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ORIGINAL ARTICLE

Differential Diagnosis in Crimean-Congo Hemorrhagic Fever: A Comprehensive Analysis in an Endemic Region During the COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Endemik Bir Bölgede Kırım Kongo Kanamalı Ateşinde Ayırıcı Tanı: Kapsamlı Bir Analiz

Esma Eryılmaz Eren[1], Zeynep Türe[2], Azade Kanat[1], Ayşin Kılınç Toker[1], İlhami Çelik[1]

[1]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Training and Research Hospital, Kayseri, Türkiye

[2]Department of Infectious Diseases, Private Gürlife Hospital, Eskişehir, Türkiye

Abstract

Introduction: Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne zoonotic viral infection, causing non-specific symptoms like headache, fever, sore throat, myalgia, and arthralgia. Due to its overlapping signs with various diseases, differential diagnosis becomes crucial, especially in the endemic regions. This study aimed to compare patients tested with a pre-diagnosis of CCHF.

Methods: Adult patients who presented with nonspecific symptoms such as headache, fever, and bleeding, were tested for CCHF between April 2019 and December 2022 were included. CCHF diagnosis is based on detecting RNA via real-time polymerase chain reaction or immunoglobulin M using enzyme-linked immunosorbent assay. Patients were categorized into three groups: Group 1 (Non-infectious disease), Group 2 (Infectious/Non-CCHF disease), and Group 3 (CCHF). Diagnoses and clinical features were determined for Groups 1 and 2. Laboratory parameters of all three groups were compared.

Results: Among 259 patients, 152 were diagnosed with CCHF, and 107 with non-CCHF conditions. coronavirus disease 2019 (COVID-19) was the most prevalent infectious disease, while toxic hepatitis led non-infectious cases. CCHF patients displayed distinctive laboratory values, with lower white blood cell count, lymphocyte count, platelet count, creatinine, fibrinogen, and higher Aspartate Aminotransferase, Alanine Aminotransferase, and Lactate dehydrogenase compared to other groups.

Discussion and Conclusion: The differential diagnosis of CCHF is crucial in endemic countries, with COVID-19 emerging as a significant associated disease. CCHF is discerned from infectious diseases by lower blood count parameters and higher liver function tests.

Keywords: COVID-19; Crimean-Congo hemorrhagic fever; Differential diagnosis; Infectious diseases

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Correspondence: Zeynep Türe, M.D. Eskişehir Özel Gürlife Hastanesi, Enfeksiyon Hastalıkları Kliniği, Eskişehir, Türkiye
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Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne zoonotic viral infection caused by the Crimean-Congo hemorrhagic fever virus, prevalent from Southern Russia and the Black Sea region to South Africa.[1] It is endemic in Türkiye, with a reported mortality rate of up to 30%.[2,3] CCHF presents in three different clinical forms: mild, moderate, and severe, exhibiting non-specific initial symptoms. The key symptoms include headache, fever, sore throat, weakness, fatigue, myalgia, and arthralgia. Liver involvement is common, along with potential petechial rash and bleeding tendencies. Severe cases may lead to vascular leaks, multi-organ failure, and shock. Laboratory findings commonly include thrombocytopenia, leukopenia, elevated liver enzymes, and prolonged activated partial thromboplastin time and prothrombin time.[4–6]

Due to non-specific signs and symptoms, CCHF can be confused with various diseases. Identifying other diseases mimicking epidemiological, clinical, and laboratory features becomes essential. The differential diagnosis includes infectious diseases such as brucellosis, other zoonotic diseases, malaria, sepsis, and viral hepatitis, as well as non-infectious diseases like autoimmune diseases, malignancies, and drug toxicity.[7–10]

This study presents cases initially pre-diagnosed with CCHF but later diagnosed with different conditions in our clinic situated in an endemic region for CCHF.

The aim of this study is to determine the infectious and non-infectious disease diagnoses of patients investigated with a preliminary diagnosis of CCHF and to reveal symptomatic, clinical and laboratory differences.

Materials and Methods

Study Place and Design

This study was conducted in a tertiary health institution with a 1600 bed capacity, located in the Central Anatolia region, where patients were transferred from neighboring provinces. The hospital had a capacity of 250 intensive care beds. This hospital had blood product replacement, hemodialysis, chemotherapy and plasmapheresis facilities. An average of 25 to 50 patients diagnosed with CCHF were treated annually. The study was designed retrospectively on adult patients investigated with a preliminary diagnosis of CCHF.

Ethical Approval

The clinical research was approved by the local ethics committee (2023; 768). This study was conducted in conformity with the principles outlined in the Helsinki Declaration.

Selection of Cases

Adult patients (>18 years) were hospitalized between April 2019 and December 2022 with non-specific symptoms such as headache, fever, and bleeding. Demographics, symptoms, laboratory findings, and patient outcomes were recorded.

Patients suspected of CCHF underwent a thorough examination for ticks, complete blood count, biochemistry parameters, and coagulation panel sampling. Additional tests included examining blood, urine, stool, and other samples for infectious agents, Brucella agglutination, viral hepatitis antibodies, and blood smears for infectious and non-infectious causes. Further diagnosis involved autoimmune markers, thorax and abdomen imaging, and histopathological examination in the presence of pathological findings (Table 1).

CCHF diagnosis relied on serum samples collected at admission and transferred to the Public Health Virology Laboratory, Republic of Türkiye Ministry of Health, Ankara. Real Time-Polymerase Chain Reaction (RT-PCR) and/or CCHF immunoglobulin M positivity in serum confirmed CCHF cases.

Demographic characteristics, occupations, living areas and presenting symptoms of patients investigated with a preliminary diagnosis of CCHF but diagnosed other than CCHF were obtained from patient files. According to the final diagnosis, the patients were categorized into three groups: Group 1 (Non-infectious disease), Group 2 (Infectious/Non-CCHF disease), and Group 3 (CCHF). Laboratory values of patients in all three groups at the time of presentation were compared.

Statistical Analysis

The collected information was processed using Statistical Package for Social Sciences (SPSS) for Windows version 22.0 (IBM Corp, Armonk, NY, USA). Shapiro-Wilks test and histogram graphs were used to assess whether the distribution is normal or not. Laboratory values at the time of admission were compared between CCHF, non-CCHF infectious diseases and non-infectious diseases groups using the Kruskal Wallis test. $P<0.05$ was determined as statistically significant on all tests.

Results

A total of 259 patients suspected of CCHF and tested were included in the study. Figure 1 shows the distribution, with 152 CCHF and 107 non-CCHF patients. Of the non-CCHF patients, 70 (77.7%) were male, with a median age of 50.0

Table 1. Categorized groups and methods used for definitive diagnosis

Group 1 Non-infectious diseases	Group 2 Infectious/non-CCHF diseases	Group 3 CCHF
Malignancy: Histopathologic examination	**Brucellosis:** Brucella agglutination ≥1/160 and/or positive blood culture	CCHF PCR positive /IgM positive
Drug-related pancytopenia: Detailed history and exclusion of other diagnoses	**Acute viral hepatitis:** HBs Ag /Anti HAV IgM positive/Anti CMV IgM or other viral Ig M positivity by ELISA	
Toxic hepatitis: Herbal medicine history and liver failure	**Malaria:** Blood smear and/or plasmodium PCR	
Autoimmune diseases: Positive autoimmune markers	Infective endocarditis: Blood culture positivity and transthoracic/transesophageal echocardiography	
HUS/TTP/ITP: Blood smear and auto antibody	**Atypic pneumoniae:** Direct radiography or thorax tomography	
	Acute gastroenteritis: Stool microscopy, culture or PCR examination	
	COVID-19: Oropharyngeal/nasopharyngeal PCR test positivity	

CCHF: Crimean-Congo hemorrhagic fever; CMV: CytomegalovirusHUS; ELISA: Enzyme linked immunosorbent assay; HAV: Hepatitis A virus; HBS Ag: Hepatitis B surface antigen; ITP: Immune thrombocytopenic purpura; PCR: Polymerase chain reaction; HUS: Hemolytic uremic syndrome, TTP: Thrombotic thrombocytopenic purpura.

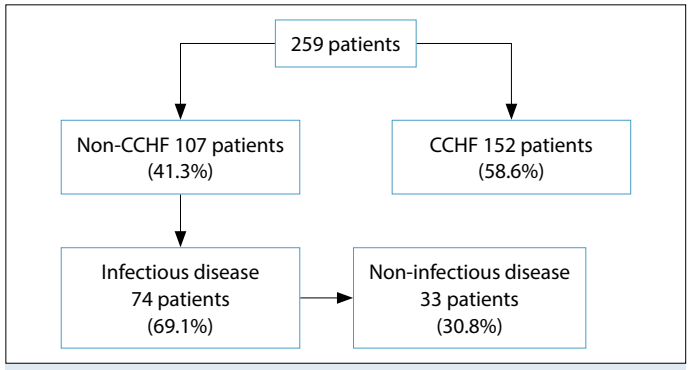

Figure 1. Flowchart of cases according to the diagnosis.

(18.0–87.0) years. Demographics and clinical characteristics of non-CCHF patients are detailed in Table 2, highlighting that 57.0% lived in rural areas, and 43.0% were involved in farming/livestock. The most common complaints at admission were fever (76.6%) and myalgia (75.7%). Bleeding symptoms were seen in 16.6% of patients.

Diagnosis of patients with 69.1% having infectious diseases and 30.9% non-infectious conditions were presented in Figure 1. Coronavirus disease 2019 (COVID-19) accounted for 24.3% of infectious cases, while other common infections included brucellosis (12.2%) and acute gastroenteritis (17.6%). The most prevalent non-infectious condition was drug-related, with 33.2% diagnosed with drug-induced toxic hepatitis and 9.1% with drug-induced pancytopenia. Malignancies were observed in 24.2%, autoimmune diseases in 15.1%, and hemolytic diseases in 18.1% of cases (Table 3).

Table 2. Clinical and demographics characteristics of 107 cases

	Patients n (%)
Age, median (min–max)	50.0 (18.0–87.0)
Gender, Male	70 (65.4)
History	
Rural area	61 (57.0)
Livestock/farming	46 (43.0)
Tick bite	30 (28.0)
Symptoms	
Fever	82 (76.6)
Myalgia	81 (75.7)
Vomiting/nausea	82 (76.6)
Diarrhea	24 (22.4)
Confusion	12 (11.2)
Conjunctival suffusion	4 (3.8)
Bleeding symptoms	
Hematemesis	12 (11.2)
Petechia	8 (7.5)
Melena	5 (4.7)

Min: Minimum; Max: Maximum.

Laboratory values on admission were compared between infectious and non-infectious diseases (Table 4). The white blood cell count was the highest in patients with non-infectious diseases and the lowest in patients with CCHF diagnosis ($p<0.001$). The median lymphocyte count at the time of admission was highest in the non-CCHF

Table 3. Distribution of patients not diagnosed with CCHF according to their diagnosis

Diagnosis	Patients n=107 (%)
Infectious diseases	**74 (69.1)**
COVID-19	18 (24.3)
Brucellosis	9 (12.2)
Acute gastroenteritis	13 (17.6)
Atypic pneumonia	9 (12.2)
Bacterial sepsis	12 (16.2)
Acute viral hepatitis	5 (6.8)
Malaria	3 (4.1)
Infective endocarditis	1 (1.4)
Epstein barr virus	1 (1.4)
Measles	2 (2.7)
Lyme disease	1 (1.4)
Non-infectious disease	**33 (30.9)**
Hemolytic disease	
TTP	3 (9.1)
ITP	2 (6.0)
Atypic HUS	1 (3.0)
Autoimmune disease	
RA	2 (6.1)
SLE	1 (3.0)
Vasculitis	1 (3.0)
Wilson disease	1 (3.0)
Drug related conditions	
Toxic hepatitis	11 (33.3)
Drug-related pancytopenia	3 (9.1)
Malignancies	
Lymphoma/Leukemia	3 (9.1)
Myelodysplastic syndrome	3 (9.1)
Prostate adenocarcinoma, bone marrow metastasis	2 (6.0)

COVID-19: Coronavirus disease 2019; TTP: Thrombotic thrombocytopenic purpura; ITP: Immune thrombocytopenic purpura; HUS: Hemolytic uremic syndrome; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

infectious diseases group and lowest in the CCHF patient group (p=0.005). The hemoglobin level was the lowest in patients with non-infectious diagnosis and the highest in patients with CCHF diagnosis (p<0.001). The median platelet level was lower in the CCHF patient group compared to the other groups (p<0.001). The aspartate aminotransferase level was the highest in the CCHF patient group and this difference was p<0.001. Lactate dehydrogenase levels were higher in the non-infectious group (p<0.001); and among the coagulation parameters, active partial thromboplastin time was found to be the highest in the CCHF group (p<0.001).

Discussion

This study focuses on patients initially suspected of CCHF but diagnosed with alternative conditions, emphasizing the importance of obtaining a definitive diagnosis in CCHF-endemic regions. Among 107 recorded patients, 69% had infectious and 31% non-infectious diseases. In endemic regions, CCHF should be considered in the preliminary diagnosis of patients presenting with non-specific symptoms or disease symptoms. In studies conducted in various regions of our country, the positivity rate in patients with a preliminary diagnosis of CCHF was reported as 40–50%. A six-year data were scanned in a hospital in the east of Türkiye in 1378 patients with a preliminary diagnosis of CCHF; CCHF was diagnosed in 521 patients.[11] In another study reported from the Black Sea region, PCR was performed on serum samples from 117 patients with a preliminary diagnosis of CCHF and the diagnosis of CCHF was confirmed in 74 patients.[12] Nevertheless, in a face-to-face survey conducted on 100 patients diagnosed with CCHF in an endemic region, it was reported that the patients had visited at least one (0–3) physician before the diagnosis.[13] Especially in endemic regions, CCHF should be considered in the differential diagnosis of patients presenting to any physician for any reason other than infectious diseases. Especially in European countries, the detection of the virus in ticks and the reporting of sporadic cases have increased publications on awareness on this subject.[14,15] It should be kept in mind in differential diagnosis when traveling to endemic areas as well as living in endemic areas.

Differential diagnosis of CCHF becomes challenging when considering symptoms, physical examination, and laboratory findings.[16,17] During the pandemic period, Gül et al.,[18] reported a patient initially diagnosed with CCHF and COVID-19 was later identified with Brucellosis. Coinfections of CCHF with Brucellosis, malaria, and COVID-19 have been reported in endemic areas.[19–21] Isolation precautions and personal protective equipment use during the pandemic period did not change the number of cases. In a study conducted by Igan et al.[11] in an endemic region, it was reported that the highest positivity rate from serum samples sent was during the pandemic period. Age also plays a crucial role in differential diagnosis, with viral upper respiratory tract infection being common in pediatric cases, while hemophagocytic lymphohistiocytosis has been reported among non-infectious causes.[22] In a retrospective

Table 4. Laboratory findings of patients according to groups

Laboratory tests, Median (min-max)	Group 1 Non-infectious disease n=33	Group 2 Infectious disease- Non-CCHF n=74	Group 3 CCHF n=152	p
White blood cell counts 10^3/L	6.64 (0.30–33.14)[a]	6.29 (0.15–24.01)[a]	2.49 (0.71–25.00)[b]	<0.001
Lymphocyte count × 10^3/L	1.09 (0.11–9.56)[a]	0.80 (0.13–3.82)[a]	0.66 (0.12–5.40)[b]	0.005
Hemoglobin	11.00 (6.10–16.00)[a]	13.40 (7.00–17.20)[b]	14.35 (6.50–19.30)[b]	<0.001
Platelets count × 10^3/mm^3	65.00 (6.00–262.00)[a]	103.50 (12.40–289.00)[b]	53.50 (5.00–180.00)[a]	<0.001
Creatinine, mg/dL	1.00 (0.37–6.70)[a]	1.00 (0.30–9.00)[a]	0.81 (0.30–5.30)[b]	0.007
Aspartate aminotransferase, U/L	58.00 (11.00–2199.00)[a]	61.00 (10.00–2250.00)[a]	214.50 (18.00–7296.00)[b]	<0.001
Alanine aminotransferase, U/L	92.00 (7.00–3293.00)[a]	73.00 (10.00–2582.00)[a]	120.50 (12.00–2642.00)[b]	0.025
Lactate dehydrogenase, U/L	363.00 (11.00–8991.00)[a]	272.00 (15.00–3241.00)[a]	538.50 (165.00–5567.00)[b]	<0.001
aPTT (seconds)	33.00 (19.00–94.00)[a]	29.55 (14.00–110.00)[b]	36.25 (16.40–180.00)[a]	<0.001
PT (seconds)	18.80 (11.20–54.00)[a]	14.40 (10.00–34.40)[b]	13.65 (9.20–180.00)[b]	<0.001
INR	1.28 (0.94–3.60)[a]	1.14 (0.90–2.60)[a]	1.05 (0.80–12.00)[b]	<0.001
Fibrinogen	2675.00 (82.00–1033.00)[a]	3330.00 (192.00–9000)[a]	303.00 (37.00–4960.00)[b]	<0.001

Different letters indicate statistically significant differences. CCHF: Crimean-Congo hemorrhagic fever; aPTT: Activate partial tromboplastine time; PT: Protrombine time; Min: Minimum; Max: Maximum.

study comparing the clinical and laboratory findings of adult and child patients diagnosed with CCHF, adults had lower lymphocyte, and platelet counts and higher liver transaminase and creatinine levels than children.[23]

COVID-19, characterized by endothelial damage and increased systemic inflammatory response, presents symptoms similar to many viral diseases, emerging as the primary viral disease to consider in CCHF-endemic areas.[24,25] Other infectious diseases such as acute gastroenteritis and atypical pneumonia, as well as endemic conditions like Brucellosis, should be carefully considered in the differential diagnosis of CCHF due to their overlapping symptoms and high incidence of under/over and pancytopenia.[26]

Although infectious and non-infectious diseases share similarities with CCHF, our findings demonstrate that CCHF patients exhibit lower white blood cells, lymphocytes, and platelet values in laboratory results compared to both groups. In this evaluation, parameters such as disease severity score or age of the patients are also important. In a retrospective study comparing the clinical and laboratory findings of adult and child patients diagnosed with CCHF, adults had lower lymphocyte, and platelet counts and higher liver transaminase and creatinine levels.[23] Chronic processes manifested in the non-infectious and non-CCHF groups resulted in higher anemia. Additionally, creatinine, AST, and LDH values were elevated in the CCHF group, possibly indicating increased toxicity. These parameters change not only for CCHF but also according to the severity score of CCHF. In a retrospective study comparing laboratory parameters according to the severity of CCHF, it was observed that parameters such as C-reactive protein, lactate dehydrogenase, lymphocyte count, and white blood cell were related to the severity score.[27] The diagnostic algorithm should be managed according to both infectious and non-infectious causes, considering many parameters such as the region where the patients live, their profession, and laboratory values. Thus, the relevant isolation measures will be initiated early for diseases such as COVID-19 and CCHF; and early diagnosis of diseases such as malignancy will contribute to prognosis.

The limitations of this study are that it was conducted in a single center, its retrospective design, and the number of cases when the diseases in the differential diagnosis were evaluated alone. The fact that patients with CCHF and non-CCHF have different severity scores makes it difficult to make a definitive distinction according to laboratory values. It may be more important to increase the number of cases and categorize the diseases in the differential diagnosis to make a comparison.

Conclusion

In conclusion, differential diagnosis of CCHF remains pivotal in endemic countries, with COVID-19 emerging as a significant associated disease. CCHF can be distinguished from infectious diseases by lower blood count parameters and higher liver function tests. Despite the difficulty in differentiating the three groups based on symptoms and initial laboratory findings, our results can offer relative guidance.

Ethics Committee Approval: The Kayseri City Training and Research Hospital Ethics Committee granted approval for this study (date: 03.01.2023, number: 768).

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