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Epidemiologic, Clinical and Laboratory Criteria and Final Diagnoses in PCR Negative Suspected Crimean-Congo Hemorrhagic Fever Patients

Omer Karasahin[1], Emine Fusun Karasahin[2]

[1]*Erzurum Regional Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Erzurum, Türkiye*
[2]*Erzurum Provincial Health Directorate Presidency of Public Health Services, Department of Public health, Erzurum, Türkiye*

Abstract

Introduction: Crimean-Congo hemorrhagic fever (CCHF) disease can be confused with many diseases due to flu-like nonspecific initial symptoms and laboratory findings in endemic areas. In this study, it was aimed to evaluate the final diagnosis of patients hospitalized with suspected CCHF diagnosis, but without CCHF virus detection.

Materials and Methods: This retrospective cohort study was conducted between March 2016 and September 2022. We included 662 patients who met the definition of potential cases according to the CCHF case definition. The baseline symptoms, laboratory findings and epidemiologic characteristics of patients in whom CCHF virus was not detected were compared with patients in whom the diagnosis of CCHF disease was confirmed and then grouped together with their final diagnosis.

Results: There was no difference in baseline complaints, living in a rural area and frequency of thrombocytopenia in those without CCHF virus compared to CCHF patients. Of these patients, 80.1% were diagnosed with infectious diseases and 19.9% with non-infectious diseases. The most common infectious diseases were respiratory tract infections (22.2%) and brucellosis (17.7%); non-infectious diseases were hematologic diseases (8.2%).

Conclusion: In endemic areas, the presence of fever and thrombocytopenia is not sufficient for the diagnosis of CCHF. Reference methods should be used rapidly for the definitive diagnosis of CCHF. After CCHF is excluded, it is important to know the infectious and non-infectious diseases in the differential diagnosis and their frequencies in order to prevent delay in diagnosis and treatment.

Key words: Crimean-congo hemorrhagic fever; differential diagnosis, delayed diagnosis

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a deadly zoonotic disease caused by a virus in the *Nairovirus* genus of the Bunyaviridae family (1). Early diagnosis of CCHF is essential for planning effective treatment strategies and infection control (2). The diagnosis may be missed because of nonspecific symptoms at presentation. In our country, there are diagnostic algorithms based on a combination of presenting symptoms, epidemiological risk factors, and clinical findings. In addition, the regional reference laboratory network enables rapid diagnosis confirmation in cases of suspected CCHF (3, 4) However, approximately half of suspected CCHF patients presenting to the hospital have negative polymerase chain reaction (PCR) test and/or immunoglobulin M (IgM) results (5). At this point, knowing the diseases to include in the differential diagnosis is important for the early and effective treatment of patients in whom CCHF is not detected (6, 7). In CCHF-endemic areas, infectious and non-infectious diseases should be considered in the differential diagnosis of patients with similar symptoms (7, 8). In the literature, there is only one study evaluating the diagnoses of suspected CCHF patients with negative PCR/IgM tests. In that study, which was also conducted in our country, approximately 60% of patients were diagnosed with other infectious diseases, while the rest were found to have non-infectious diseases (9). The aim of this study was to compare the epidemiological risk factors, presenting symptoms, laboratory findings and epidemiological risk factors of patients hospitalized for potential CCHF who tested negative for CCHF virus with confirmed cases of CCHF, and then to evaluate their final diagnosis.

Materials and Methods

Patient selection: This retrospective cohort study was conducted between March 2016 and September 2022. During the study period, 856 patients were examined for CCHF and the

*Corresponding Author: Omer Karasahin, Associate Professor, Erzurum Research and Education Hospital, Department of Infectious Diseases and Clinical Microbiology, Erzurum, Turkey **Email:** mrkrshn@hotmail.com **Orcid:** Omer Karasahin 0000-0002-4245-1534, Emine Fusun Karasahin 0000-0003-4145-8117

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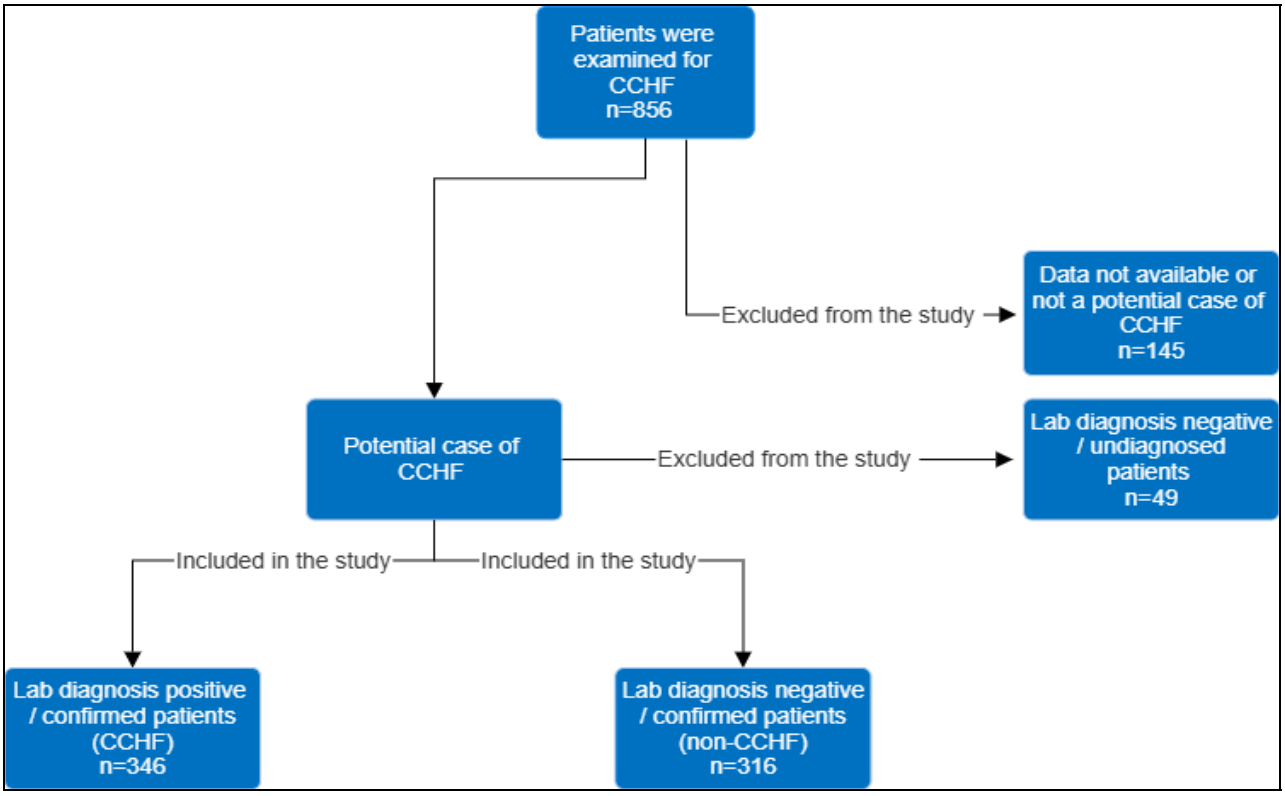

Figure 1. The study flowchart is presented

diagnosis was confirmed in 346 of those patients. The definitive diagnosis of CCHF was made upon detection of CCHF virus in serum samples with reverse transcriptase polymerase chain reaction (RT-PCR) and/or positive CCHF IgM in the reference laboratory. Of the 510 patients whose serum samples resulted negative for CCHF virus or CCHF IgM, 316 patients who met the criteria for potential CCHF and had available data were included in the study. Of the 194 patients excluded from the study, 46 were not analyzed because they did not have a final diagnosis despite meeting the criteria for potential CCHF. The study flowchart is presented in figure 1. Clinical criteria were defined as the presence of at least 2 of 4 clinical criteria: (1) fever (≥38 °C), listlessness, headache, generalized body pain, joint pain, diarrhea, (2) signs of bleeding in the skin and mucosa, (3) thrombocytopenia and/or leukopenia unexplained for another reason, (4) elevated ALT and AST unexplained for another reason. Epidemiologic criteria include the presence of at least one of the following: (1) history of tick bite or tick contact, (2) history of contact with animal blood, tissue or secretions, (3) living in a rural area or history of travel to a rural area (4) history of close contact with a diagnosed case within 2 weeks prior to the onset of illness. The definition of a potential case of CCHF is defined as a case that meets the clinical definition and fulfills at least one of the epidemiological criteria (3, 10). Patients who met the definition of potential cases but were not detected with CCHF virus (non-CCHF) were grouped as those with infectious and non-infectious final diagnoses. Presenting symptoms of fever (≥38 °C), listlessness, headache, generalized body pain, joint pain, diarrhea and signs of bleeding in the skin and mucosa were recorded. Epidemiological details related to tick bite or tick contact, living in a rural area or history of travel to a rural area and history of contact with animal blood, tissue or secretions were obtained by examining the patients' records. A history of close contact with a diagnosed case within 2 weeks before the onset of the disease was not included because none of the patients had a history of close contact with a diagnosed case. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet and leukocyte count values determined at presentation to the hospital were recorded from the hospital information management system. According to the cut-off values of the local commercial laboratory kits, platelet counts <150 x 10^3/L were defined as thrombocytopenia and <4.00 x 10^3/L as leukopenia; AST and ALT values ≥40 U/L were defined as elevated AST and ALT.

Table 1: Comparison of CCHF patients with non-CCHF patients in terms of presenting complaints, laboratory and epidemiologic characteristics

	Non-CCHF (n=316)	CCHF (n=346)	P*
Age, median (range)	53 (16 – 97)	47 (16 – 92)	0.015
Gender, male, n (%)	179 (56.6)	202 (58.4)	0.652
Epidemiological history, n (%)			
Living in a rural area or history of traveling to a rural area	286 (90.5)	312 (90.2)	0.885
Contact with animal blood, tissue or secretions	185 (58.5)	282 (81.5)	<0.001
Tick bite or tick contact	49 (15.5)	207 (59.8)	<0.001
Presenting symptoms, n (%)			
Fever (≥38 °C)	280 (88.6)	308 (89.0)	0.867
Headache	235 (74.4)	271 (78.3)	0.231
Generalised body pain	244 (77.2)	283 (81.8)	0.144
Listlessness	276 (87.3)	311 (89.9)	0.303
Diarrhea	88 (27.8)	100 (28.9)	0.764
Joint pain	148 (46.8)	183 (52.9)	0.120
Findings of bleeding of the skin and mucosa	46 (14.6)	93 (26.9)	<0.001
Laboratory findings, n (%)			
Elevated AST	159 (50.3)	253 (73.1)	<0.001
Elevated ALT	136 (43.0)	180 (52.0)	0.021
Leukopenia	142 (44.9)	285 (82.4)	<0.001
Thrombocytopenia	250 (79.1)	284 (82.1)	0.334
Mortality, n (%)	10 (3.2)	14 (4.0)	0.544

***** Mann-Whitney U tests and Chi-square were applied.

Ethical approval: Ethics committee approval was obtained from the local ethics committee. (Erzurum Regional Training and Research Hospital, Clinical Research Ethics Committee 20.12.2021, Decision no: 2021-22-280)

Statistical analysis: For descriptive statistics, categorical data were presented as frequency distribution and percentage, and continuous variables were presented as median (range). Chi-square test was used to compare categorical data between the groups, and Mann-Whitney U tests were used to compare continuous data since parametric hypothesis testing conditions could not be met. The data were analyzed using SPSS version 21.0 statistical software package and $p<0.05$ was considered significant.

Results

This study included 662 patients who were diagnosed as potential CCHF cases. The median age of these patients was 49 years (range, 16-97) and 381 (57.6%) were male. 316 patients had negative CCHF PCR and IgM test results, and 346 patients had positive CCHF PCR and/or IgM test results. The comparison of CCHF patients and non-CCHF patients in terms of presenting complaints, laboratory findings and epidemiologic characteristics during the study period is presented in Table 1. Non-CCHF patients were significantly older ($p=0.015$). Resides in rural area, presenting complaints and thrombocytopenia were not significantly different between the two groups (Table 1). Findings of bleeding of the skin and mucosa were significantly more frequent in CCHF patients ($p<0.001$). In addition, tick bite or tick contact, contact with infected tissue or blood/body fluids were significantly more frequent in CCHF patients ($p<0.001$). Among the laboratory findings, elevated AST, ALT and leukopenia were more frequent in CCHF patients (Table 1). The final diagnoses of non-CCHF patients were grouped as infectious and non-infectious diseases. In the infectious diseases group, respiratory infection was the most frequent diagnosis. Lower respiratory tract infection was observed in 26 patients (37.1%), upper respiratory tract infection in 22 patients (31.4%), tonsillopharyngitis (*Streptococcus pyogenes*) in 12 patients (17.1%), influenza A in 4 patients (5.7%), influenza B in 4 patients (5.7%), and acute bacterial sinusitis in 2 patients (2.9%). All patients diagnosed as having brucellosis had *Brucella* standard tube agglutination test titer of ≥ 1/160, and *Brucella* spp. were isolated in the blood

cultures of 12 patients (21.8%). No causative pathogen was detected in 31 (77.5%) of the patients diagnosed as having acute gastroenteritis.

Table 2: Distribution of patients diagnosed with diseases other than CCHF

	n (%)
INFECTIOUS DISEASES	253 (80.1)
Respiratory tract infection	70 (22.2)
Brucellosis	56 (17.7)
Acute Gastroenteritis	40 (12.7)
Sepsis	32 (10.1)
Urinary Tract Infection	19 (6.0)
Intra-abdominal infection	18 (5.7)
Cellulitis	9 (2.8)
Acute viral hepatitis	4 (1.3)
Q fever	2 (0.6)
Salmonellosis	2 (0.6)
NON-INFECTIOUS DISEASES	63 (19.9)
Hematologic diseases	26 (8.2)
Drug intoxication	10 (3.2)
Gastrointestinal bleeding	9 (2.8)
Solid organ malignancy	8 (2.5)
Systemic lupus erythematosus	4 (1.3)
Pulmonary thromboembolism	3 (0.9)
Liver cirrhosis	3 (0.9)
Kikuchi-Fujimoto disease	1 (0.3)

Table 3: Distribution of symptoms, epidemiologic details and laboratory findings in non-CCHF patients compared to other infectious or non-infectious diseases

	Infectious Diseases	Non-Infectious Diseases	p
Presenting symptoms, n (%)			
Fever (≥38 °C)	232 (91.7)	48 (76.2)	0.001
Headache	191 (75.5)	44 (69.8)	0.358
Generalised body pain	200 (79.1)	44 (69.8)	0.119
Listlessness	222 (87.7)	54 (85.7)	0.664
Diarrhea	70 (27.7)	18 (28.6)	0.886
Joint pain	124 (49.0)	24 (38.1)	0.120
Bleeding**	22 (8.7)	24 (38.1)	<0.001
Epidemiological details, n (%)			
Living in a rural area or history of travel to a rural area	225 (88.9)	61 (93.8)	0.056
Contact with animal blood, tissue or secretions	151 (59.6)	34 (53.9)	0.410
Tick bite or tick contact	42 (16.6)	7 (11.1)	0.190
Laboratory findings, n (%)			
Elevated AST	131 (51.8)	28 (44.4)	0.298
Elevated ALT	118 (46.6)	18 (28.6)	0.010
Leukopenia	108 (42.7)	34 (54.0)	0.107
Thrombocytopenia	194 (76.7)	56 (88.9)	0.021

***Chi-square were applied. ****Findings of bleeding of the skin and mucosa, **AST:** aspartataminotransferase, **ALT:**alaninaminotransferase

Of those for whom a pathogen was detected, *Entamoeba histolytica* was identified in 4 patients (10.0%), *Campylobacter* spp. in 3 patients (7.5%), and *Shigella* spp. in 2 patients (5.0%). Sepsis was detected in 32 patients (9.9%). The focus of infection was the urinary tract in 14 patients (43.8%), the lower respiratory tract in 8 patients (25.0%), catheter-associated bloodstream infection in 3 patients (9.4%), and was not detected in 7 patients (21.9%). Of the intra-abdominal infections diagnosed, 8 (44.4%) were acute cholecystitis, 4 (22.2%) were intra-abdominal abscess, 2 (11.1%) were acute cholangitis, 2 (11.1%) were pelvic inflammatory disease, 1 was acute pancreatitis, and 1 was acute appendicitis. Four patients had acute viral hepatitis, 2 (50.0%) with acute viral hepatitis B and 2 (50.0%) with acute viral hepatitis A. Among the non-infectious

diagnoses, hematological diseases (n=26, 8.2%) were most common. These included idiopathic thrombocytopenic purpura in 7 patients (26.9%), megaloblastic anemia in 4 patients (15.4%), myelodysplastic syndrome (MDS) in 4 patients (15.4%), and acute leukemia in 4 patients (15.4%), while acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and cold agglutinin disease were diagnosed in 1 patient each. Drug intoxication with non-steroidal anti-inflammatory drugs (NSAIDs) was diagnosed in 4 patients (40.0%), methotrexate in 3 patients (30.0%), and valproic acid, warfarin, and methimazole in 1 patient. The distribution of patients receiving non-CCHF diagnoses is presented in Table 2. The distribution of symptoms, epidemiological details and laboratory findings in non-CCHF patients according to other infectious or non-infectious diseases is presented in Table 3. While fever and ALT elevation were observed more frequently in infectious diseases, thrombocytopenia and bleeding were significantly more frequent in non-infectious diseases. Ten patients died (3.1%). Of these, 6 patients had sepsis, 2 had gastrointestinal bleeding, and 2 had hematological disease.

Discussion

CCHF is one of the first diseases that comes to mind between March and October in endemic regions when patients are present with high fever and thrombocytopenia. However, as these two findings are also observed together in many other conditions, the differential diagnosis includes many infectious and non-infectious systemic diseases (9, 11). Knowing which diseases to include in the differential diagnosis of CCHF will prevent unnecessary testing and medical treatment and can also save lives by enabling early and effective treatment planning (2, 9). Therefore, this study examined the frequency, epidemiological risk factors, presenting symptoms, and laboratory findings of diseases included in the differential diagnosis of CCHF in an endemic area from a real-life perspective. Infectious diseases were diagnosed in 80.1% of the patients in our study, with respiratory tract infections, brucellosis, and acute gastroenteritis being the most common. Among non-infectious diagnoses, hematological disorders, solid organ malignancies, and adverse drug effects were common. The typical course of CCHF infection has four distinct phases: incubation, prehemorrhagic, hemorrhagic, and convalescence (2). The prehemorrhagic phase, which is when most patients present to the hospital, is characterized by flu-like symptoms (12). These symptoms are primarily confused with respiratory tract infections and influenza (9). Eight patients in our study received a final diagnosis of influenza. In addition, in our study we also observed the thrombocytopenia and/or leukopenia seen in severe respiratory tract infections (13). As in previous studies, respiratory tract infection was the most common disease in the differential diagnosis of CCHF (9, 14). This is because in addition to having similar clinical and laboratory characteristics, respiratory tract infections are the most common community-acquired infections requiring hospital admission (15). Moreover, CURB-65 and hemorrhage in the lower respiratory tract, where treatment and follow-up decisions are made, were prognostic decision makers in CCHF(16). This proves that they have similar initial clinical findings. As in CCHF, the endothelium is an important target in sepsis. This results in similar clinical and laboratory findings (17). In addition, both conditions cause high serum levels of many proinflammatory cytokines such as tumor necrosis factor alpha and interleukin 6 through a process mediated by antigen-presenting cells (18). Confusion with sepsis occurs due to similarities such as initially presenting with high fever, chills, malaise, confusion, and hemorrhage due to disseminated intravascular coagulation and lymphocyte apoptosis in severe disease (19). In our study, sepsis was the most common cause of death (60%) This shows that in the differential diagnosis of CCHF, sepsis is one of the diagnoses that should be considered for rapid intervention (20). Brucellosis and CCHF are two zoonotic infectious diseases with similar initial symptoms, laboratory findings, and risk groups. Brucellosis causes thrombocytopenia through hypersplenism and granulomatous lesions of the bone marrow (21). In regions where brucellosis is endemic, it should be considered in patients presenting with fever (22). A high proportion of brucellosis patients in our study had fever and thrombocytopenia. Previous studies suggested that brucellosis should definitely be included in the differential diagnosis of viral hemorrhagic fever and that patients diagnosed as having CCHF or brucellosis should be screened for other diseases (23). Two of our patients who worked in animal husbandry and presented with fever and thrombocytopenia tested positive for *Coxiella burnetii* phase 2 IgM and IgG in indirect immunofluorescence antibody assay and were diagnosed as having Q fever. As demonstrated in

a case report in the literature, Q fever is another zoonotic infection that should be kept in mind due to its similar clinical, laboratory, and epidemiological features (24). Previous reports have indicated that acute gastroenteritis should be included in the differential diagnosis of CCHF (25, 26). Because viral gastroenteritis is limited to the gastrointestinal epithelium, it rarely causes severe inflammation and thrombocytopenia (27). However, acute bacterial gastroenteritis can cause leukopenia or thrombocytopenia (28). Although fever and thrombocytopenia were observed less frequently in patients diagnosed with acute gastroenteritis in our study, it was included in the differential diagnosis of CCHF in these patients, who commonly resided in rural areas and had close contact with animals, because of their symptoms of generalized body pain, fever and diarrhea. High fever, abdominal pain, and thrombocytopenia as well as elevated serum transaminase levels have been observed in intra-abdominal infections, especially acute cholecystitis and cholangitis. After ruling out CCHF, these patients were diagnosed using abdominal imaging and were provided with the necessary antibiotic and surgical treatment. Patients with hematological malignancy frequently have pancytopenia due to malignant cell infiltration of the bone marrow, and bleeding secondary to thrombocytopenia. Pancytopenia is also frequently observed in megaloblastic anemia and causes a bleeding tendency. The clinical findings of febrile neutropenia and acute leukemia are also confused with CCHF (8). As in our study, hematological diseases are the leading non-infectious diseases in the differential diagnosis of CCHF (9).

High-dose methotrexate is often used in the treatment of malignancy, while lower doses of methotrexate are also currently used in the treatment of rheumatologic and inflammatory diseases. In the literature, there is a case report describing a patient with rheumatoid arthritis (RA) who presented with the most common findings of CCHF such as fever, myalgia, bleeding, and cytopenia, and was diagnosed as having methotrexate intoxication (29). In our study, two patients with a diagnosis of RA and one patient with a diagnosis of Crohn's disease were receiving methotrexate, and their fever and thrombocytopenia were attributed to adverse effects of methotrexate after ruling out CCHF. The adverse effects of methotrexate cause symptoms similar to CCHF such as fever, gastrointestinal problems, rash, thrombocytopenia, leukopenia, and elevated transaminases (30). Our study had a large cohort because it was conducted in a hospital that is considered a referral center for the Northern and Eastern Anatolia regions, where CCHF is endemic. This enabled the evaluation of a wide range of CCHF-negative patients.

Study limitations: The most important limitation of the study is its retrospective design. In addition, diagnoses of non-CCHF patients were recorded with patient epicrises, laboratory and pathology results. Patients whose records could not be reached or whose results could not be obtained were excluded from the study. This is a limitation that may partially affect the frequency of the disease.

Conclusion

in endemic areas, the presence of fever and thrombocytopenia is not sufficient for the diagnosis of CCHF. Delays in diagnosis can lead to fatalities in patients in the differential diagnosis. Reference methods should be used rapidly for the definitive diagnosis of CCHF. After CCHF is excluded, it is important to know the infectious and non-infectious diseases in the differential diagnosis and their frequencies in order to prevent delay in diagnosis and treatment.

Ethical approval: Ethics committee approval was obtained from the local ethics committee. (E-37732058-514.99) There are no conflicts of interest for all authors No financial support was received from any person or organization in this study.

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