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Importance of pulmonary involvement in Crimean–Congo hemorrhagic fever

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Abstract:

BACGROUND AND AIM: Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease caused by a virus belonging to the Bunyaviridae family. The aim of this study is to evaluate respiratory and radiological findings of cases and the impact on mortality.

MATERIALS AND METHODS: This retrospective study included patients who were diagnosed by the polymerase chain reaction test as CCHF and examined in terms of pulmonary and radiological findings. Two hundred and forty-one patients reviewed retrospectively. Clinical, laboratory, demographic characteristics, pulmonary symptoms, examination and radiological findings, and treatment results were recorded, and data of all surviving and nonsurviving patients were compared.

RESULTS: A total of 241 patients (157 males and 84 females) were enrolled in the current study. The mean age of the patients was 49.7 ± 19.50 years. A total of 66 patients had chest X-ray (CXR) findings, and the most common were ground-glass opacity ($n = 31$, 33.7%), consolidation ($n = 23$, 25%), and pleural effusion (12%, 13%). The presence of respiratory system examination findings, pulmonary symptoms, and CXR findings were statistically significant in the nonsurvival group ($P < 0.005$).

CONCLUSIONS: Respiratory system findings seem to be an important factor in mortality patients with CHF cases, so we believe that detailed pulmonary evaluation and timely supportive treatment will be important in these cases.

Keywords:

Chest computed tomography, chest X-ray, Congo hemorrhagic fever, mortality

Introduction

Crimean–Congo hemorrhagic fever (CCHF) is a zoonotic disease caused by a virus belonging to the Bunyaviridae family, which can be transmitted as a result of high mortality in humans, mostly due to contact with ticks and infected blood and body fluids. The principal vectors are *Hyalomma* ticks [Figure 1]. CCHF usually affects many organs. Mortality rates vary between 3% and 80% depending on the virus strain and epidemiological characteristics.[1]

Although there are many studies on CCHF, there are few studies on respiratory system involvement and findings. In this study, we aimed to investigate the respiratory and radiological findings of CCHF cases diagnosed and treated in our center retrospectively, and the main purpose was to evaluate the effect of pulmonary involvement on mortality.

Materials and Methods

Patients who were hospitalized in Gaziosmanpaşa University Medical

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Faculty Infectious Diseases Clinic between January 2015 and August 2019 with the diagnosis of CCHF were evaluated. Local ethics committee approval was obtained from the clinical research ethics committee of the Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (protocol no. 19-KAEK-183). The medical records of 241 patients who were diagnosed by the polymerase chain reaction (real-time PCR) test were reviewed retrospectively. We examined the pulmonary involvement in terms of severity, duration, treatment, and outcome of the disease. Radiological interpretations made by an experienced pulmonologist. Clinical, laboratory, demographic characteristics, pulmonary symptoms, examination and radiological findings, and treatment results were recorded, and data of all surviving and nonsurviving patients were compared. Patients with incomplete data and hospitalized with a preliminary diagnosis of CCHF but whose PCR test was negative were excluded from the study.

The Statistical Package for the Social Sciences (IBM SPSS Inc., version 22, Chicago, IL) was used for the analysis of statistical data. Descriptive data were given as mean, standard deviation, median, number, or percentage, and Student's *t*-test for matched groups and independence between variables were analyzed using Chi-square independence analysis; $P < 0.05$ was considered statistically significant.

Results

In our study, 157 (65.1%) male and 84 (34.9%) female patients with a mean age of 49.7 ± 19.50 were evaluated. A total of 66 patients (27.3%) had chest X-ray (CXR) findings, the most common ground-glass opacity ($n = 31$, 46.9%), consolidation ($n = 23$, 34.8%), and pleural effusion (12, 18.1%). The most common chest computed tomography (CCT) findings were pleural effusion ($n = 5$, 56%), consolidation ($n = 4$, 45%), and atelectasis ($n = 4$, 45%) [Table 1]. When the surviving and nonsurviving patient groups were compared, only the late admission time from the demographic characteristics to the hospital had a negative effect on mortality ($P < 0.005$). Presence of pulmonary symptoms, respiratory system examination and CXR findings [Table 2]; also from laboratory parameters which were; height white blood cell (WBC), lymphocyte count, blood urea nitrogen (BUN), creatine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), direct serum bilirubin (D-bilirubin), total serum bilirubin (T-bilirubin), ferritin, partial thromboplastin time(s) (PTT), activated PTT (APTT), and low platelet count were found to have a negative effect on mortality [Table 3] ($P < 0.005$).

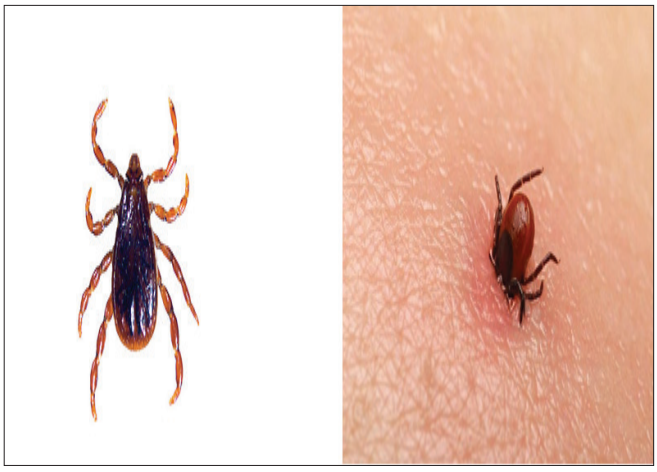

Figure 1: *Hyalomma* ticks

Discussion

CCHF is an acute viral disease that affects many organs and may be characterized by diffuse ecchymosis, internal bleeding, and impaired liver function with lethal potential. In addition to clinical findings, laboratory abnormalities such as leukopenia, thrombocytopenia, high muscle, and liver enzymes are present in most patients.[2] After biting a tick, the CCHF virus crosses the epithelium, reaches endothelial cells, and causes damage to the cells. This damage in endothelial cells occurs either directly by the effect of the virus or indirectly as a result of the activation of immunological and

Table 1: Chest X-ray and computed tomography findings of patients

	n (%)
Chest X-ray (*n*=241)	
No	175 (72.6)
Yes	66 (27.4)
CCT (*n*=241)	
Unappropriated	232 (96.3)
Appropriated	9 (3.7)
CXR findings (*n*=92)	
Ground-glass opacity	31 (46.9)
Consolidation	23 (34.8)
Pleural effusion	12 (18.1)
Sequela changes	11 (16.6)
Hitler pathology	7 (10.6)
Atelectasis	3 (4.5)
Mediastinal pathology	2 (3.0)
Others (pleural calcification, etc.)	3 (4.5)
CCT findings (*n*=20)	
Pleural effusion	5 (56)
Consolidation	4 (45)
Atelectasis	4 (45)
Ground-glass opacity	3 (33)
Mediastinal/Hitler pathology	2 (22)
Pulmonary vascular pathology	1 (11)
Others (emphysema)	1 (11)

CXR: Chest X-ray, CCT: Chest computed tomography

Table 2: Comparison of demographic characteristics, pulmonary symptoms, pulmonary examination, and chest X-ray graphy findings in survival and nonsurvival groups

Variables	Survived (*n*=224), *n* (%)	Nonsurvival (*n*=17), *n* (%)	*P*
Age (year), mean±SD	49.08±19.19	58.58±21.83	0.052
Admission time (day), mean±SD	3.94±2.37830	6.00±2.42	**0.001**
Gender			
Male	143 (59.3)	14 (5.8)	0.186
Woman	81 (33.6)	3 (1.2)	
Occupation			
Homemaker	65 (29.6)	3 (1.2)	0.72
Farming	50 (20.7)	3 (1.2)	
Animal husbandry	36 (14.9)	4 (1.6)	
Tradesman	24 (9.9)	4 (1.6)	
Student	23 (9.5)	1 (0.4)	
Officer	18 (7.4)	1 (0.4)	
Unknown	7 (2.9)	1 (0.4)	
Other	1 (0.4)	0	
Smoking habit			
No smoking	140 (58.0)	12 (4.9)	0.85
Quitted smoking	41 (17.0)	3 (1.2)	
Smoking	39 (16.1)	2 (0.8)	
Unknown	4 (1.6)	0	
Place of residence			
Rural	125 (51.8)	13 (5.3)	0.12
Urban	99 (41.0)	4 (1.6)	
Tick contact history			
Yes	173 (71.7)	15 (6.2)	0.38
No	51 (21.1)	2 (0.8)	
Pulmonary symptoms			
No	193 (80)	2 (0.8)	**0.001**
Yes	31 (12.8)	15 (6.2)	
Pulmonary examination findings			
No	201 (83.4)	4 (1.6)	**0.001**
Yes	23 (9.5)	13 (5.3)	
CXR findings			
No	174 (72.1)	1 (0.4)	**0.001**
Yes	50 (20.7)	16 (6.6)	

Bold values indicate statistically significant. SD: Standard deviation, CXR: Chest X-ray

inflammatory pathways.[3] Cytokines, chemokines, and other pro-inflammatory mediators are released, resulting in endothelial cell activation and endothelial damage, vascular permeability increases, intrinsic coagulation system is activated, and disseminated intravascular coagulation develops.[4]

Direct pulmonary interstitial tissue invasion by the CCHF virus has not yet been reported.[5] Some studies are reporting the effects of CCHF on different organs.[6,7] However, few publications are reporting the effects of this disease on the respiratory system. A retrospective study of the evaluation on 183 cases by Doğan *et al*.[8] reported that cough and dyspnea were more common symptoms and that there were only 6 cases with hemoptysis, and 33 had abnormal CXR findings, 19 of which were parenchymal infiltration. Symptoms of dyspnea, chest pain and hemoptysis, and infiltration on lung radiographs are indicative of poor prognosis and may indicate mortality.[9] Another study by Aktaş *et al*. examined 165 patients with CCHF. In the first examination, single and/or multiple pathological findings were detected in 93 (56.4%) patients which of these 74 (44.8%) consolidation, 64 (39.8%) pleural effusion, 49 (29.7%) ground-glass opacity, and 30 (18.2%) atelectasis due to CXR.[10] In our study, we detected abnormal CXR findings in 66 (27.4%) patients retrospectively. The most common findings were ground-glass opacity (31, [46.9%]), consolidation (23 [34.8%]), pleural effusion (12 [18.1%]), and sequela changes (11 [16.6%]). Although chest radiographs are not sufficient for detailed evaluation, infiltration may be seen on radiographs in cases such as pulmonary parenchymal bleeding. CCT is useful for detecting pulmonary parenchymal bleeding in patients.[11] In a study of 563 CCHF cases by Aktaş *et al*.,[12]

Table 3: Comparison of laboratory results on survival and nonsurvival groups

Variables	Mean±SD		*P*
	Survived (*n*=224)	Nonsurvival (*n*=17)	
WBC	2.643±2.121	6.382±5.385	**0.000**
Neutrophil count	2.206±7.710	4.914±4.519	0.326
Lymphocyte count	0.804±0.556	1.151±0.840	**0.01**
Monocyte count	0.234±0.2505	0.201±0.241	0.871
Basophil count	0.034±0.114	0.061±0.084	0.663
RBC	4.808±0.595	4.957±0.581	0.985
Hgb	13.63±2.696	14.46±1.646	0.678
HCT	39.59±5.220	41.71±4.789	0.791
RDW	14.09±8.111	13.31±1.308	0.689
PLT	55,460.71±38,272.14	28,511.76±16,181.466	**0.004**
PDW (mean±SD)	14.67±7.905	13.66±4.650	0.841
CRP	19.59±34.578	65.36±84.236	**0.001**
BUN	13.68±6.672	37.88±27.933	**0.000**
Creatine	0.78±0.314	1.90±1.373	**0.000**
ALT	165.01±178.256	590.05±689.000	**0.000**
AST (mean±SD)	312.20±355.915	1107.82±860.299	**0.000**
LDH	687.72±479.810	2269.11±1528.441	**0.000**
CK	752.41±926.260	1769.05±1496.430	**0.000**
D-bilirubin	0.31±0.833	1.01±1.359	**0.001**
T-bilirubin	0.66±0.614	1.71±1.612	**0.000**
D-dimer	3.87±9.157	11.67±8.394	0.542
Procalcitonin	0.66±1.021	2.38±2.765	0.021
Ferritin	6493.50±11,244.509	12,168.25±22,318.092	**0.003**
PTT, %	96.44±25.498	56.35±25.321	0.624
PTT, s	14.08±4.321	20.21±6.742	**0.012**
INR	1.16±0.644	1.78±0.819	0.064
APTT (mean±SD)	46.10±15.565	54.42±27.830	**0.000**
Fibrinogen	229.62±69.959	167.88±110.165	0.094

Bold values indicate statistically significant. WBC: White blood cell, RBC: Red blood cell, Hgb: Hemoglobin, HCT: Hematocrit, RDW: Red cell distribution width, PLT: Platelet, PDW: Platelet distribution width, CRP: C-reactive protein, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatinine kinase, D-bilirubin: Direct serum bilirubin, T-bilirubin: Total serum bilirubin, PTT: Partial thromboplastin time, INR: International normalized ratio, APTT: Activated partial thromboplastin time, SD: Standard deviation

CCT scans of 40 patients taken within the indication were examined; the most common CCT findings were parenchymal infiltration (32 [80%]), pleural effusion (31 [77.5%]), and alveolar infiltration (28 [70%]). In our study, only nine patients were evaluated with CCT, and pleural effusion (5 [56%]), consolidation (4 [45%]), and atelectasis (4 [45%]) were the most common findings. The radiological findings of our two cases are shown in Figures 2 and 3.

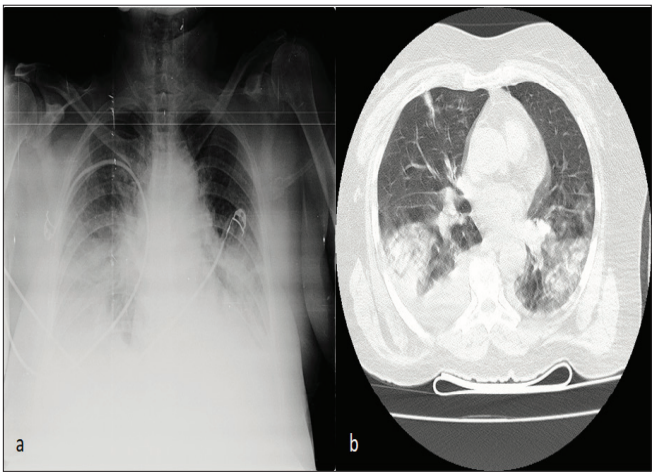

Figure 2: Radiological findings of a 46-year-old man patient at admission who was nonsurvival during follow-up; (a) Unilateral pleural effusion and consolidation at chest X-ray graphy. (b) Ground-glass opacities, consolidation with air bronchograms, and bilateral pleural effusion at chest computed tomography

The lungs are one of the organs frequently affected by CHF, although the literature on lung involvement is very limited. Pulmonary symptoms as dyspnea, chest pain, and hemoptysis are indicative of a worse prognosis and more often seen in those who will die from CCHF.[9,13] Bilgin *et al*.,[1] found no association between respiratory symptoms and survival in 128 patients. However, Doğan *et al*.[8] evaluated 108 patients with CCHF and demonstrated that pathological CXR findings were higher among the CCHF patients who died than among the survivors, but the difference was not significant. Furthermore, there was a very statistically significant relationship between the CXR findings of patients and between cough symptoms at the nonsurvivals to survivals on Aktaş *et al*.'s study.[10] The study of 283

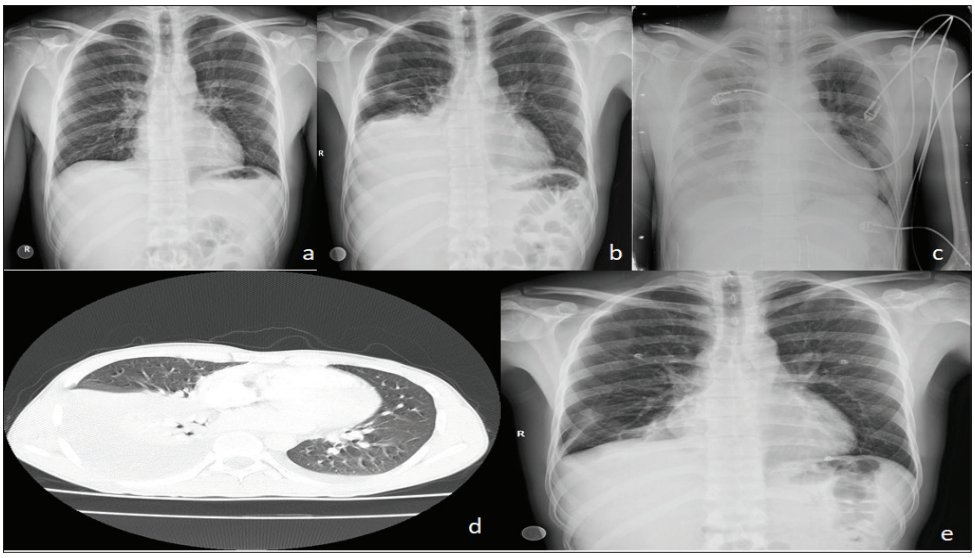

Figure 3: The follow-up radiological findings of a 28-year-old male who was survival; (a) Admission chest X-ray graphy. (b) Follow-up, treatment 2nd day (under antiviral treatment). (c) Follow-up, treatment 5th day (antiviral + blood product replacement therapy). (d) Follow-up, treatment 2nd-day computed thorax tomography. (e) Treatment result 10th day chest X-ray

CCHF patients evaluated by Sannikova *et al*. reported that acute respiratory distress syndrome may develop as a pulmonary pathology and that the severity of the disease is associated with high inflammatory cytokine levels and that hemoptysis may be observed in such patients.[14] We found in our study that those who had pulmonary symptoms and CXR findings were statistically significant on mortality ($P < 0.05$). Furthermore, mortality criteria were defined by Swanepoel *et al*.[9] According to these criteria, leukocyte count of >10,000/mm^3, thrombocyte count of <20,000/mm^3, AST levels of >200 U/L, ALT levels of >150 U/L, APTT of >60 s, and fibrinogen of <110 mg/dL in the first 5 days of the disease are indicators of a severe course. AST, ALT, and LDH levels are higher in patients with a severe course.[15,16] We have seen in our study that height WBC, lymphocyte count, BUN, creatine, ALT, AST, LDH, CK, D-bilirubin, T-bilirubin, ferritin, PTT(s), APTT, and low platelet count were statistically significant in nonsurvival patients ($P < 0.05$).

In light of these findings, based on the results of our study, there was a statistically significant relationship between CXR findings, presence of pulmonary symptoms, and some laboratory results between CCHF and mortality. Therefore, in addition to laboratory and general symptoms in CCHF patients, all CCHF patients with pulmonary symptoms found to be pathological CXR should be considered at high risk. One of the main limitations of our study was that it was a retrospective and the second was that not all patients with CXR findings were evaluated with CCT and finally the treatment results of the patients were not compared with the all findings.

Conclusions

CCHF is a viral disease that causes a serious public health problem, which can be fatal, especially in some regions. In addition to clinical findings and laboratory abnormalities, we believe that pulmonary evaluation (detailed physical examination, symptoms, and radiological evaluation) must be considered, which we think has a negative effect on survival.

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Conflicts of interest
There are no conflicts of interest.

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