0002-4406-014X, Mehmet Parlak, https://orcid.org/0000-0002-6235-4862, Zülal Özkurt, https://orcid.org/0000-0001-5554-8768, Zahide Koşan, https://orcid.org/0000-0002-1429-6207

***Sorumlu Yazar / Corresponding Author:** Dr. Emine Parlak, **e-posta / e-mail:** eparlak1@yahoo.com

Geliş Tarihi / Received: 01-12-2020 **Kabul Tarihi / Accepted:** 17-12-2020 **Yayın Tarihi / Online Published:** 31-12-2020

Atıf Gösterimi/How to Cite: Parlak E., Kesmez C., Köksal Alay H., Parlak M., Özkurt Z., Koşan Z. Epidemiological and Biochemical Evaluation of Patients Under Monitoring With A Diagnosis of Crimean-Congo Hemorrhagic Fever, J Biotechnol and Strategic Health Res. 2020;4(3):320-327

Özet

Amaç	Kırım Kongo Kanamalı Ateşi (KKKA), ilk kez 1944 yılında Kırım'da tanımlanmış bir viral hemorajik ateştir. Ülkemizde ilk 2002 yılında Tokat ve çevresindeki salgınla dikkati çekmiştir. Bu çalışmada KKKA hastalarının klinik, epidemiyolojik ve laboratuvar özelliklerinin değerlendirilmesi amaçlanmıştır.
Yöntem	Bu çalışma, Atatürk Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları Kliniği'nde Nisan 2012-Ağustos 2013 tarihleri arasında KKKA tanısıyla takip edilen erişkin yaştaki hastalar arasında yapılmıştır. Veriler prospektif olarak toplanıp, IBM-SPSS 20 paket programına kaydedildi. İstatistik analizlerinde Mann-Whitney U, Ki-kare ve Fisher exact testi kullanıldı.
Bulgular	Kırım Kongo Kanamalı Ateşi tanısı Refik Saydam Hıfzısıhha Merkezinde hasta serumlarında Enzyme-linked immunosorbent assay (ELISA) ile anti-CCFV IgM ve/veya virüs antijeni real time Polimeraz zincir reaksiyonu (RT-PCR) yöntemi ile konuldu. Toplam 121 olgu alındı. Hastaların 59 (%48,7)'i erkek, 62 (%51,2)'si kadın olup, yaş ortalaması 50.04 ± 18.22 (16-86) yıl idi. Hastaların %62,8'sinde kene teması saptanmıştır. İnkübasyon süresi 3.9±2,7 gün idi. Hastalardan 5 (%4,1)'i ölmüştür.
Sonuç	KKKA keneler tarafından taşınan ölümcül bir viral infeksiyondur. Korunmada en önemli faktör kene temasını önlemektir. Endemik bölgede yaşayanlar eğitilmeli, günlük kene kontrolü yapılması anlatılmalıdır. Hastalara yüksek ateş, kas ağrısı, baş ağrısı şikâyetleri ve kene teması mutlaka sorulmalıdır. KKKA olgularının erken tanı ve tedavi ile mortalite ve morbiditelerinin azaltılabileceğine inanmaktayız.
Anahtar kelimeler	Kırım Kongo Kanamalı Ateşi, mortalite oranı, Türkiye

Abstract

Aim	*Crimean-Congo Hemorrhagic Fever (CCHF) is a viral hemorrhagic fever. To evaluate the clinical, epidemiological and laboratory characteristics of patients with CCHF.*
Methods	*This study was performed with adult patients under monitoring with diagnosis of CCHF at the Atatürk University Faculty of Medicine Infectious Diseases Clinic between April 2012 and August 2013.*
Results	*Diagnosis of CCHF was based on presence of Enzyme-linked immunosorbent assay (ELISA) anti-CCFV IgM and/or virus antigen at Refik Saydam Hygiene Center (RSHM) in patient serum and/or real time Polymerase Chain Reaction (PCR). One hundred twenty-one cases were included. Fifty-eight (48.7%) of patients were male and 62(51.2%) female, with a mean age of 50.04 ± 18.22 (16-86) years. Contact with ticks was determined in 62.8% of patients. Length of incubation was 3.9±2.7 days. Five patients (4.1%) died.*
Conlusion	*CCHF which is carried by ticks is a fatal viral infection. The most important factor in protection is the prevention of tick contact. People living in endemic regions must be educated and instructed how to perform daily tick checks. Patients have got high fever, myalgia, headache and tick bite must be asked in history. We believe that early diagnosis and treatment of CCHF cases may significantly reduce morbidity and mortality.*
Key words	*Crimean-Congo Hemorrhagic Fever, mortality rate, Turkey*

GİRİŞ

Crimean-Congo Hemorrhagic Fever is the most common viral hemorrhagic fever worldwide.[1] The disease is active in more than 30 countries, particularly in Africa, Asia, Southeast Europe and the Middle East.[2] The agent involved in CCHF is an RNA virus belonging to the species Nairovirus from the Bunyaviridae. The virus is particularly carried by Hyalomma marginatum marginatum ticks.[1,3] The virus is transmitted to humans through infected ticks or through contact with blood, tissue or body fluids from viremic animals or also nosocomially.[4]

The incubation period is 3-7 days.[1] Initial symptoms characterized by a sudden increase in body temperature (39-41 ºC), headache, muscular pain and dizziness may also be accompanied by diarrhea, nausea and vomiting. Reddening in the face neck and chest and scleral and conjunctival hyperemia are also observed.[2] Fever lasts for a mean 4-5 days. The target cells in CCHF are mononuclear phagocytes, endothelial cells and hepatocytes. Increased capillary permeability and coagulation function disorders create a disposition to bleeding.[1] Thrombocytopenia results from a decrease in platelet production, platelet breakdown and endothelial injury. Endothelial injury can activate platelet accumulation and degranulation and intrinsic coagulation mechanisms.[1,5] Ecchymotic hemorrhages may appear in wide areas on the extremities on days 3-6 of the disease. The most common hemorrhages are from the nose and gums, although hematemesis, melena, hematuria, hemoptysis and intra-abdominal and vaginal bleeding may also be seen in severe cases.[6,7]

METHOD

One hundred twenty-one patients definitively diagnosed with CCHF with RT-PCR and/or ELISA and hospitalized for monitoring at the Atatürk University Medical Faculty Infectious Diseases and Clinical Microbiology Clinic between April 2012 and August 2013 were included in the study. Patients were divided into mild-moderate and severe groups on the basis of Swanepoel criteria[5] and the modified criteria recommended by Ergönül et al.[4] Swanepoel et al.[5] described at least one of the following laboratory values in the first 5 days after onset of symptoms – leukocyte number ≥ 10,000/mm3, platelet number ≤ 20,000/mm3 aspartate aminotransferase (AST) value ≥ 200 IU/L, alanine amino transferase (ALT) value ≥ 150 IU/L, activated partial thromboplastin time (aPTT) ≥ 60 sec or a fibrinogen level ≤ 110 µg/dl as representing severe cases, and the absence of any of these as mild-moderate cases.

Blood samples were collected from patients in order to obtain 2 ml of serum. After being stood for 30 min, blood specimens were centrifuged at 2000 rev/min for 5 min for serum separation. Sera were then placed into Eppendorf tubes. Serum specimens were then sent to the CCHF National Reference Center under appropriate transportation conditions for serological and virological tests used in the diagnosis of CCHF. Tests were studied using the in-house method in the virology laboratory. Commercial kits were not employed. The patients enrolled in this study were those with specific IgM antibody positivity as a result of tests performed by the laboratory or in whom presence of CCHFV in sera was confirmed with PCR.

Data analysis was performed on Statistical Package for Social Sciences (IBM-SPSS; Ver: 20.0) software with a Microsoft Windows database. $p< 0.05$ was regarded as significant for all tests. Numeric data were expressed as mean plus standard deviation and categoric data as number and percentage. The Mann Whitney U, Fischer's exact and chi-square tests were used in data analysis.

RESULTS

The study involved 121 patients, 58 (48.7%) men and 62 (51.2%) women, with a mean age of 50.04 ± 18.22 (16-86). There was no significant difference between the groups in terms of sex and age. Median for non-normally distributed age was 53. In terms of severity criteria, 48 (39.7%) were in the severe group and 73 (60.3%) in the mild-moderate group. Mean age of the non-surviving patients was

59.4±19.4 (median 67), and mean age of the surviving patients was 49.64±18.15 (median 53) (p=0.1959). Age was determined to have no effect on survival. We attributed this to the low number of non-surviving patients. Mean age of the severe cases was 45.73±16.96 (median 57), and mean age of the mild cases was 52.8±16.96 (median 45) (p=0.033). Five of the patients enrolled (4.1%) died. Cause of death in one patient was atrial fibrillation. Sudden loss of consciousness immediately followed by cardiopulmonary arrest developed in another. One hundred sixteen (95.9%) patients were discharged in a healthy condition.
A history of contact with ticks was present in 76 (62.8%) patients. Mean length of incubation was 3.9±2.7 days. Patients presented in a mean 4.8 ± 2.5 days after onset of symptoms. Mean length of hospitalization was 7.92±4.07 days. Blood and blood products were required by 49 (40.5%) patients.

All patients lived in rural areas or had a history of visiting such areas. Forty (33.1%) patients worked in animal husbandry and 32(26.4%) in farming, while 34 (28.1%) were housewives, 6 (5%) were self-employed, 3 (2.5%) were retired, 3 (2.5%) were shepherds and 2(1.7%) were students. Patients' demographic characteristics are shown in Table 1.

Table 1. Clinical and demographic characteristics of patients with CCHF infection

n=121	%
Female sex	51.2
Age years (mean age±SD)	50.04 ± 18.22
Tick bite history	62.8
Severe group	39.7
Vocation	
Animal husbandry	33.1
Housewives	28.1
Farming	26.4
Other	12.4
Died	4.1
Symptoms and signs	
Malaise	99.2
Lack of appetite	88.4
Fever	86
Myalgia	85
Hepatomegaly	73.6
Splenomegaly	63.6
Facial hyperemia	63.6
Headache	62
Nausea	64.5
Conjunctival hyperemia	48.8
Diarrhea	31.4
Hemorrhagic manifestations	18.2
Confusion	7.4

The most commonly observed symptoms were malaise (99.2%), fever (86%), myalgia (85%) and lack of appetite (88.4%). Headache (62%), nausea (64.5%), vomiting (44.6%), diarrhea (31.4%) and confusion (7.4%) were also seen. Hemorrhage was observed in 22(18.2%) patients during hospitalization or at subsequent monitoring. The most common forms of bleeding were gingival, nasal and vaginal. Melena was present in one (1.6%) patient. Patients' symptoms are shown in Table 1.

The most common physical examination findings were hepatomegaly (73.6%), splenomegaly (63.6%), facial hyperemia (63.6%) and conjunctival hyperemia (48.8%). Severe hemorrhage occurred in 7 (5.8%) patients during monitoring. Four of these patients died and 3 were discharged in a healthy condition. Hemorrhage into the rectus muscle occurred in one patients and hemarthrosis in one.

Radiologically, panbronchiolitis was present in one (0.8%) patient and diffuse pneumonic infiltration in 2 (1.7%) of the non-surviving patients, and no clinical and laboratory findings of secondary bacterial or viral infection were determined in these. Bradycardia was seen in 3 (2.5%) patients, and these were discharged in a healthy condition. Atrial fibrillation developed in one (0.8%) patient, who did not survive. Patients' physical examination findings are shown in Table 1.

Patients were divided into mild-moderate or severe cases on the basis of laboratory findings and clinical poor prognosis criteria. The laboratory parameters white blood cell counts (WBC), platelet (Plt), AST, ALT, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), prothrombin time (PT), aPTT and International normalized ratio (INR) values were investigated in this study. Baseline laboratory values of the fatal and recovered groups are presented table 2. Laboratory values of the severe and mild-moderete groups are show in table 3. Clinical characteristics of the severe and mild-moderete groups are show in table 4.

Table 2: Comparison between died and recovered CCHF patient's laboratory values

	Died (n=5) (Mean ±SD)	Recovered (n=116) (Mean ±SD)	p value
WBC(103/mm3)	2700±1680.8	2101.21±1203.8	0.446
PLT(/mm3)	29400±15339.5	48836±33942.6	0.214
AST(IU/L)	**1849±1773.5**	**387.51 ± 491.4**	**0.007**
ALT(IU/L)	**649.80±469.9**	**216.89 ± 334.1**	**0.01**
CK(IU/L)	**3086.80±2836.3**	**722.39 ± 853.3**	**0.004**
LDH(IU/L)	**3395±2929.5**	**813.99± 966.9**	**0.01**
PT(sec)	11.98±2.6	12.65±8.9	0.84
aPTT(sec)	52.34±28.1	36.43±8.1	0.13
INR	1.19±0.2	1.08±0.2	0.29

CCHF: Crimean-Congo hemorrhagic fever; WBC: white blood cell counts; PLT: platelets; AST aspartate aminotransferase; ALT alanine amino transferase; CPK Creatine phosphokinase; LDH lactate dehydrogenase; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio.

Table 3: Comparison of mild/moderate and severe patient's laboratory values

	Mild-moderate (n=73) (Mean ±SD)	Severe (n=48) (Mean ±SD)	p value
WBC(103/mm3)	2096±831.48	2170.8±1661.3	0.54
PLT(/mm3)	**64671.2±31756.0**	**22.729.2±15773.3**	**0.001**
AST(IU/L)	**252.2±448.7**	**745.5±786.1**	**0.001**
ALT(IU/L)	**134.3±130.9**	**387.6±495.1**	**0.001**
CK(IU/L)	**531.6±548.8**	**1258.8±1499.7**	**0.001**
LDH(IU/L)	**563.9±414.7**	**1463.2±1713.4**	**0.001**
PT(sec)	11.6±1.9	14.2±13.6	0.39
aPTT(sec)	**33.51±5.97**	**42.5±12.2**	**0.001**
INR	1.06±0.19	1.13±0.27	0.64

CCHF: Crimean-Congo hemorrhagic fever; WBC: white blood cell counts; PLT: platelets; AST aspartate aminotransferase; ALT alanine amino transferase; CPK Creatine phosphokinase; LDH lactate dehydrogenase; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio.

Table 4. Comparison of clinical characteristics between the severe patients and the mild-moderete patients

Clinical characteristics and signs	p*
Myalgia	0.007
Lack of appetite	0.039
Diarrhea	0.006
Hemorrhagic manifestations	0.001
Confusion	0.028
Abdominal pain	0.03
Facial hyperemia	0.004
Lung auscultation findings	0.011
Blood products used	0.001

Note: *p value between the severe and mild-moderate patient groups

DISCUSSION

CCHF is a viral zoonotic infection seen in Africa, Asia, Eastern Europe and the Middle East. CCHF is an important problem for Turkey because of its high mortality. The first case in Turkey was reported in 2002.[1,8]

The virus is transmitted to human through bites by infected ticks or contact with blood and tissues during the slaughter of viremic animals.[1] One study examined predispo-

sing factors in 123 cases of CCHF and reported a history of tick bite in 44%, animal contact with tick bite in 37% and contact with a patient with CCHF in 6%. No predisposing factor was determined in 17%, but the possibility of tick bite was reported.[9] Studies in Turkey have determined a history of ticks in 50-60% of cases.[10-12] The incubation period of the disease is 1-9 days following tick bites. It is 3-10 days after the index case among hospital personnel.[1,13] Ozkurt et al.[14] determined a history contact with ticks in 45% of patients. Length of incubation in subjects with a history of tick contact is reported at 4 days. Mean length of incubation in our patients with a history of tick contact was 3.9±2.7 days.

Distribution between the sexes varies among countries, depending on the extent to which women participate in agriculture.1 Ozkurt et al.[14] reported 46.7% female patients and 53.3% male; percentages between male and female genders were similar and no significant difference was determined. In our study, 47.9% of patients were male and 51.2% female. No significant difference was determined in terms of gender distribution. Mean age of the patients in our study was 50.04 ± 18.22. Our findings are in agreement with those of previous epidemiological studies.[8,10,15] Agricultural workers, individuals engaged in animal husbandry (such as farmers, shepherds, abattoir workers and butchers), veterinarians, individuals in contact with sick animals, health workers in endemic regions, military personnel and campers are at high risk of the disease.[16] Ninety percent of cases in Turkey involve subjects working in farming and animal husbandry.[1] Cases are of active working age, and therefore concentrate more in people who work in agriculture and livestock raising than in tick exposure.[10,12] In our study, 33.1% of patients were engaged in animal husbandry, 26.4% in farming and 28.1% were housewives, and all housewives worked in farming or livestock raising. Three patients (2.5%) were shepherds. Two (1.7%) were students, 3 (2.5%) were retired and 6 (5%) were self-employed. The most important risk factors are working in agriculture or animal husbandry and visiting rural areas.[1] Examination of the epidemiological features in our CCHF patient group showed that all patients lived in rural areas or had a history of visiting such areas. Health workers are the second most affected group. CCHF infections and deaths among health workers are reported parallel to epidemics in the general population.[17-20] Percutaneous exposure, procedures on patients with gastrointestinal system hemorrhage, and contact with patients undergoing emergency operations but not yet diagnosed with CCHF are the most risky situations.[1] None of our personnel had a history of nosocomial transmission.

Fever of sudden onset of 39-40 °C, lethargy, diffuse joint pains, head ache and sore throat are seen. Symptoms such as nausea, vomiting, diarrhea and abdominal pain may sometimes be observed. Early symptoms may be hypotension, conjunctival hyperemia, reddening in the skin and malar rash in the face.[21] There is a predisposition to mucosal and cutaneous bleeding in subjects with deep thrombocytopenia and hemostasis panel impairment. Hemorrhagic symptoms such as gingival bleeding, epistaxis, hematuria, hemoptysis and bleeding in internal organs may be seen. Mental confusion and agitation may be seen in severe cases.[1,6,14] Symptoms in our patients were, in order, lethargy in 992%, lack of appetite in 88.4%, fever in 86%, diffuse body pain in 85%, nausea in 64.5%, headache in 62%, vomiting in 44.6%, abdominal pain in 42.1% and bleeding in 18.2%.Physical examination findings in our patients, again in order, were facial hyperemia in 63.6%, conjunctival hyperemia in 48.8%, cutaneous eruption in 22%, cough in 16% and altered mental state in 16%. Various pulmonary examination findings, such as rales, rhonchi and wheezes were present in respiratory sounds in 37.6% of patients. Cardiac examination findings of bradycardia were reported in 3 (2.5%) patients. Our findings were in agreement with the literature.[10-12,22]

Serum AST, ALT, CPK and LDH values were generally elevated in our patients.[11,12] Hepatosplenomegaly was reported in 1 in 3 patients. Hepatomegaly has been repor-

ted in 20-40% of cases in Turkey and splenomegaly in 14-23%.[10,14] In their study of patients with CCHF, Burt et al.[23] determined presence of the virus in hepatocytes and reported that injury in the hepatic parenchyma was associated with the direct cytopathic effect of the virus. Rodrigues et al.[24] reported that CCHFV replication in hepatocytes induced apoptosis through a cytopathic effect. These studies support the idea that elevation in hepatic transaminases is a result of the virus' cytopathic. In this study we determined hepatomegaly in 73.6% of patients in this study and splenomegaly in 63.6%. Elevated hepatic transaminase levels were determined in almost all our patients. Serum AST, ALT, LDH and CK levels were significantly higher in non-surviving compared to surviving patients. PT, PTT and INR were longer in severe patients. We think that AST and ALT elevation is a common laboratory finding in patients with CCHF and is of prognostic significance.

Leukopenia, thrombocytopenia and anemia are also seen in CCHF. Severe thrombocytopenia is present from the early stage of the disease in fatal cases. Leukocytosis has been seen in some severe cases.[25,26] Anemia is not generally seen in the early stage of the disease, although a decrease in hemoglobin may be determined in the late period in clinically severe cases.[1,21] The cytopenia seen in patients with CCHF is thought to be related to hemophagocytic syndrome. Histopathological findings compatible with hemophagocytosis have been encountered in bone marrow biopsies from patients with CCHF in Turkey.1 Endothelial injury is although though to possibly contribute to platelet breakdown.[1,5] Thrombocytopenia was present in all the patients in our study. Severe thrombocytopenia was present from the early period in patients with a severe-fatal course. Prolonged PT and aPTT, increased fibrin breakdown products and a decrease in fibrinogen levels may be seen clinically severe cases.[1,25] AST and ALT values > 700 IU and> 900 IU have high sensitivity in severe cases. Blood count and biochemical tests return to normal levels in 5-9 days in surviving cases.[1] Bakır et al.[10] reported higher INR, AST, LDH and CK levels in non-surviving patients. That study also reported that splenomegaly and impaired consciousness are predictors of mortality. One study from Turkey stated that elevated AST and ALT (>700 and>900 U/L) levels are more sensitive in identifying fatal cases.[1] Leukocytosis was seen in only one in five non-surviving patients. Another study identified cerebral bleeding, severe anemia, severe dehydration, prolonged diarrhea, myocardial infarction, pulmonary edema and pleural effusion as factors contributing to mortality.[27] Ergonul et al.[28] identified high viremia and very high transaminase values as markers of poor prognosis and determined intense and prolonged viremia in fatal cases. Viremia levels were shown to have prognostic attributes, levels in fatal cases being 1000 times higher than in surviving patients.[29] In a same study from Turkey, Çevik et al.[29] suggested that viral load is a factor showing prognosis in cases of CCHF. Saksida et al.[30] reported that an effective immune response suppressed viral replication in surviving patients, while viremia could not be controlled due to insufficient immunity in non-surviving patients. These studies all show that the disease will be fatal if viral replication cannot be suppressed by the immune system. Vascular leakage, multi-organ failure, shock and hemorrhage all show severe disease in patients with CCHF. Death occurs in 5-14 days.[31] Impaired consciousness, splenomegaly, somnolence, hematemesis, melena, high fever, disseminated intravascular coagulation (DIC) and kidney failure have all been reported as clinically defined poor prognosis.[10,22] AST, ALT, CPK and LDH values were >1000 in all our fatal cases. In addition, various degrees of impaired consciousness were present in these cases. The fatality rate in cases of CCHF is approximately 5-30%.[1,12] One study from Turkey reported a death rate of 5% in cases.[25] Bakır et al.[26] assessed mortality at 10 %. Ozkurt et al.[14] determined a mortality rate of 10%. CCHFV strains in Turkey are 95-98% homologous with strains in Russia and Kosovo. Mortality rates in an epidemic in Kosovo in 2001 were similar to those in Turkey at 8.6%. The disease was observed to be more severe in advanced age. Advanced age did not increase fatality in our study. Tasdelen et al.[32] however, identified advanced age as an early

marker of poor prognosis and fatality. The mortality rate in our study was 4.1%. Various degrees of impaired consciousness were present in all our fatal cases. Severe DIC related pulmonary and GIS bleeding occurred in one of our cases. Acute renal failure developed in 2 of our cases. Myocardial infarction occurred in one of our fatal cases. Non-surviving patients' platelet levels at presentation were < 20000. A severe course was observed in one case with accompanying chronic hepatitis B. Aspartate aminotransferase values increased to 13,000 in a patient with HBV DNA > 2000 IU/ml and not receiving antiviral therapy. Pleural effusion and bleeding into the abdomen were observed. The patient was monitored under intensive care conditions, and double filtration was performed 5 times. The patient was discharged in a healthy condition. Variation in clinical picture and fatality levels was attributed to the geographic diversity and virulence of the violence and appropriate early support therapy.[1,11]

In conclusion, CCHF should be considered in patients with high fever, myalgia, lack of appetite and pancytopenia if the epidemiological history is compatible. Aspartate aminotransferase, ALT, CK and LDH elevation were identified as poor prognostic criteria in non-surviving patients. Advanced age, AST, ALT, CK and LDH elevation, low platelet levels and prolonged PTT and hospitalization indicated a severe course. Hemorrhagic manifestations, diarrhea, myalgia, lack of appetite, confusion, abdominal pain, facial hyperemia, lung auscultation findings and used to blood products indicated a severe course.

''This study was not supported by any institution or pharmaceutical agency. No conflict of interest was declared by the authors."

Kaynaklar

1. *Ergonul O. Crimean-Congo hemorrhagic fever. Lancet Infect Dis 2006; 6: 203-214.*
2. *Tuygun N, Tanir G, Caglayık DY, et al. Pediatric cases of Crimean-Congo hemorrhagic fever in Turkey. Pediatrics International 2012; 54:402-406.*
3. *Leblebicioglu H, Bodur H, Dokuzoguz B, et al. Case management and supportive treatment for patients with Crimean-Congo hemorrhagic fever. Vector Borne Zoonotic Dis 2012; 12(9): 805-811.*
4. *Dilber E, Cakir M, Acar EA, et al. Crimean-Congo hemorrhagic fever among children in north-eastern Turkey. Ann Trop Paediatr 2009;29: 23-28.*
5. *Swanepoel R, Gill DE, Shepherd AJ, et al. The clinical pathology of Crimean-Congo hemorrhagic fever. Rev Infect Dis 1989; 11(Suppl 4): 794-800. 1-4.*
6. *Cevik MA, Erbay A, Bodur H, et al. Clinical and laboratory features of Crimean-Congo haemorrhagic fever: predictors of fatality. Int J Infect Dis 2008; 12: 374-379.*
7. *Leblebicioglu H. Crimean-Congo haemorrhagic fever in Eurasia. Int J Antimicrob Agents 2010; 36(1): S43-S46.*
8. *Ertugrul B, Uyar Y, Yavas K, et al. An outbreak of Crimean-Congo haemorrhagic fever in western Anatolia, Turkey. Int J Infec Dis 2009;13: e431-e436.*
9. *Anonymous.SouthAfrica1981.http//www.angefire.com/punk/lymedisease/cchf81.html*
10. *Bakir M, Ugurlu M, Dokuzoguz B, et al. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures. J Med Microbiol 2005: 54 385-389.*
11. *Ergonul O, Celikbas A, Baykam N, et al. Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited. Clin Microbiol Infect 2006; 12 (6): 551-554.*
12. *Karti SS, Odabasi Z, Korten V, et al. Crimean-Congo Hemorrhagic Fever in Turkey. Emerg Infect Dis 2004; 19: 1379-1384.*
13. *Parlak E, Koşan Z, Ertürk A, et al. A nosocomial outbreak of Crimean-Congo hemorrhagic fever. J Microbiol Infect Dis 2015;5(1): 5-9.*
14. *Ozkurt Z, Kiki I, Erol S, et al: Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy, J Infect 2006; 52 (3): 207-215.*
15. *Shepherd AJ, Swanepoel R, Leman PA, et al. Comparison of methods for isolation and titration of Crimean-Congo hemorrhagic fever virus. J Clin Microbiol 1986; 24: 654-656.*
16. *LeDue JW. Epidemiology hemorrhagic fever viruses. Rev Infect Dıs 1989:11 (Suppl 11):S370-5.*
17. *Ftika L, Maltezou HC. Viral haemorrhagic fevers in healthcare settings. J Hosp Infect 2013; 83(3):185-192.*
18. *Aradaib IE, Erickson BR, Mustafa ME, et al. Nosocomial outbreak of Crimean-Congo hemorrhagic fever, Sudan. Emerg Infect Dis 2010;16: 837-839.*
19. *Gürbüz Y, Sencan İ, Öztürk B, et al. A case of nosocomial transmission of Crimean—Congo hemorrhagic fever from patient to patient. Int J Infect Dis 2009;13:e105—e107.*
20. *Mardani M, Namazee N. Close contact precautions could prevent an outbreak of Crimean-Congo Hemorrhagic Fever: A case series report from southern part of Tehran. Int J Prev Med 2013;4(6):715–719.*
21. *Ergönül Ö. Crimean-Congo hemorrhagic fever virus: new outbreaks, new discoveries. Curr Opin Virol in 2012; 2: 215-220.*
22. *Jamil B, Hasan RS, Sarwari AR, et al. Crimean-Congo hemorrhagic fever: experience at a tertiary care hospital in Karachi, Pakistan. Trans R Soc Trop Med Hyg 2005;99(8):577-661.*
23. *Burt FJ, Swanepoel R, Shieh WJ, et al.. Immunohistochemical and in situ localization of Crimean-Congo hemorrhagic fever virus in human tissues and implications for CCHF pathogenesis. Arch Pathol Lab Med 1997; 121(8): 839-846.*
24. *Rodrigues R, Paranhos-Baccalà G, Vernet G, Peyrefitte CN. Crimean Congo hemorrhagic fever virus infected hepatocytes induce ER-stress and apoptosis crosstalk. PLoS One 2012;7(1):e29712.*
25. *Duygu F, Kaya T, Baysan P. Re-evaluation of 400 Crieman-Congon Hemorrhagic Fever Cases in an Endemic area: Is Ribavirin treatment suitable? Vector Borne Zoonotic Dis 2012;12(9): 812-816.*
26. *Bakır M, Engin A, Gozel MG, et al. A new perspective to determine the severity of cases Crimean-Congo hemorrhagic fever. J Vector Borne Dis 2012; 49(2):105-110.*
27. *Whitehouse CA. Crimean-Congo hemorrhagic fever. Antiviral Res 2004; 64:145-60.*
28. *Duh D, Saksida A, Petrovec M, et al. Viral load as predictor of Crimean-Congo haemorrhagic fever outcome. Emerg Infect Dis 2007; 13: 1769-72.*
29. *Cevik MA, Erbay A, Bodur H, et al. A. Viral load as a predictor of outcome in Crimean-Congo hemorrhagic fever. Clin Infect Dis 2007; 45(7): e 96-100.*
30. *Saksida A, Duh D, Wraber B, et al. Interacting roles of immune mechanisms and viral load in the pathogenesis of crimean-congo hemorrhagic fever. Clin Vaccine Immunol 2010;17(7):1086-1179.*
31. *Bente DA, Whitehouse CA. Crimean-Congo hemorrhagic fever. Antiviral research 2013; 100:159-189.*
32. *Tasdelen Fisgin N, Tanyel E, Doganci L, et al. Risk factors for fatality in patients with Crieman-Congo hemorrhagic fever. Trop Doct 2009; 39:158-160.*