We need more accuracy in Crimean Congo Hemorrhagic Fever diagnosis upon initial presentation in endemic areas

Ilkay Bozkurt 1,2

1. Department of Clinical Microbiology and Infectious Diseases. Ondokuz Mayis University School of Medicine, Samsun, Turkiye
2. Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom

Corresponding author: Dr Ilkay Bozkurt
Department of Clinical Microbiology and Infectious Diseases, Ondokuz Mayis University School of Medicine, Samsun, Turkiye
Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool
L3 5QA, United Kingdom
Email: drilkaybozkurt@gmail.com
Phone number: +905056746597

Authorship confirmation/contribution statement

Ilkay Bozkurt: Study conception and design, data collection, analysis and interpretation of results, writing- reviewing and editing

We need more accuracy in Crimean Congo Hemorrhagic Fever diagnosis upon initial presentation in endemic areas

Background: The primary aim of this study was to highlight the considerable rate of misdiagnosis associated with Crimean-Congo Hemorrhagic Fever (CCHF) during initial hospital admission.

Materials and Methods: A comprehensive face-to-face survey was carried out on hospitalized patients living in endemic areas with confirmed diagnosis of CCHF. The structured questionnaire covered demographic information, specifics of hospital admissions before diagnosis, and adherence to the diagnostic criteria for CCHF as determined by the Ministry of Health (MoH).

Results: This cohort consisted of 100 patients with a mean age of 44 (20-77) years, of which 65 (65%) were male. Each patient had undergone at least one hospital visit (0-3) before receiving the confirmed diagnosis of CCHF. Only 45 (45%) patients were thoroughly evaluated in line with the clinical diagnostic criteria set forth by the Ministry of Health (MoH), while 21% had initially received provisional CCHF diagnoses before final confirmation.

Conclusions: This study indicates the urgent necessity to improve diagnostic accuracy for CCHF during the initial presentation in endemic regions.

Crimean-Congo Hemorrhagic Fever (CCHF) is an emerging infectious disease with a broad geographic distribution (WHO 2024). The World Health Organization has identified CCHF as a research priority in emergency contexts (WHO 2024). This vector-borne zoonotic disease has the potential for dissemination and significant epidemic outbreaks, primarily transmitted through tick bites (Leblebicioglu H 2010). While the exact pathogenesis remains unclear, cytokine dysregulation is believed to drive disease progression and contribute to the high fatality rate associated with CCHF (Bente DA et al. 2013). The incubation period ranges from 1 to 13 days, and patients typically present with flu-like symptoms and gastrointestinal issues (Al-Abri SS et al. 2017). It is a multisystemic disease that can be fatal, with a mortality rate of approximately 5% reported in Turkiye. Future directions for managing CCHF include enhanced surveillance, preventive measures, and therapeutic interventions (Fletcher TE et al. 2017). In the context, Turkiye where an average of 1500 cases of CCHF are reported annually, a Phase-1 trial (UMIT-1) for CCHF treatment was initiated last year (Clinical Trails 2024). There is currently no approved antiviral treatment available. Therefore, accurate initial assessment, proper triage, and effective management of patients are crucial. To address this, a standardized questionnaire was developed, including patient demographics, number of admissions, and pre-diagnosis information. This questionnaire aimed to determine whether patients were evaluated based on clinical and epidemiological findings consistent with CCHF during their initial presentation and diagnosis.

This face-to-face survey involved the assessment of 100 hospitalized patients residing in endemic regions with confirmed diagnoses of CCHF. Ethical approval for the study was provided by Ondokus Mayis Research Ethics Committee (OMU KAEK 2023/186). Diagnostic confirmation was achieved through the detection of CCHF RNA by using reverse transcription polymerase chain reaction (RT-PCR). Among the patients, 65 (65%) were male, and the average age was 44 (20-77) years. Prior to their CCHF diagnosis or suspicion, patients had undergone evaluations at least once (0-3). Forty-five percent of the patients were properly assessed in accordance with the clinical and epidemiological diagnostic criteria outlined by the Ministry of Health (MoH) (Turkish Ministry of Health 2024) for CCHF. However, 33% of the patients were partially questioned within the framework of the MoH criteria, and 22% were not thoroughly questioned based on either epidemiological or clinical criteria. Only 21% of the patients underwent initial management or triage with a preliminary diagnosis of CCHF prior the confirmation of the diagnosis. Notably, 51% of the patients received their diagnosis during their second hospital admission, while 21% and 7% were diagnosed with CCHF during their third and fourth admissions, respectively.

Patients were most commonly assessed by the emergency department physician followed by the family physician on the initial diagnosis. The initial diagnoses were predominantly upper respiratory tract infection gastroenteritis 26(26%), 13(13%), heat prostration 12(12%), fever without specific diagnosis 8(8%), anemia 7(7%), food poisoning 6(6%), urinary tract infection 4 (4%), leukemia 2(2%), carbon monoxide poisoning 1(1%).

Misdiagnosis can be attributed to several factors, including nonspecific initial symptoms, junior hospital doctors' limited knowledge or experience, particularly in emergency services, high workloads, and variations in disease presentation due to seasonal and regional factors. Diagnostic errors may also result from inadequate attention to the epidemiological or medical history of patients, as well as a flexible adherence to the MoH's diagnostic criteria. CCHF has no specific symptoms, the development of basic algorithms can aid in ensuring accurate diagnosis and appropriate triage of patients.

Misdiagnosis presents a risk of nosocomial transmission of CCHF. The absence of a preliminary diagnosis implies that adequate personal protective equipment was not utilized, and patients were not appropriately isolated. Healthcare workers are at risk of CCHF transmission due to the disease's ability to mimic various infectious and non-infectious inflammatory conditions. This risk is higher in case of unnecessary invasive procedures without proper precautions.

In the literature, a significant number of patients (n=95, 68%) initially received a misdiagnosis of various infections instead of CCHF (Tasdelen Fisgin N et al. 2010). Our study demonstrates a consistent lack of improvement in the initial diagnosis of CCHF over the past decade. The existing literature emphasizes the importance of practical screening in the differential diagnosis on admission (Kayadibi H et al. 2019).

We still need to improve our diagnostic strategies in the endemic region. While fatal cases may temporarily raise awareness, healthcare providers in these areas should sustain a heightened vigilance toward CCHF. Raising awareness can be achieved through continuous education, the incorporation of artificial intelligence tools, the adoption of straightforward diagnostic algorithms, routine in-person or virtual meetings during peak seasons, and leveraging support from written and visual media.

References

1. Al-Abri SS, Abaidani IA, Fazlalipour M, Mostafavi E, et al. Current status of Crimean-Congo haemorrhagic fever in the World Health Organization Eastern Mediterranean Region: issues, challenges, and future directions. Int J Infect Dis. 2017;58:82-89 PubMed .

2. Bente DA, Forrester NL, Watts DM, McAuley AJ, et al. Crimean-Congo haemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res. 2013;100(1):159-89.

3. Clinical Trials, UMIT-1 Trial Favipiravir & Ribavirin for the Treatment of CCHF (UMIT-1) Available at https://classic.clinicaltrials.gov/ct2/show/NCT05940545 (date of access 19 Mar 2024).

4. Fletcher TE, Gulzhan A, Ahmeti S, Al-Abri SS, et al. Infection prevention and control practice for Crimean-Congo haemorrhagic fever - A multi-center cross-sectional survey in Eurasia. PLoS One. 2017;12(9):e0182315.

5. Kayadibi H, Yapar D, Akdogan O, Ulusu NN, et al. Hitit Index to distinguish patients with and without Crimean-Congo hemorrhagic fever. Ticks Tick Borne Dis. 2019;10(5):1035-1040.

6. Leblebicioglu H. Crimean-Congo haemorrhagic fever in Eurasia. Int J Antimicrob Agents. 2010;36:S43-6.

7. Tasdelen Fisgin N, Doganci L, Tanyel E, Tulek N. Initial high rate of misdiagnosis in Crimean Congo haemorrhagic fever patients in an endemic region of Turkiye. Epidemiol Infect. 2010;138(1):139-44.

8. Turkish Ministry of Health - General Directorate of Public Health Agency- Crimean Congo hemorrhagic fever Available at https:// hsgm.saglik.gov.tr/depo/birimler/zoonotik-ve-vektorel-hastaliklar-db/Dokumanlar/Sunumlar/KKKA_Sunum_Hekimlere_Yonelik_2023.pdf (date of access 19 Mar 2024).

9. World Health Organization (WHO) Crimean Congo haemorrhagic fever (CCHF) Available at https://www.who.int/health-topics/crimean-congo-haemorrhagic-fever#tab=tab_1(date of access 17 Jan 2024).

10. World Health Organization (WHO) Prioritizing diseases for research and development in emergency contexts Available at https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts (date of access 12 Jan 2024)

Table 1: National diagnostic criteria and case classification for Crimean-Congo haemorrhagic fever in Turkiye (8)

Epidemiological Criteria (within two weeks before the onset of illness):

1. History of tick contact or tick attachment
2. History of contact with animal blood, tissue and secretions
3. History of living in or traveling to rural areas
4. History of close contact with a definitively diagnosed case

Clinical description (At least two of the following four clinical criteria):

1. The existence of at least two of the following complaints:

Fever (≥38°C), fatigue, headache, widespread body pain, joint pain, and diarrhoea

2. Signs of skin and mucosal bleeding
3. Thrombocytopenia and/or leukopenia unexplained for another reason
4. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation that cannot be explained by any other reason

Laboratory Criteria:

1. Virus isolation
2. Detection of virus-specific IgM antibody positivity
3. A >4 fold increase in virus-specific IgG titre in acute and convalescent period sera
4. Detection of viral nucleic acid

Case Classification

Probable Case: A case that meets the clinical definition and meets at least one of the epidemiological criteria

Definite Case: Probable case confirmed by at least one of the laboratory criteria.

Acknowledgments

We thank the Samsun Public Health Laboratory for performing the CCHF PCR examination.

Author Disclosure Statement

No conflicting financial interests exist.

Funding Information

No funding was received for this article.