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CHEST RADIOLOGY

The pulmonary findings of Crimean–Congo hemorrhagic fever patients with chest X-ray assessments

Fatma Aktaş[1] · **Turan Aktaş**[2]

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Abstract

Background Crimean–Congo hemorrhagic fever (CCHF), characterized by fever and/or hemorrhage, is a zoonotic viral disease with high mortality. The agent causing CCHF is a Nairovirus. The virus is typically transmitted to humans through tick bites. CCHF is a life-threatening disease observed endemically over a wide geographical regions in the world, and there is limited information about pulmonary findings in CCHF patients.

Purpose We aimed to investigate the pulmonary findings belonging to a large CCHF patient cohort and to determine if there is any relationship between laboratory findings and disease severity.

Materials and methods A total of 165 patients who were diagnosed with CCHF and examined through chest X-ray (CXR) due to respiratory symptoms at their first examination and/or during their hospitalization were included in this study. In addition to demographical and laboratory findings of the patients, chest X-rays were also examined.

Results Of the 165 patients examined, 96 were male (58.2%) and 69 were female (41.8%). The mean age was 51.64 ± 17.95 years (4–81 years). Single and/or multiple pathological findings were detected in 93 patients (56.4%) as a result of chest X-ray during their first examination. On chest X-ray, consolidation in 74 patients (44.8%), pleural effusion in 64 patients (39.8%), ground glass opacity in 49 patients (29.7%), and atelectasis in 30 patients (18.2%) were detected.

Conclusion According to the results of our study, it can be suggested that radiological examination in lungs should be performed primarily with CXR and pulmonary involvement (pleural effusion and consolidation) affects survival in CCHF negatively.

Keywords Crimean–Congo hemorrhagic fever · Chest X-ray · Pleural effusion · Consolidation

Introduction

Crimean–Congo hemorrhagic fever (CCHF), characterized by fever and/or hemorrhage, is a zoonotic viral disease with high mortality. The agent causing CCHF is a Nairovirus, which is a RNA type from the bunyaviruses family. The virus is typically transmitted to humans through tick bites. Rare transmissions to medical staff as a result of contact with blood or blood products have also been reported. The general non-specific symptoms of CCHF are fever, malaise, anorexia, nausea/vomiting, and myalgia, which are observed after the contact. However, ecchymosis, petechia, vaginal bleeding, and epistaxis can also be observed. In addition, intracranial bleeding, gastrointestinal bleeding, and alveolar hemorrhage that are life-threatening and often responsible for mortality can be observed as well [1–4]. The geographical location, exposure to animals with ticks, and contact with suspicious infected blood and blood products in the patients' history are helpful in diagnosis. CCHF can cause sudden and severe bleedings and death in the end [1].

There have been many studies performed on CCHF in the literature. However, the number of studies related to pulmonary imaging in CCHF is very rare and limited despite the increasing number of cases in the world and in our country [1–4]. On the other hand, we have a distinct advantage of studying the CCHF patients due to the increase in the frequency of the disease in our region.

✉ Fatma Aktaş
fatmakokcu79@hotmail.com

[1] Department of Radiology, Faculty of Medicine, Gaziosmanpaşa University School of Medicine, 60100 Tokat, Turkey

[2] Pulmonary Diseases Department, VERSA Hospital, Nevşehir, Turkey

There are four distinct phases in the clinical follow-up of CCHF. These are incubation phase, pre-hemorrhagic phase, hemorrhagic phase, and convalescent phase [1, 14]. Since patients have cold-like symptoms in pre-hemorrhagic phase, there may be some difficulties in differential diagnosis. Therefore, examination with chest X-ray (CXR) (which is specific for pulmonary pathologies) must be considered. We may propose simple pulmonary imaging such as CXR to be used within the following 5 days after the first examination as an effective tool to evaluate clinical course and severity of the disease.

The aim of this study was to investigate the chest X-ray findings of CCHF patients with respiratory findings and to determine if there is any relationship between the laboratory findings and severity of the disease.

Materials and methods

A total of 464 patients with confirmed CCHF were admitted to Emergency Department and Department of Infectious Diseases and Clinical Microbiology between January 2011 and December 2016. The cases were evaluated retrospectively. A total of 165 patients, who had posteroanterior CXR due to respiratory symptoms at the first examination and/or during hospitalization, were included in this study. Patients using medicines that may cause pulmonary toxicity and having acute or chronic lung diseases, malignancies, heart diseases, and blood diseases, and a history of thoracic radiotherapy or surgery in addition to CCHF were excluded from the study. Additionally, patients who were clinically diagnosed with pulmonary infection (such as cough sputum) and who were diagnosed with other microorganisms in their cultures were not included in the study as well.

Ethical approval was obtained from ethics committee of the university. In addition to demographical findings of the patients such as age, gender, occupation, place of residence, tick exposure, clinical findings, and medical history, laboratory findings and radiological images of lungs were evaluated. Posteroanterior CXR was performed on all patients during the first examination. CXR was evaluated by two experienced radiologists. The radiologists evaluated each patient's CXR together in order to avoid interobserver variability and decided to share the findings jointly. The CCHF diagnosis was made based on the detection of virus genome by using enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR).

Statistical analysis

Data are expressed as mean ± standard deviation. Independent sample *t* test was used to compare the continuous data between the groups. Chi-square tests were used to compare the categorical data between/among the groups. Categorical variables were presented as a count and percentage. Kaplan–Meier method was used for survival probabilities. A *p* value of less than 0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY).

Results

Of total patients, 96 were male (58.2%) and 69 were female (41.8%). The mean age was 51.64 ± 17.95 years (4–81 years). The majority of the patients [95 patients (57.6%)] lived in the city. There were no comorbidities in 124 patients (75.2%) in medical history examinations; on the other hand, there was chronic disease in 40 patients (24.8%). Out of 40 patients with comorbidity, 23 were found to have hypertension, three of them had diabetes mellitus, 13 were diagnosed with both hypertension and diabetes mellitus, and one of them had hypothyroids. The demographical and clinical characteristics of the patients can be seen in Table 1. Considering complaints and symptoms of the patients at the first examination, the most frequent symptoms were fever (98.8%), malaise (84.2%), and myalgia (35.8%). The frequency of general symptoms of the patients observed during the first examination is presented in Table 2.

Based on the laboratory findings, the mean values of liver-specific enzymes such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), creatine kinase (CK), and lactate dehydrogenase (LDH) were seen to be high.

Single and/or multiple abnormal imaging findings were detected in 93 patients (56.4%) as a result of CXR examination during the first examination. The CXR examination of 72 patients (43.6%) was normal. In addition, 36 patients (21.8%) found to have normal CXR findings at the first examination became symptomatic during clinical follow-up, and then, they were examined with CXR again within the first 5 days (Fig. 1a, b). Those 36 patients whose CXR findings were obtained on the fifth day as a result of radiological evaluation were also included in this study. As a result of CXR findings obtained based on the first examination and clinical follow-up within the first 5 days, consolidation in 74 patients (44.8%), pleural effusion in 64 patients (39.8%), ground glass opacity in 49 patients (29.7%), and atelectasis in 30 patients (18.2%) were detected (Fig. 2). The CXR findings are demonstrated in Table 3 in detail. In the comparative assessment of CXR findings and laboratory findings, there was a statistically significant relationship between CXR findings and laboratory findings (Table 4).

Twenty-three (17%) of the 165 patients who were diagnosed with pathology based on chest radiography had thorax

Table 1 Demographical and clinical features of CCHF patients

Variables	*n*	%
Sex		
Female	69	41.8
Male	96	58.2
Inhabitancy		
Rural	70	42.4
Town	95	57.6
Exposure with ticks		
Yes	95	57.6
No	68	41.2
Contact with blood component	2	1.2
Smoking		
Yes	100	60.6
No	63	38.2
Ex-smoker	2	1.2
Background		
Disease (+)	41	24.8
Disease (−)	124	75.2
Clinical course place		
Department	126	76.4
Intensive care unit	6	3.6
Both	33	20.0
Treatment		
Supportive treatment	158	95.8
Supportive treatment + antiviral	7	4.2
Survival		
Survival	146	88.5
Non-survival	19	11.5

Table 2 Symptoms of the CCHF patients in applications and clinical course

Symptoms	*n* (%)
Fever	163 (98.8%)
Malaise	139 (84.2%)
Myalgia	59 (35.8%)
Vomiting	40 (24.2%)
Abdominal pain	37 (22.4%)
Headache	36 (21.8%)
Diarrhea	34 (20.6%)
Hemorrhage	27 (16.4%)
Somnolence	24 (14.5%)
Eruption	23 (13.9%)
Loss of appetite	16 (9.7%)
Dizziness	14 (8.5%)
Cough	13 (7.9%)
Hemoptysis	9 (5.4%)

CT. The results of the thorax CT revealed that 20 of these patients (86%) had pleural effusion, 12 of them (52%) had consolidation, nine (39%) had atelectasis, and 14 (60%) had ground glass densities. Moreover, two patients (8%) were identified with extensive alveolar density promoting alveolar hemorrhage (Fig. 3). Four patients who were diagnosed with consolidation based on CXR were not observed to have any consolidation on CT. In a similar vein, four patients, claimed to have ground glass densities on CXR, and one patient, claimed to have pleural effusion, were not found to have these findings according to the results of the thorax CT. On the other hand, four patients who were not diagnosed with ground glass density in CXR were seen to have it after thorax CT was performed. As to two patients who were not found to have atelectasis in CXR, it was seen based on the thorax CT results that they had atelectasis.

The relationship between the survival and CXR findings was discussed. There were statistically significant results in both groups ($p < 0.001$). Moreover, the mortality rate was calculated as 11.5% in this study and there were statistically significant results in comparative assessment of each CXR findings with the survival separately. The comparison of survival and CXR findings of patients is shown in Table 5.

Discussion

CCHF is a life-threatening zoonotic viral disease that can be seen endemically in many regions in the world. CCHF is more common in males since contact with ticks is more frequent in males [5–9]. The most frequent clinical symptoms are fatigue (92.3%), fever (89.4%), myalgia (69.7%), headache (68.1%), and nausea (64.7%); 23% of patients had bleeding (petechiae, epistaxis, gingival bleeding, vaginal bleeding, and bleeding in internal organs) [10]. Sumer [7] reported in their study that the majority of patients diagnosed with CCHF were males (51.8%). Bilgin et al. [11] also reported the ratio of males as 51.6% in a similar type of study. The male patient ratio (58.2%) was found to be higher in our study. This situation might be related to the possibility that males work in occupations with high risk of being in contact with ticks.

As in many other viral diseases, CCHF may cause symptoms of pulmonary involvement and may lead to death. Although lung is one of the organs CCHF affects frequently, the literature information regarding pulmonary involvement is very limited [12–14]. The study conducted by Sannikova et al. in Russia has the largest number of patients (283 patients) among those studies. The relationship between high inflammatory cytokine levels with ARDS and clinical severity of CCHF was revealed in their study. Hemoptysis was found to be the most frequent symptom in their study [14]. On the other hand, cough and dyspnea were indicated as the most common symptoms in the study conducted by Doğan et al. in Turkey [12]. The presence of symptoms such as dyspnea, chest pain, and hemoptysis was reported to be poor

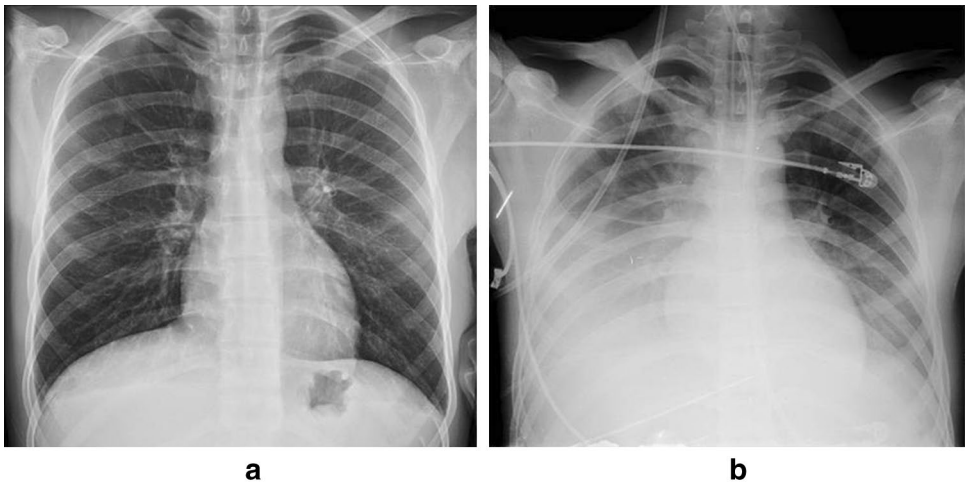

Fig. 1 A 24-year-old male patient complaint with fever and malaise. **a** Chest X-ray at the initial hospital admission is normal, **b** massive pleural effusion is detected on chest X-ray at the fifth day

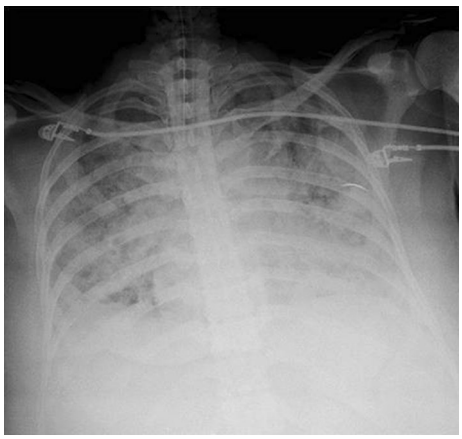

Fig. 2 A 54-year-old female patient complaint with fever and cough. Bilateral pleural effusion and ground glass opacities on chest X-ray

Table 3 Total CXR findings of CCHF patients

CXR findings	*n*	%
Pleural effusion		
Bilateral	34	20.6
Right side	18	10.9
Left side	12	7.3
None	101	61.2
Atelectasis		
Present	30	18.2
None	135	81.8
Consolidation		
Bilateral	41	24.8
Right side	25	15.2
Left side	8	4.8
None	91	55.2
Ground glass opacity		
Bilateral	30	18.2
Right side	15	9.1
Left side	4	2.4
None	116	70.3

prognosis criteria in their study. There was no relationship between respiratory symptoms and the survival in the study with 128 patients by Bilgin et al. [11]. There was a statistically significant relationship between cough symptom and survival in our study ($p=0.023$). However, hemoptysis was detected in a total of nine out of 27 patients with hemorrhage (six of those patients died).

There have been a very limited number of studies on pulmonary radiological findings in CCHF in the literature. CXR is the first preferred imaging method in CCHF since it is easily accessible and applicable. Further investigation opportunities may be limited for patients due to the general condition disorder in CCHF. The first and most frequent examination preferred in the studies by Doğan et al. and Bilgin et al. was CXR [11, 12]. All radiological imagings of lungs were performed according to CXR. In the study by Sannikova et al. [14], ARDS and alveolar hemorrhage diagnosis were generally established based on clinical findings and CXR. CXR was also used in all patients' examination of lungs in our study. There were abnormal radiological findings in 93 (56.4%) of the 165 patients in our study. There were abnormal CXR findings in 33 of 108 patients in the study by Doğan et al. [12] and in 32 of 128 patients in the study by Bilgili et al. [11]. The number of patients with CXR was higher in our study than the other studies in the literature. This may be caused by the inclusion of patients whose CXR findings emerged on the fifth day of clinical follow-up. There were 36 patients included in our study through follow-up. There was no significant relationship between the comparison of patients with pathological findings in CXR and survival in the studies by Doğan et al. and Bilgin et al. [11, 12]. On the other hand, there was a very statistically significant

Table 4 Laboratory findings of the patients' groups according to the total CXR

Values	Total CXR		
	RF (+) ($n=93$)	RF (−) ($n=72$)	p
	Mean ± SD	Mean ± SD	
ALP	157.23 ± 127.32	96.1 ± 50.36	**< 0.001**
ALT	345.24 ± 658.39	119.6 ± 134.98	**0.002**
AST	1055.04 ± 2270.2	240.04 ± 299.8	**0.001**
BUN	26.2 ± 22.7	15.83 ± 8.36	**< 0.001**
D.BIL.	0.8 ± 1.5	0.48 ± 1.66	0.197
GGT	203.5 ± 226.4	98.1 ± 121.7	**< 0.001**
CK	1191.7 ± 1871.2	509.81 ± 617.31	**0.001**
CRE	1.38 ± 1.36	0.87 ± 0.26	**0.001**
LDH	1425.7 ± 1678.9	592.4 ± 382.7	**< 0.001**
T.BIL.	1.22 ± 1.84	0.59 ± 1.06	**0.006**
U.ACID	5.6 ± 3.23	4.59 ± 1.74	**0.011**
WBC	2.86 ± 2.5	2.22 ± 1.3	**0.035**
NEU	1.89 ± 2.06	1.25 ± 1.05	**0.011**
RBC	4.67 ± 0.63	4.95 ± 0.54	**0.003**
HGB	12.59 ± 2.31	13.47 ± 1.61	**0.005**
HTC	37.26 ± 6.43	40.22 ± 4.48	**0.001**
PLT	43.18 ± 41.47	59.0 ± 35.7	**0.011**
MPV	10.66 ± 2.57	9.76 ± 2.52	**0.027**
PTT%	85.03 ± 28.39	101 ± 25.05	**< 0.001**
PTT	14.41 ± 4.18	12.43 ± 3.31	**0.001**
APTT	58.16 ± 28.09	42.63 ± 11.64	**< 0.001**
FERR.	8375.6 ± 13,891.6	4558 ± 8596.49	**0.032**
PRC.	3.59 ± 13.08	1.4 ± 7.09	0.202
SED.	21.01 ± 18.15	16.68 ± 18.39	0.133
CRP	39.74 ± 43.28	26.65 ± 37.4	**0.043**

Bold values are indicates statistically significant

RF radiological finding, *ALP* Alkaline phosphatase, *CXR* chest X-ray, *ALT* alanine aminotransferase, *RF* radiological findings, *AST* aspartate aminotransferase, *SP* survival patients, *BUN* blood uremia nitrogen, *NSP* non-survival patients, *D. BIL.* direct bilirubin, *SD* standard deviation, *GGT* gamma glutamyl transferase, *CK* creatine kinase, *CR* creatinine, *LDH* lactate dehydrogenase, *T. BIL.* total bilirubin, *U.ACID* uric acid, *WBC* white blood cell, *NEU* neutrophile, *RBC* red blood cell, *HGB* hemoglobin, *HTC* hematocrit, *PLT* platelet, *MPV* mean platelet volume, *PTT%* % partial thromboplastin time, *PTT* partial thromboplastin time, *APTT* activated partial thromboplastin time, *PRC.* procalcitonin, *SEDIM.* sedimentation, *CRP* C-reactive protein

relationship between the CXR findings and the survivals of patients in our study ($p < 0.001$).

Pleural effusion, one of the findings that can be seen in the clinical follow-up of CCHF, was observed in 64 patients (37.8%) in our study. Pleural effusion was observed bilaterally in 34 (20.6%) patients. There was no pleural effusion in any of the patients in the study of Doğan et al., but pleural thickening was observed only in seven patients (6.5%). There was pleural effusion in only one patient in the study of Bilgin et al. [11, 12]. Interestingly, there was a very significant relationship between pleural effusion and survival in our study ($p < 0.001$). Other CXR findings such as consolidation, ground glass opacity, and atelectasis were observed in 74, 49, and 30 patients, respectively. The number of patients with respiratory symptoms was much higher in our study than the number of patients in the other studies. The pathophysiological mechanism of pleural effusion has not been clearly demonstrated in CCHF. However, it has been stated that it can share similarities with mechanism of pulmonary pathologies such as pleural effusion, pneumonitis, hemoptysis, and alveolar hemorrhage in other febrile viral hemorrhagic diseases [15, 16]. It has been suggested that pulmonary findings emerge due to the increase in capillary permeability in febrile viral hemorrhagic diseases. Particularly, virus in the circulatory system causes an increase in pulmonary capillary permeability causing capillary endothelial damage [17]. In a study performed on dengue hemorrhagic fever, a total of 468 CXR taken from 363 patients were examined and parenchymal infiltration and pleural effusion were observed in more than half of the patients on the third day of follow-up. These findings were stated as the most frequent radiological findings. Moreover, these radiological findings were found to be closely related to laboratory findings of leukocyte count, platelet count, APTT, ALT, and albumin levels in the same study [18]. Similar to other febrile viral hemorrhagic diseases (in particular to dengue hemorrhagic fever), clinical conditions must be kept in mind in CCHF. Replacement therapy was also performed with blood and blood products in some patients with sudden decrease in hemoglobin values and with alveolar hemorrhage findings in our study. In conclusion, pleural effusion and other findings related to pulmonary involvement can be seen in CCHF due to endothelial damage caused by viral load in the circulation, increased capillary permeability, and hemorrhages due to low platelet.

In the study by Aktaş et al. [3], thorax CT findings of 40 patients were evaluated, and then, CT and CXR findings of the patients were compared. The results of the study revealed that there was no statistically significant difference between the two examination techniques in terms of detecting parenchymal infiltration, alveolar infiltration, and pleural effusion. In our study, 23 of the 129 patients went through both CT and CXR examinations. When these patients were compared, it was found that there was consolidation in CXR of the four patients and pleural effusion in one patient while they were not observed in thorax CT. On the other hand, based on thorax CT results, ground glass density was detected in four patients and atelectasis in two patients, and these were not observed in CXR. However, there was a time period changing from 2 to 14 days between CXR and

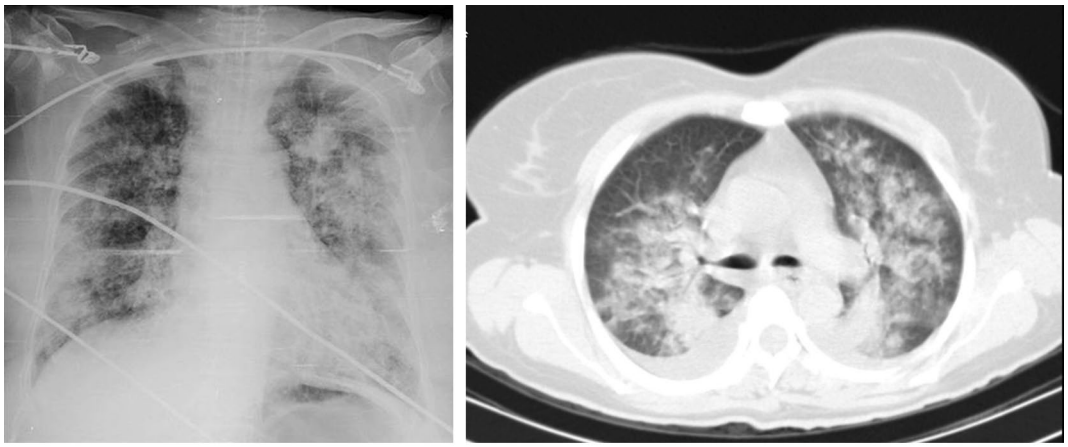

Fig. 3 **a** A 35-year-old female patient complaint with fever and cough. Bilateral extensive patchy consolidation and ground glass opacities, **b** bilateral extensive alveolar density promoting alveolar hemorrhage

Table 5 Association between survive and CXR findings

	Survival ($n=146$) n (%)	Non-survival ($n=19$) n (%)	p
Total CXR findings			
Radiological findings (+)	75 (51.4)	18 (94.7)	<0.001
Radiological findings (−)	71 (48.6)	1 (5.3)	
Pleural effusion			
Bilateral	23 (15.8)	11 (57.9)	<0.001
Right side	14 (9.6)	4 (21.1)	
Left side	10 (6.8)	2 (10.5)	
None	99 (67.8)	2 (10.5)	
Atelectasis			
Present	20 (13.7)	10 (52.6)	<0.001
None	126 (86.3)	9 (47.4)	
Consolidation			
Bilateral	32 (21.9)	9 (47.4)	0.044
Right side	21 (14.4)	4 (21.1)	
Left side	7 (4.8)	1 (5.3)	
None	86 (58.9)	5 (26.3)	
Ground glass opacity			
Bilateral	19 (13)	11 (57.9)	<0.001
Right side	11 (7.5)	4 (21.1)	
Left side	3 (2.1)	1 (5.3)	
None	113 (77.4)	3 (15.8)	
Fifth day CXR findings			
Radiological findings (+)	23 (15.8)	13 (68.4)	<0.001
Radiological findings (−)	123 (84.2)	6 (31.6)	

thorax CT examinations. Therefore, there was a possibility of response to the treatment and spontaneous regression or progression in the findings.

The mortality rate of CCHF generally ranges from 2 to 80%. The mean mortality rate has been reported as 30–50% [19–22]. The mortality rate was found to be 30–62% in the study by Bakır et al. [15]. In our study, it was 11.5%. This rate was lower compared to the existing literature. This result can be associated with the fact that CCHF is endemic in this region; therefore, medical staff and people are informed about the disease, and thus, they are alert. In addition, the experience in the clinical follow-up might also contribute to the decrease in mortality rate besides improvements in medical care conditions in CCHF and increase in awareness of the seriousness of the disease.

It is known that mortality and some laboratory parameters prolonged a PTT, increased INR, high ALT, AST and LDH, low platelet, and increased leukocyte are related to each other [23, 24]. Moreover, it is claimed that age, bleeding, melena, hepatomegaly, organ failure, and somnolence increase the mortality [23, 25–27]. Apart from these findings, based on the results of our study, there was a statistically significant relationship between the CXR findings of CCHF and mortality. For this reason, all of the CCHF patients who were found to have pathologic CXR result should be considered at high risk.

Our choice to conduct a retrospective study is the first limitation; on the other hand, medical information of the patients and their radiological images has been recorded in a proper way. Thus, there was an easy access to their data. The other limitation was the inability to confirm the CXR findings of the patients as not all of these patients had thorax CT.

In conclusion, CCHF is a serious public health problem that can be fatal. We investigated the specific pulmonary findings in CCHF through CXR and the effects of these findings on the course of disease and survival in this study. According to the results of our study, we suggest that

radiological imaging of pulmonary system should be performed primarily with CXR. Pulmonary involvement (pleural effusion, consolidation, and ground glass opacity) affects the survival in CCHF negatively, and further examination should be performed with thorax CT in case of necessity. Radiological findings emerging on the fifth day of our study were demonstrated to be related closely to both survival and many laboratory findings. Although not as detailed as chest CT, as the access to CXR is more common and it is easy to be applied (such as portable CXR in non-stabilized patients), it can be the first option to investigate pulmonary involvement in CCHF patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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