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# An evaluation of the laboratory and clinical data of the Crimean-Congo hemorrhagic fever patients during the COVID-19 pandemic

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**Abstract**

In this study, the purpose was to investigate the demographic, laboratory, and clinical characteristics of the Crimean-Congo Hemorrhagic Fever (CCHF) cases that were treated in our hospital during the Coronavirus disease-2019 (COVID-19) pandemic. It was also investigated whether the patients hospitalized with a provisional diagnosis of CCHF who tested negative for CCHF PCR were infected with COVID-19. In our study, data (epidemiological, clinical, laboratory, prognosis) from 38 patients diagnosed with CCHF through reverse-transcriptase polymerase chain reaction (PCR) and viral-RNA and/or Immunoglobulin M antibodies using ELISA between May 2020 and November 2022 were investigated retrospectively. Of all the patients, 23 were CCHF PCR (+) and 15 were CCHF PCR (-).15 (65.2%) of PCR (+) patients and 9 (60%) of PCR (-) patients were engaged in farming. 65.2% of PCR (+) and 26.7% of PCR (-) patients presented with a history of tick bites. 21 (91.3%) of PCR (+) and 12 (80%) of PCR (-) patients had a history of rural living. Among the PCR (+) patients, 65.2%, 17.4%, and 17.4% received treatment for CCHF in 2022, 2021, and 2020 respectively. 87% of PCR (+) and 60% of PCR (-) patients were discharged after full recovery. The most common symptoms were fever, diffuse body ache, weakness, and headache. Significant differences were found between PCR (+) and PCR (-) patients in terms of leukocytes, LDH, INR, NEU, PLT, fibrinogen, and NLR values. 3 patients hospitalized with a provisional diagnosis of CCHF tested negative for CCHF PCR and positive for COVID-19 PCR. Thoracic CT, clinical, and laboratory findings of these patients showed no differences from the other patients. The possibility of misdiagnosis should be considered in CCHF and COVID-19 infections due to their similar symptoms and indications. Extensive multicentric studies need to be conducted to investigate the causes of the increased number of CCHF cases during the pandemic.

**Keywords:** Crimean-Congo hemorrhagic fever, COVID-19, pandemic, tick

## 1. Introduction

The coronavirus disease-2019 (COVID-19) that has affected millions of people worldwide has been effective in our country since March 2020. The common symptoms observed in COVID-19 patients are highly similar to the symptoms in patients with Crimean-Congo Hemorrhagic Fever (CCHF) (1). There have also been cases of mixed infections of CCHF and COVID-19 during the COVID-19 pandemic (2). Thus, CCHF cases and epidemics are an additional threat to the pandemic coronavirus infection in endemic countries such as Türkiye, Iran, Oman, Russia, and Pakistan. This may lead to misdiagnosis and improper treatment in these regions (3).

The World Health Organization Regional Office for the East Mediterranean presented various risk factors for the emergence of zoonotic diseases and arboviruses in the background of the COVID-19 infection. Climatic and environmental changes, humanitarian emergencies, conflicts, insufficient healthcare systems, poor supervision and inadequate laboratory facilities, domestication, and animal slaughter during religious holidays are some of these risk factors (4).

CCHF is zoonotic disease caused by the *Nairovirus* that is transmitted to humans through *Ixodidae* tick bites (*Hyalomma marginatum* in our country) and unprotected contact with the blood or tissue of animals in the viremia stage or infected humans (5). There are also studies reporting nosocomial and sexual transmission of the disease (6). Moreover, it has been reported that the transportation of virus-infected ticks through migratory birds influences CCHF transmission (7).

The COVID-19 infection has many common clinical, laboratory, and radiographic characteristics with the CCHF (8). Fever, weakness, nausea, vomiting, stomachache, myalgia, diffuse bleeding, petechia, ecchymosis, hepatic dysfunction, and diffuse body ache are some of the common symptoms of CCHF. On the other hand, fever, dry cough, weakness and shortness of breath (dyspnea), and loss of taste and smell

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perception are common symptoms of COVID-19 (9). Both diseases are diagnosed with PCR tests. An important finding for both CCHF and COVID-19 is the ground-glass opacification in Chest Tomography (CT) scan findings. However, there is no evidence for the CCHF virus' direct invasion to the pulmonary interstitial tissue (10).

In this study, the goal was to investigate the laboratory and clinical characteristics of the CCHF cases treated in our hospital during the COVID-19 pandemic. Moreover, it was aimed to demonstrate that the patients hospitalized with a provisional diagnosis of CCHF who tested negative for CCHF PCR may have been subject to misdiagnosis and are infected with COVID-19.

## 2. Materials and Methods

Laboratory and clinical characteristics of the cases treated at our hospital for Crimean-Congo hemorrhagic fever between 2020-2022 were investigated retrospectively. Patients who were tested in the Microbiology Reference Laboratory of the Public Health Institution of Turkey and were diagnosed with positivity of CCHF virus IgM antibodies by ELISA and/or detection of CCHF virus RNA positivity by real-time reverse transcriptase (RT) polymerase chain reaction (PCR) were included in the study. Patients' demographic data including sex, occupation, and place of residence; their contact with ticks, onset year of the disease, symptoms, and findings; laboratory findings including hemogram, C-reactive protein (CRP), creatine kinase (CK), lactic dehydrogenase (LDH), activated partial thromboplastin time (aPTT), and international normalized ratio (INR); and the recovery and mortality rates were investigated.

Ethical permission for the study was obtained by Ethic Committee from Elazig Firat University, with decision numbers 12-23 and 18.11.2021.

### 2.1. Statistical Analysis

Statistical Package for Social Science for Windows (SPSS) 24.0 package was used to analyze the data. A chi-square test of independence was performed to investigate whether there were statistically significant differences between CCHF PCR (-) and PCR (+) patients regarding demographics, anamnesis, physical examination findings, laboratory findings, and epidemiological history findings. Furthermore, an independent samples t-test was performed to investigate the statistically significant differences in the laboratory findings of CCHF PCR (-) and PCR (+) patients. The results were considered significant with 99% ($p<0.01$) and 95% ($p<0.05$) confidence levels.

## 3. Results

A total of 38 patients were included in the study. 23 of these patients were PCR (+) and 15 were PCR (-). The demographic characteristics of the patients show that 65.2% of the PCR (+) patients and 80% of the PCR (-) patients were male. 8 (34.8%) of the PCR (+) patients and 3 (20%) of the PCR (-) patients were female. There were no significant differences between groups in terms of sex ($p=0.326$) (Table 1). 15 (65.2%) of the PCR (+) patients and 9 (60%) of the PCR (-) patients were engaged in farming. There were no significant differences between groups in terms of occupation (housewife, student, teacher, retiree, technician) ($p=0.147$) (Table 1). There were no significant differences in the cities that patients were residing in. However, 7 (30.4%) of the PCR (+) patients and 10 (66.6%) of the PCR (-) patients came to our hospital from the city of Elazığ (Table 1). Of the PCR (+) patients, 65.2%, 17.4%, and 17.4% received treatment for CCHF in 2022, 2021, and 2020 respectively. Of the PCR (-) patients, 46.7%, 33.3%, and 20% received treatment for CCHF in 2022, 2021, and 2020 respectively ($p=0.461$) (Table 1). 65.2% of the PCR (+) and 26.7% of the PCR (-) patients had a history of tick bites. 21 (91.3%) of the PCR (+) and 12 (80%) of the PCR (-) patients had a history of living in rural areas. 87% of PCR (+) and 60% of PCR (-) patients were discharged after full recovery. Inpatients in the clinic and the intensive care unit were given outpatient treatment and discharged. We did not have any patients who died (Table 1).

**Table 1.** Epidemiological and demographic characteristics of Crimean-Congo Hemorrhagic Fever cases

| | | PCR (+) n:23 | PCR (-) n:15 | *p* |
|---|---|---|---|---|
| **Year** | 2020 | 4 (%17.4) | 3 (%20) | 0.461 |
| | 2021 | 4 (%17.4) | 5 (%33.3) | |
| | 2022 | 15 (%65.2) | 7 (%46.7) | |
| **Gender** | female | 8 (%34.8) | 3 (%20) | 0.326 |
| | male | 15 (%65.2) | 12 (%80) | |
| **Job** | Farmer | 15 (%65.2) | 9 (%60) | 0.147 |
| | Housewife | 6 (%26.1) | 2 (%13.3) | |
| | Student | 0 (%0) | 1 (%6.7) | |
| | Teacher | 2 (%8.7) | 0 (%) | |
| | Retired | 0 (%) | 1 (%6.7) | |
| | Technician | 0 (%) | 2 (%13.3) | |
| **Clinical status** | service | 1 (%4.3) | 4 (%26.7) | 0.134 |
| | *ICU | 0 (%) | 2 (%13.3) | |
| | service+healing | 2 (%8.7) | 0 (%) | |
| **City** | Healing | 20 (%87) | 9 (%60) | 0.449 |
| | Elazig | 7 (%30.4) | 10 (%66.6) | |
| | Bingol | 5 (%21.7) | 1 (%6.7) | |
| | Tunceli | 3 (%13) | 2 (%13.3) | |
| | Bitlis | 4 (%17.4) | 1 (%6.7) | |
| | Diyarbakir | 1 (%4.3) | 0 (%) | |
| | Sivas | 1 (%4.3) | 1 (%6.7) | |
| | Kahramanmaras | 1 (%4.3) | 0 (%) | |
| | Agri | 1 (%4.3) | 0 (%) | |
| **Tick Bite** | | 15 (%65.2) | 4 (%26.7) | 0.063 |
| **Country side life** | | 21 (%91.3) | 12(%80) | 0.235 |

***ICU:** Intensive care units, ***p<0.05**

Investigating the symptom and findings of the patients, 73.9% of the PCR (+) and 66.7% of the PCR (-) patients presented with fever; 78.3% of the PCR (+) and 73.3% of the PCR (-) patients presented with a headache; and 87% of the PCR (+) and 73.3% of the CCHF PCR (-) patients presented with diffuse body ache. There were no significant differences between PCR (+) and PCR (-) patients in terms of fever, headache, and diffuse body ache variables. PCR (+) and PCR

(-) patients showed significant differences in weakness (p=0.025) such that weakness was observed in all of PCR (+) patients and only 80% of PCR (-) patients. Other symptoms and findings did not differ significantly in PCR (+) and PCR (-) patients (Table 2).

**Table 2.** Symptoms and findings of Crimean-Congo Hemorrhagic Fever cases

| | PCR (+) n:23 | PCR (-) n:15 | *P* |
|---|---|---|---|
| Fever | 17 (%73.9) | 10 (%66.7) | 0.630 |
| Headache | 18 (%78.3) | 11 (%73.3) | 0.727 |
| Diffuse body ache | 20 (%87) | 11 (%73.3) | 0.290 |
| Weakness | 23 (%100) | 12 (%80) | **0.025*** |
| Nausea/vomiting | 10 (%43.5) | 8 (%53.3) | 0.552 |
| Diarrhea | 7 (%30.4) | 4 (%26.7) | 0.802 |
| Stomach ache | 5 (%21.7) | 6 (%40) | 0.225 |
| Ecchymosis | 0 | 1 (%6.7) | 0.210 |
| Debris | 2 (%8.7) | 2 (%13.3) | 0.649 |
| Bleeding | 2 (%8.7) | 2 (%13.3) | 0.649 |
| Bloody diarrhea | 1 (%4.3) | 1 (%6.7) | 0.754 |
| Consciousness disorder | 0 | 1 (%6.7) | 0.210 |
| Bleeding gums | 1 (%4.3) | 0 | 0.413 |

There were significant differences between PCR (+) and PCR (-) patients in terms of anemia (p=0.002), leukopenia (p=0.037), LDH level (p=0.004), and INR level (p=0.047). 4.3% of the PCR (+) and 46.7% of the PCR (-) patients presented with anemia. Leukopenia was observed in 73.9% of the PCR (+) and 40% of the PCR (-) patients. High LDH level were observed in all PCR (+) patients whereas only in 66.7% of the PCR (-) patients. The INR value was 1.2 and above in 73.8% of the PCR (+) and 40% of the PCR (-) patients (Table 3).

**Table 3.** Laboratory parameters of Crimean-Congo Hemorrhagic Fever cases at the time of application-1

| | | PCR (+) n:23 | PCR (-) n:15 | *P* |
|---|---|---|---|---|
| **Anemia** | | **1 (%4.3)** | **7 (%46.7)** | **0.002**** |
| **AST/ALT increase** | | **21 (91.3)** | **11 (%73.3)** | 0.138 |
| **Lung Infiltration (CT)** | | **1 (%4.3)** | **1 (%6.7)** | 0.754 |
| **Leukopenia** | | **17 (%73.9)** | **6 (%40)** | **0.037*** |
| **CK increase** | | **17 (%73.9)** | **9 (%60)** | 0.367 |
| **Creatinine** | 1.4 and below | **21 (%91.3)** | **14 (%93.3)** | 0.242 |
| | 1.5 – 2.4 | **2 (%8.7)** | **0** | |
| | 2.5 and above | **0** | **1 (%6.7)** | |
| **Thrombocytopenia** | | **22 (%95.7)** | **13 (%86.6)** | 0.315 |
| **LDH increase** | | **23 (%100)** | **10 (%66.7)** | **0.004**** |
| **INR increase** | 0.9 and below | **2 (%8.7)** | **2 (%23.4)** | **0.047*** |
| | 0.9-1.2 | **4 (17.5)** | **7 (%46.6)** | |
| | 1.2 and above | **17 (%73.8)** | **6 (%40)** | |
| **aPTT** | 11 sec and under | **20 (%87)** | **9 (%60)** | 0.056 |
| | 15 sec and above | **3 (%13)** | **6 (%40)** | |
| **aPTT rate** | 75% and below | **21 (%91.3)** | **14 (%93.3)** | 0.821 |

Significant differences were found in terms of NEU (p=0.0001), CRP (p=0.002), fibrinogen (p=0.001), and NLR (p=0.002) between PCR (+) and PCR (-) patients. Accordingly, the mean value of NEU was determined as 1.22±0.82 in PCR (+) patients and 5.35±3.68 in PCR (-) patients. NEU value was found to be higher in PCR (-) patients compared to PCR (+) patients. The mean value of PLT was determined as 49.30±28.14 in PCR (+) patients and 95.06 ±58.76 in PCR (-) patients. PLT value was found to be higher in PCR (-) patients compared to PCR (+) patients. The mean value of CRP was determined as 99.34 ±51.25 in PCR (+) patients and 21.21±13.26 in PCR (-) patients. CRP value was found to be higher in PCR (+) patients compared to PCR (-) patients. The mean value of fibrinogen was determined as 2.31 ± 0.56 in PCR (+) patients and 3.93±2.06 in PCR (-) patients. Fibrinogen value was found to be higher in PCR (-) patients compared to PCR (+) patients. The mean value of NLR was determined as 2.32±1.81 in PCR (+) patients and 7.58 ± 7.53 in PCR (-) patients. NLR value was found to be higher in PCR (-) patients compared to PCR (+) patients. No significant differences were observed between the two groups in terms of MPV, LYM, D-Dimer, and PLR values (Table 4).

**Table 4.** Laboratory parameters of Crimean-Congo Hemorrhagic Fever cases at the time of application-2

| | PCR (+) n:23 | PCR (-) n:15 | *P* |
|---|---|---|---|
| **MPV** | 8.73 ± 0.74 | 8.59 ± 0.87 | 0.586 |
| **NEU** | 1.22 ± 0.82 | 5.35 ± 3.68 | **0.0001*** |
| **LYM** | 0.75 ±0.58 | 1.01 ± 0.89 | 0.286 |
| **PLT** | 49.30 ± 28.14 | 95.06 ±58.76 | **0.003*** |
| **CRP** | 99.34 ±51.25 | 21.21 ± 13.26 | **0.002*** |
| **D-DIMER** | 6.39 ± 5.21 | 4.63 ± 0.22 | 0.402 |
| **FIBRINOGEN** | 2.31 ± 0.56 | 3.93 ± 2.06 | **0.001*** |
| **PLR** | 109.28 ± 91.25 | 118.95 ± 78.85 | 0.753 |
| **NLR** | 2.32 ± 1.81 | 7.58 ± 7.53 | **0.002*** |

3 patients hospitalized with a provisional diagnosis of CCHF tested negative for CCHF PCR and positive for COVID-19 PCR. However, there were no significant differences in the clinical, laboratory, and thoracic computerized tomography (CT) findings.

## 4. Discussion

The COVID-19 pandemic has led to various arbovirus epidemics in different regions and countries such as Brazil, Kenya, and Asia (10,11). There has been a CCHF epidemic in addition to the COVID-19 pandemic in our country as well. The majority of the cases were detected in the northern regions of Middle and Eastern Anatolia and middle regions of the

Black Sea region (10). Barkay and colleagues (12) reported an increase in the number of CCHF cases, especially in Eastern Türkiye, compared to previous years after the start of the COVID-19 pandemic in 2020. They argued that this increase in the number of CCHF cases is related to several factors including the increased residence in rural areas during the COVID-19 pandemic, the possibility of developing resistance to acaricides used against ticks, and ecological and climatic causes. In our study, we also detected an increase in the number of CCHF cases during the pandemic and especially in 2022.

CCHF is an important public health issue in Türkiye due to high mortality rates (1). CCHF can be seen in people of any age and sex. However, it has been reported to be more common in middle-aged working people as well as people who have a high risk of tick contact due to working in animal husbandry (13). The majority of patients included in our study are engaged in farming (PCR (+) = 65.2%, PCR (-) = 60%). Studies show that approximately 60% of CCHF patients have a history of tick bites (14). A study reported that 67.6% of patients had a history of tick bites and all of them lived in the rural areas (15). Kadanalı and colleagues (16) reported that 50.8% of patients had a history of tick bites and 93.6% of them lived in the rural areas. In our study, we found that 65.2% of CCHF PCR (+) and 26.7% of PCR (-) patients during the pandemic had a history of tick bites. Furthermore, 21 (91.3%) of CCHF PCR (+) and 12 (80%) of the PCR (-) patients had a history of living in the rural areas. It is easier to diagnose patients who have a history of tick bites with CCHF. However, it may be challenging to diagnose patients with CCHF when they do not have a history of tick bites and show symptoms similar to COVID-19 infection.

There is a possibility that COVID-19 conceals or imitates other inflammatory diseases in endemic regions (17). Thus, viral infections such as CCHF can lead to diagnostic confusion in patients infected with COVID-19 (10). There are also studies reporting co-infections of COVID-19 and CCHF (18,19,20). Our data includes 3 patients who were hospitalized with a provisional diagnosis of CCHF and tested positive for COVID-19. One of these patients had a history of tick bites and all of them had a history of visiting rural areas.

COVID-19 infection has atypical characteristics that complicate the diagnosis. The initial symptoms of COVID-19 are fever, cough, myalgia, and fatigue (21). A study showed that 83% of COVID-19 patients had fever, 82% had a cough, 31% had dyspnea, 11% had muscle pain, 8% had a headache, 2% had chest pain, 2% had diarrhea, and 1% had nausea and vomiting (22). CCHF also presents with non-disease-specific symptoms such as weakness, fever, headache, myalgia, nausea, and vomiting (10). Similarly, the most common symptom in our patients was weakness and it was 100% in CCHF PCR positive patients and 80% in CCHF PCR negative patients. Other most common symptoms were diffuse body ache (87%), headache (78.3%), and fever (73.9%) in CCHF PCR positive patients. Our COVID-19 PCR positive patients also displayed nonspecific symptoms such as fever, headache, diffuse body ache, diarrhea, and stomachache.

The most common abnormal laboratory findings observed in COVID-19 infection are thrombocytopenia, lymphopenia, prolonged prothrombin time, active partial thromboplastin time prolongation (hypercoagulability), high levels of D-dimer, and increase in ALT, AST, and LDH (23). Similarly, CCHF laboratory findings also show thrombocytopenia, lymphopenia, high levels of liver enzymes, and prolonged aPTT (17). A study by Baran and colleagues (24) reported as high LDH and CK (100%), thrombocytopenia and lymphopenia (90%), high AST levels (90%), and high ALT levels (70%). In a study by Alkan-Çeviker and colleagues (25), thrombocytopenia (95%), increased levels of AST and ALT (72%), leukopenia (69%), neutropenia (42%), increased levels of LDH (47.9%), and PTZ (25.3%) and aPTT prolongation (16.9%) have been reported in CCHF patients. The increase in neutrophils in CCHF patients leads to excessive cytokine release, decrease in the number of lymphocytes and monocytes, impaired immunity, and decrease in humoral antibody response. Inflammation emerges in tissues and organs. The increase in proinflammatory cytokines in CCHF patients causes hemophagocytic cell activation which leads to a rapid decrease in the number of leukocytes and thrombocytes. Thrombocytopenia is one of the primary laboratory parameters of CCHF (26). In a study, it was reported that the leukocyte and thrombocyte levels of CCHF patients are lower compared to the patients in the control group (27). Similarly, Doğan and colleagues (28) also reported lower levels of leukocyte, lymphocytes, and platelet in the CCHF patient group. Our study shows similar results to the literature. Our CCHF patients showed a decrease in leukocytes and thrombocyte levels. There were significant differences between CCHF PCR (+) and PCR (-) patients in terms of anemia, leukopenia, high LDH levels, and high INR levels. These indications were higher in the CCHF PCR (+) group. Thrombocytopenia was also observed in high levels in CCHF PCR (+) (95.7%) and PCR (-) (86.6%) patients but no significant difference was found between the two groups. NLR and PLR are biomarkers that indicate inflammation. Erturk and colleagues (29) reported similar levels of NLR and PLR in CCHF patients and the control group. Turkdogan and colleagues (30) reported significantly low levels of NLR in CCHF patients and that this relates to the severity of the disease. In our study, NLR levels were found to be significantly low in the CHHF PCR (+) group. No significant differences were found between the two groups in terms of PLR levels.

It has been shown that COVID-19 and CCHF do not only show similarities in clinical symptoms but also in CT findings (10). No direct invasion of the CCHF virus into the lung interstitial tissue was shown, but the ground-glass opacification is an important finding of the CCHF. It is co-observed with pleural effusion and consolidation due to

alveolar hemorrhage (9). In our study, there were nonspecific imaging findings in the CT results of CCHF patients. There were also no discriminatory findings in the CT results of COVID-19 positive patients.

It is possible to lose co-infected patients who have both COVID-19 and CCHF due to bad clinical course (19). In our study, all patients were discharged after full recovery. We did not have any patients who died. Patients who were COVID-19 PCR (+) and who were receiving inpatient treatment in the clinic or the intensive care unit were discharged with outpatient follow-up.

The constant attention to COVID-19 by public health officials and distraction from other infectious agents have led to different epidemics in various countries. It is important to keep in mind that there may diagnostic confusions between CCHF and COVID-19 due to the similarities in the clinical picture where CCHF is endemic, and that these infections may co-occur. Further research is needed for the development of diagnostic algorithms for the differential diagnosis of these diseases.

**Ethical statement**

Elazig Firat University Ethics Committee, dated:18.11.2021, approval number:12-23

**Conflict of interest**

The authors declared no conflict of interest.

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None to declare.

**Authors' contributions**

Concept and design: P.Ö.; data collection or processing: P.Ö., M.Ö.; analysis and interpretation: P.Ö., M.Ö.; writing: P.Ö., M.Ö.

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