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A Comparison of Clinical and Laboratory Features of Crimean-Congo Hemorrhagic Fever in Children and Adults: A Retrospective Single-Center Cohort Study and Literature Review

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Abstract

Background: Crimean-Congo hemorrhagic fever (CCHF) is a major emerging infectious disease threat, and children are reported to have a milder disease course compared with adults, in contrast to other viral hemorrhagic fevers. The aim of this study was to compare adult and pediatric patients with CCHF to improve understanding of pathogenesis and the natural history of the disease.

Materials and Methods: A retrospective analysis of all children and adults admitted with confirmed CCHF between 2011 and 2020. Epidemiological, clinical, and laboratory features were collated on proformas, together with clinical management details. The Severity Grading Score (SGS) system was used to stratify mortality risk. Data from children were compared with adults in the same center and with other published pediatric cohort studies.

Results: A total of 47 children with a median (ranges) age of 14 (2–17) years and 176 adults with a median (ranges) age of 52 (18–83) years with confirmed CCHF were included. The most frequent symptoms in adults were fever, muscle-joint pain, headache, nausea, and vomiting; the most frequent in children were fever, anorexia, nausea, vomiting, and abdominal pain. Adults had lower lymphocyte and platelet counts and higher liver transaminase and creatinine levels than children. SGS values were lower in children, but 97.9% children received ribavirin compared with 8.5% of adults ($p < 0.001$), and they had associated longer median lengths of hospital admission (10 vs. 7 days, $p < 0.001$). Mortality of 1 out of 47 (2.1%) children was similar to 11 other cohorts reported in Türkiye and lower than 13.1% in adults (23/176) in the same center ($p = 0.059$).

Conclusions: Children have lower CCHF-related mortality, less severe disease, and different clinical syndromes at presentation. The majority of published case definitions for screening for CCHF in the main endemic countries do not differentiate between adults and children and omit four of the five most common presenting features in children.

Keywords: Crimean-Congo hemorrhagic fever, children, mortality, comparison, scoring

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an emerging infectious disease threat that is geographically widespread in more than 30 countries in Africa, Asia, and Europe (Fig. 1). It is a zoonotic disease caused by the tick-borne CCHF virus (CCHFV), recognized in 1973 as the causative agent of two separate illnesses, Congo fever (identified in 1956) and Crimean fever (identified in 1944) (Al-Abri et al., 2017; WHO, 2022). CCHF is one of nine diseases prioritized by the World Health Organization for research and development because of its epidemic potential, high case fatality rate, and lack of medical countermeasures (WHO, 2023; WHO, 2022). It can be transmitted by many different types of ticks, especially *Hyalomma marginatum*, which can tolerate a wide range of temperature and humidity conditions and is extending its range in Europe (Al-Abri et al., 2017). In the last 10 years, autochthonous cases of CCHF have been reported for the first time in Spain (Negredo et al., 2021), and in 2022–2023 there was a large increase in cases in Iraq (Alhilfi et al., 2023).

Infection is transmitted to humans by tick bites, by contact with the blood and body fluids of infected animals, or by direct human-to-human transmission (Al-Abri et al., 2017). Nosocomial transmission is a risk for health care workers, and infection of other patients and family members can also occur (Leblebicioglu et al., 2016a). Although the pathogenesis of CCHF remains uncertain, endothelial cell activation develops with intense cytokine release. The bleeding that gives the disease its name is probably closely related to endothelial cell activation and impaired clot development and stabilization (Fletcher et al., 2019).

The incubation period is 1–13 days, and the most common symptoms in adults are fever, chills, headache, fatigue, diarrhea, nausea-vomiting, and muscle-joint pain (Al-Abri et al., 2017). Based on large seroprevalence studies, it has been estimated that up to 90% of people infected are asymptomatic (Bodur et al., 2012). While mortality rates vary between countries, in Türkiye, the mortality rate for CCHF is ~5% (Al-Abri et al., 2017), with an annual incidence of around 1000 confirmed cases, predominantly occurring in the central Anatolian region. All of the CCHF cases are confirmed by both PCR and immunofluorescence assay (IFA) tests.

Children comprise a minority of patients diagnosed with CCHF and have a milder clinical course and a lower overall mortality rate than adults (Tezer et al., 2010). In a large cohort of patients in Türkiye, 3.5% (59/1670) cases were aged 0–9 years and 12.6% (210/1670) were aged 10–19 years (Yilmaz et al., 2009). Several different clinical scoring systems have been described to assess the severity of CCHF in adults on admission to the hospital (Bakır et al., 2015; Özbay, 2023), but none have been validated in children.

Previous research on the pathogenesis of CCHF has compared pediatric cases with healthy pediatric controls, with limited comparisons undertaken between adult and pediatric

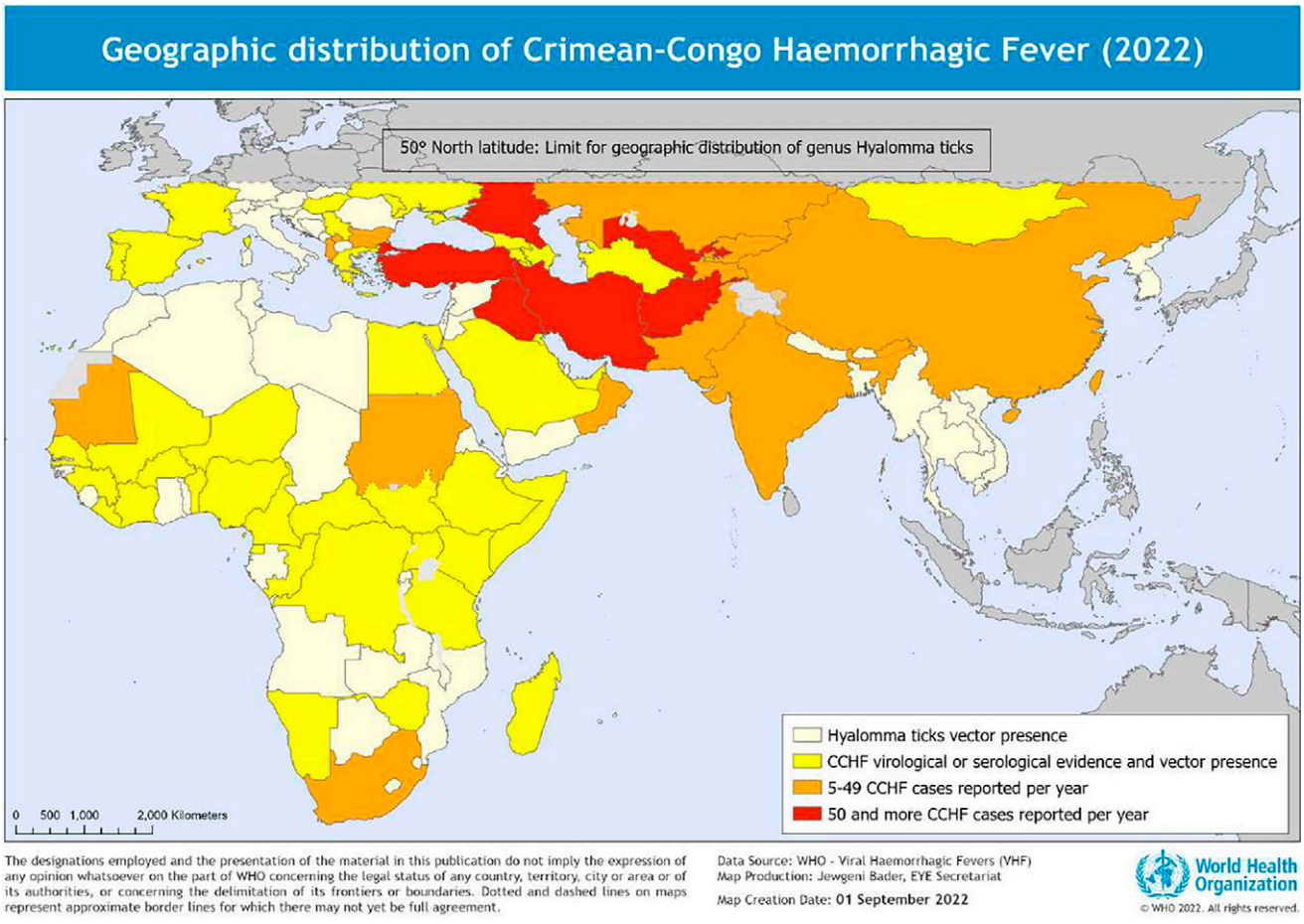

FIG. 1. Geographic distribution of Crimean-Congo hemorrhagic fever.

cohorts. Higher levels of interleukin-10 have been reported in severe pediatric illness compared with mild/moderate illness (Kızılgun et al., 2013). A recent study in Sivas in Türkiye showed no difference in the range of serum cytokine levels between 34 children and 36 adults (Ozsurekci et al., 2013).

The milder disease reported in children with CCHF contrasts with other viral hemorrhagic fevers such as Ebola virus disease (EVD). Pediatric outcomes in EVD are poor, particularly in those aged <5 years, and a recent report from the Democratic Republic of the Congo showed higher Ebola virus viral loads in children than in adults (Nanclares et al., 2016). However, in a recent large cohort study in Nigeria, there was no evidence of lower mortality in children with Lassa fever compared with adults (Duvignaud et al., 2021). Fatal cases of CCHF in children are rare in Türkiye, and there has not previously been a comprehensive comparative study between children and adults.

This study includes a review of clinical and diagnostic features of published data for children with CCHF and describes the clinical and diagnostic features in a treatment cohort of patients of all ages admitted with CCHF to a single tertiary center. Severity at presentation, biomarkers, and clinical outcomes among adults and children are reported, in order to improve understanding of the differences between these groups in this center and in contrast to other settings.

Methods

Study design

This is a retrospective single-center cohort study of adults and children admitted with confirmed CCHF.

Setting

The Ondokuz Mayis University School of Medicine is a large hospital complex in Samsun, the regional capital of Anatolia, which is a region of Türkiye with a high incidence of CCHF. It provides secondary care for the city and is a tertiary referral center for more severe cases from surrounding areas. Patients with CCHF are managed in pediatric or adult infectious disease units, staffed by different specialist teams. Routine hematological and biochemical tests are performed on site, and specialist virological support is provided by the regional Public Health Agency Reference Laboratory in Samsun. Ribavirin is prescribed at the discretion of the attending physicians, based on the oral regimen recommended by the World Health Organization. This is a loading dose of 30 mg/kg, followed by 15 mg/kg four times a day for 4 days, and then 7.5 mg/kg three times a day for 6 days (Tuygun et al., 2012). Close monitoring is required, and the dose and duration of treatment may be adjusted at the discretion of the physician. The standard approach for administering blood products, including fresh frozen plasma and platelet suspensions, is as follows:

For platelet count $<20 \times 10^9$/L 1U of apheresis or 1U/15 kg of random platelets is administered.

For patients with an international normalized ratio (INR) of 1.5 times the upper limit of normal or an activated partial thromboplastin time above the upper limit of normal, FFP is administered at a dose of 10–15 mL/kg/day, divided into two doses.

The widely accepted discharge criteria include the demonstration of significant clinical improvement, as a minimum of 3 consecutive days without fever, accompanied by laboratory evidence of recovery, such as platelet counts exceeding 100×10^9/L or $>50 \times 10^9$/L and trending toward normalization, and normal bleeding profiles (Leblebicioglu et al., 2016b).

Participants

We used the hospital record system to identify all patients admitted to the hospital between July 2011 and September 2020 with possible CCHF. Those with confirmed CCHF according to national case definitions (Table 1) (Turkish Ministry of Health, 2023) were included for comparison between adults and children, defined as individuals aged <18 years. Confirmation of clinical diagnosis was by detection of CCHF RNA by PCR using the RealStar® CCHFV RT-PCR Kit 1.0 (Altona Diagnostics, Germany)/BioSpeedy® CCHFV

Table 1. National Diagnostic Criteria and Case Classification for Crimean-Congo Hemorrhagic Fever in Türkiye (Turkish Ministry of Health, 2023)

Epidemiological criteria (within 2 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 diarrhea
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 titer 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

RT-qPCR Detection Kit (Bioeksen Diagnostics, Istanbul, Türkiye), or anti-CCHF virus IgM (Euroimmun®, Luebeck, Germany) in the Public Health Agency Reference Laboratory in Samsun.

Outcomes

Outcomes of interest were severity of illness at admission, length of hospital stay, blood product use, and inpatient mortality.

Data sources

Epidemiological, clinical, and laboratory data were retrieved from the computerized hospital record systems and entered into dedicated study proformas. The severity of the illness was classified using the Severity Grading Score (SGS) (Bakır M et al., 2015).

Sample size

The size of the study was determined by the number of PCR and/or anti-CCHFV IgM IFA confirmed cases admitted to the site during the study period.

Statistical analysis

Data were stored securely and anonymized prior to tabulation and analysis using IBM SPSS V23. Data were summarized as median (range) or frequency (percentage), as appropriate. The Mann–Whitney *U* test was used to compare nonparametric data and Fisher's exact test for categorical data.

Search criteria for review of published literature of CCHF in children

We searched Medline and PubMed for studies published between May 1, 1976, and July 30, 2024, reporting clinical and epidemiological data on children with CCHF. We used the following keywords: "CCHF," "Crimean-Congo h(a)emorrhagic fever," "Children," and "Paediatrics." We included a case series of more than 20 confirmed cases that included data on clinical presentation and excluded studies where the recruitment period and cases overlapped with another larger case series that was included.

Results

Out of 490 patients admitted with suspected CCHF, 223 cases (176 adult and 47 pediatric) confirmed by CCHF PCR and/or serological testing were included in the analysis. In the adult cohort, 60.8% (107/176) were male with a median (ranges) age of 52 (18–83) years; in the pediatric group, 74.5% (35/47) were male with a median (ranges) age of 14 (2–17) years; 19.1% (9/47) were aged <10 years, including 4.2% (2/47) aged <5 years.

Severity on admission

There were no differences between the groups in the duration of symptoms prior to admission, frequency of tick exposure, or the common clinical features of fever, nausea, vomiting, and diarrhea at presentation (Table 2). Bleeding, a relatively common complication indicating severe CCHF, was seen in 22.2% of adults and 14.9% of children. Fever, muscle-joint pain, headache, nausea, and vomiting were the five most common symptoms in adults; fever, anorexia, nausea, vomiting, and abdominal pain were the five most common symptoms in children (Table 2). Four of the five most common presenting features in children (anorexia, nausea, vomiting, and abdominal pain) were omitted from the national criteria for diagnosis of CCHF in adults. Headache, arthralgia/myalgia, sore throat, and dyspnea were statistically more common in adults, and loss of appetite, abdominal pain, and conjunctival injection were more common in children.

There were several differences in laboratory findings between the adult and pediatric groups (Table 3). Children had higher white blood cell, lymphocyte, and platelet counts than adults and higher prothrombin times and INR, together with lower fibrinogen levels ($p < 0.05$). Only 27.7% (13/47) of children had platelet counts $<50 \times 10^9$/L compared with 49.4% (87/176) of adults ($p = 0.021$) (data not shown). Serum albumin and amylase levels were higher in children, who had lower serum creatinine, creatine kinase, and liver transferase levels than adults.

Almost all children received ribavirin compared with very few adults. Blood products were administered to 55.3% of adults and 39.8% of children. Eighteen out of 47 (38.3%) of the children received a median (ranges) 1.1 (0–10) units of FFP each, compared with 2.1 (0–33) given to 25% (44/176) adults ($p = 0.35$), and 53.2% (25/47) of the children received a median (ranges) 2.4 (0–10) units of platelet suspension, compared with 3.2 (0–45) given to 47.2% (83/176) adults ($p = 0.576$) (data not shown).

Clinical outcomes

Children had a longer hospital stay than adults (10 vs. 7 days, $p \leq 0.001$). Children had lower SGS than adults. Thirty-eight/47 (80.9%) of the children were in the low-risk group compared with 114/176 (64.8%) adults, with 1/47 (2.1%) children and 7/176 (4%) adults in the high-risk group (Table 4). One out of 47 (2.1%) children died compared with 13.1% (23/176) adults ($p = 0.059$) (Table 2).

We identified 13 publications that included 20 or more children admitted to hospital with CCHF (Table 5). Clinical features in our patients are similar to those in most other reports with the exception that abdominal pain appeared to be much more common in our patients (Table 5). The use of ribavirin varied between 18.5% and 98% in Turkey and was 100% in both Iranian studies. The mortality rate was 5% or less in all reports except for the two from Iran, where it was 26.5% in 1999–2006 (Sharifi-Mood et al., 2008) and 12% in 2000–2016 (Aslani et al. 2017).

Discussion

This is the first direct comparison of the clinical and laboratory features in adult and pediatric patients with CCHF. It provides insights into the milder course of disease in children and useful data for surveillance activity and case definitions. A clear description of the differences between adults and children with CCHF in Türkiye also allows data to be compared with other cohorts and with other viral hemorrhagic fevers, which cause higher mortality in children.

A clear understanding of the clinical presentation of CCHF in children and how it differs from adults is vital to ensure that

Table 2. Epidemiological and Clinical Features of CCHF in 47 Children and 176 Adults on Admission to Hospital, Sorted in Order of Their Frequency in Children

Parameter	*Child* n *(%)*	*Adult* n *(%)*	p-*Value*
Male (*n*, %)	39 (69.6)	89 (60.5)	0.299
Age (years)			
Median (min–max)	14 (2–17)	52 (18–83)	**<0.001**
Days between first symptoms and hospital admission			
Median (min–max)	3 (1–10)	2.5 (0–15)	0.073
Comorbidities	2 (4.3)	37 (21)	**0.013**
Living in or visiting a CCHF endemic area	47 (100)	162 (92)	**0.045**
Tick exposure history	31 (66)	112 (63.6)	0.902
Fever	46 (97.9)	159 (90.3)	0.131
Loss of appetite	31 (66)	42 (23.9)	**0.000**
Nausea	31 (66)	93 (52.8)	0.234
Vomiting	30 (63.8)	87 (49.4)	0.198
Abdominal pain	30 (63.8)	42 (23.9)	**0.001**
Headache	14 (29.8)	113 (64.2)	**0.000**
Skin rash	13 (27.7)	31 (17.6)	0.220
Diarrhea	11 (23.4)	56 (31.8)	0.387
Bleeding	7 (14.9)	39 (22.2)	0.373
Joint or muscle pain	6 (13)	138 (87.1)	**0.000**
Lethargy	5 (10.6)	20 (11.4)	0.656
Cough	4 (8.5)	12 (6.8)	0.544
Confused/disoriented	2 (4.3)	12 (6.8)	0.614
Sore throat	0 (0)	9 (5.1)	**0.000**
Breathing difficulty	0 (0)	15 (8.5)	**0.000**
Severe symptoms and complications	2 (4.3)	50 (28.4)	**0.001**
Conjunctival injection	15 (31.9)	6 (4.1)	**0.000**
Petechiae	7 (14.9)	29 (16.5)	0.841
Abdominal tenderness	5 (10.9)	3 (1.7)	**0.007**
Peripheral edema	2 (3.6)	2 (1.4)	0.330
Seizure	1 (2.1)	0 (0)	0.118
Hepatomegaly	1 (2.1)	2 (1.1)	0.764
Splenomegaly	0 (0)	2 (1.1)	0.666
Jaundice	0 (0)	2 (1.1)	0.665
Coinfection	3 (6.4)	18 (10.2)	0.578
Severity Grading Score			
Median (min–max)	1 (0–12)	3 (0–12)	**0.000**
Received blood products	26 (55.3)	70 (39.8)	0.081
Ribavirin use	46 (97.9)	15 (8.5)	**0.000**
Length of hospital stay (days)			
Median (min–max)	10 (3–18)	7 (1–21)	**0.000**
Case fatality rate	1 (2.1)	23 (13.1)	**0.059**

Comorbidities: Diabetes mellitus, hypertension, chronic cardiac disease, chronic renal disease, chronic pulmonary disease, rheumatologic disease, chronic liver disease, and neurological disease.

Severe symptoms and complications: Hepatic, kidney, and respiratory failure, circulatory shock, disseminated intravascular coagulation (DIC), alveolar hemorrhage, and intracerebral hemorrhage.

CCHF, Crimean-Congo hemorrhagic fever.

case definitions are appropriate for children and to underpin optimized delivery of their clinical care. We have highlighted key differences in the clinical presentation of children with CCHF, who make up around 15% of confirmed cases in Türkiye. The most common symptoms continue to be fever in both groups. However, while joint or muscle pain is reported by almost 90% of adults at presentation, this was only reported by 13% of children in our cohort. Loss of appetite is much more common in children (66% vs. 23.9%) as is abdominal pain (63.8% vs. 23.9%). As a result, the five most common symptoms in adults and children are quite different. This has relevance for diagnosis by front-line health care workers in endemic areas or during outbreaks. Health care workers may be at risk of nosocomial infection from unnecessary laparotomies performed on adults and children not recognized to have (Burney et al., 1980; Dilber et al., 2009). Case definitions need to be adjusted to protect patients from inappropriate management and to protect health care staff.

Current case definitions for suspected CCHF in the main endemic countries including Iran, Iraq, Pakistan, Russia, and Türkiye do not differentiate between adults or children or recognize four of the five most common symptoms in children.

At presentation, bleeding rates were similar between the two age-groups, as in previous pediatric reports from Türkiye, where hemorrhagic findings occurred in 23% of cases at presentation

Table 3. Laboratory Findings in 47 Children and 176 Adults on Admission to Hospital with CCHF

Parameter (normal range) Median (min–max)	*Child Median (min–max)*	*Adult Median (min–max)*	p-*Value*
Hemoglobin (11.9–14.6 g/dL)	13.95 (10.5–17.1)	14.15 (7.2–18.3)	0.712
Hematocrit (36.6%–44%)	41.95 (31–50)	41.55 (23.6–51.4)	0.567
White blood cell ($4.49–12.68 \times 10^9$/L)	2.44 (0.7–27.9)	2.0 (0.5–20)	**0.049**
Lymphocyte ($1.26–3.35 \times 10^9$/L)	0.69 (0.17–3.8)	0.5 (0.0–3.1)	**0.020**
Platelet ($173–390 \times 10^9$/L)	92 (10–237)	52 (7–262)	**0.000**
D-dimer (0–700 ng/mL)	9.65 (0.4–71)	17.8 (4.4–2062)	0.277
Activated partial thromboplastin time (25.1–36.5 s)	34.1 (7–102.8)	34.6 (21–190)	0.745
Prothrombin time (9.4–12.5 s)	14.35 (9.8–42)	12 (8.8–120)	**0.000**
International normalized ratio (INR) (0.85–1.15)	1.1 (0.8–2.95)	1 (0.0–2.5)	**0.001**
Fibrinogen (1.8–3.5 g/L)	2.3 (1.23–3.1)	2.9 (1.6–7.74)	**0.014**
Sodium (136–145 mEq/L)	135 (129–144)	137 (125–145)	**0.008**
Potassium (3.5–5.1 mEq/L)	4.07 (3.1–5.36)	3.9 (2.5–9.1)	0.343
Blood urine nitrogen (6–20 mg/dL)	13.2 (4.1–44.5)	13.9 (3.2–89.3)	0.281
Creatinine (0.5–0.9 mg/dL)	0.65 (0.38–1.4)	0.8 (0.4–5.8)	**0.001**
Glucose (74–106 mg/dL)	103 (76.6–137)	109.5 (11.9–321)	0.380
Bicarbonate (22–26 mmol/L)	21.4 (20.9–24.3)	—	—
Lactate (0.4–1.4 mmol/L)	5.2 (0.9–15)	1.1 (1.1–1.1)	0.677
Amylase (28–100 U/L)	108.5 (34.4–162)	61.25 (16–520)	**0.002**
Total bilirubin (0–1.2 mg/dL)	0.45 (0.02–2.41)	0.4 (0.1–6)	0.979
Direct bilirubin (0–0.2 mg/dL)	0.2 (0.01–0.95)	0.1 (0–4.8)	0.243
AST (0–32 U/L)	89 (17–4886)	160.95 (21.9–7516)	**0.003**
ALT (0–32 U/L)	46 (9–1559)	74.8 (8.6–1583)	**0.036**
Creatine kinase (26–192 U/L)	225 (31–2838)	378.1 (10.4–11464)	**0.031**
Albumin (3.5–5.2 g/dL)	3.9 (3.1–5.04)	3.6 (1.55–4.7)	**0.004**
C-reactive protein (0–5 mg/L)	8.65 (1–151)	11 (0–227)	0.717

(Yilmaz et al., 2009). However, hemorrhagic symptoms were reported in 76% of 50 children with confirmed CCHF in another center in Türkiye, with tonsillopharyngitis in 50% (Tuygun et al., 2012). This tertiary referral center in Ankara may manage more severe cohorts but still had a low case fatality of only 2%. SGS is a useful method for the assessment and risk stratification of patients with CCHF on admission (Fletcher et al., 2019). It is a practical way to facilitate triage and management of large cohorts in endemic areas and a useful tool for less experienced clinicians managing imported cases. In the present study, adults had higher SGS and worse clinical outcomes (Table 4).

The differences in outcomes that we describe are not related to later presentation in adults as both groups were admitted to the hospital a median of 2–3 days after the onset of symptoms. CCHF exposure risk factors may be associated with differences in viral inoculum, for example, preceding tick bite compared with blood splashes, but were also similar in the two groups. As would be expected, there were more comorbidities in the adult cohort that had a median age of 52 years.

Table 4. Fatality Rates in 47 Children and 176 Adults with CCHF, Stratified by Severity Grading Scores (Bakir et al., 2015)

	Case fatality rate	
SGS classification	*Child* n *(%)*	*Adult* n *(%)*
Low-risk	0/38 (0%)	3/114 (2.6%)
Intermediate-risk	0/8 (0%)	14/55 (25.5%)
High-risk	1/1 (100%)	6/7 (85.7%)

SGS, Severity Grading Score.

In this study, we show that children had a longer length of hospital stay than adults (10 vs. 7 days $p < 0.001$). The reasons for this may be multifactorial, including a more cautious approach for children referred from remote rural areas and associated challenges in follow-up after discharge. This is combined with a lack of guidance for pediatricians similar to that published about the timing of the discharge from hospital of adult patients. This may reduce concerns about keeping patients in the hospital until all laboratory tests have returned to normal (Tuygun et al., 2012). The other factor contributing to the longer length of stay is the almost universal use of ribavirin in children (97.9%) compared to 8.5% of adults in our center. The use of ribavirin in the treatment of CCHF remains controversial with no robust large-scale clinical trials demonstrating efficacy and the risk of bias in observational studies demonstrated in a Cochrane review (Johnson et al., 2018). Most accept that its potential benefit would be in early-stage disease and in postexposure prophylaxis (Leblebicioglu et al., 2016). In our center, antiviral use was completely shaped by the department's own preference and the clinician's decision. As the recommended treatment course of ribavirin is generally 7–10 days, combined with a lack of routine viral PCR monitoring, treatment may prolong the length of stay. The side effects generated by ribavirin may also contribute to this, the most important of which is dose-dependent hemolytic anemia, which may also have played a role in the relatively high rates of blood product use in children.

The mortality that we report for children is in line with other studies in Türkiye (Karaaslan and Çetin, 2021; Tuygun et al., 2012) (Table 5). While CCHF in children is widely considered to have a lower mortality, differences are reported in other endemic countries. Sharifi-Mood et al. (2008) described the presentation and outcome of 34 children (mean age 13.3 ± 4.6 years) with CCHF in Iran with a case fatality rate of 26.5%, much higher than in our cohort or others in Türkiye (Table 5). Time to presentation was similar at 3 days, but the epidemiological risk factors were different with a history of tick bite in only 8 out of 34 (23.5%, compared with 66% in our cohort), whereas the most common risk factor in Iran for children was direct contact with animal blood or carcasses in 14 out of 34 (41.2%). In the report by Sharifi-Mood et al. (2008), bleeding at baseline was reported by 70%, with a mean platelet count of 70×10^9/L. Other atypical features included jaundice in eight out of nine fatal cases at admission, with a mean (standard deviation) prothrombin time of only 16 (1.3) s and elevated alanine aminotransferase in only six out of nine cases. In both cohorts, ribavirin was administered to almost all children, but a subanalysis of the Iran cohort demonstrated an association between delay to treatment and mortality. In a more recent study in Iran, the case fatality rate in 161 older children was 11.8% over a 16-year period (Aslani et al. 2017). The reasons for higher mortality in children in Iran compared with Türkiye are uncertain. Other factors involved in different case fatality rates between countries might include genomic differences between circulating strains (Al-Abri et al., 2017), provision and access to supportive care, diagnostic capacity, and active surveillance and community engagement mechanisms that may identify more mild cases.

The study that we report has several limitations including its retrospective design, and it is from a single center in one endemic country. However, the single-center and within-country comparison does help to control for differences between health care settings/facilities that can affect a huge number of factors including the provision of care while also ensuring that the differences in viral/host genetic factors are minimized. Due to technical data storage challenges, baseline CCHFV viral load data were not available from the reference laboratory. This is known to be an important prognostic indicator for disease severity and outcome in adults with CCHF and patients with other viral hemorrhagic fevers. A large prospective study is planned to investigate differences in severity of disease in adults and children and to validate illness severity scoring systems in a pediatric cohort, including the potential value of including measurements of viral load.

Further studies should include prospective multicenter, multicountry evaluations of adequately sized pediatric and adult cohorts, using standardized proformas such as those developed by the International Severe Acute Respiratory and Emerging Infection Consortium (Fletcher et al., 2019). It is important that these also include dynamic changes in observations on children in hospital with CCHF, as opposed to just baseline admission data, to improve understanding of the natural history of disease. If these studies also incorporate pragmatic biological sampling of children, with appropriate approvals and informed consent, they could provide an important insight into host and viral factors that result in differences in mortality. While the mortality in children in Türkiye is low, it does exist and is higher in other countries. As articulated in the World Health Organization's R&D Blueprint, this emphasizes the need for improved diagnostics and therapeutics for CCHF and the importance of including vulnerable groups such as children in clinical trials and evaluations.

Our study is the first direct comparison of the clinical and laboratory features in adults and children with CCHF. It provides important insights into the differences in severity of the disease and outcome in these two groups. We have also summarized the published cohort data for CCHF in children, and these suggest that our findings are similar to the experience of others in Türkiye, although we highlight a high incidence of loss of appetite and abdominal pain in our cohort that should be reassessed elsewhere. For CCHF surveillance and suspected case definitions, we demonstrate remarkable differences in the clinical presentation of children while also showing similarities in important components of case management such as use of blood products. More in-depth multicountry observational studies in children and adults are required, which include investigation of host and viral factors that may explain these differences and improve understanding of disease course and pathogenesis.

Table 5. Publications Including More Than 20 Cases of Children with CCHF Admitted to Hospital

First author, year, reference	*Bozkurt et al. (current report)*	*Özbay 2023*	*Karaaslan and Çetin 2021*	*Aslani et al. 2017*	*Gayretli Aydin et al. 2015*	*Belet et al. 2014*	*Sancakdar et al. 2014*
Country	Türkiye	Türkiye	Türkiye	Iran	Türkiye	Türkiye	Türkiye
Region	Samsun	Tokat	Tokat	Southern east Iran	Ankara	Samsun	Sivas
Years	2011–2020	2011–2022	2012–2020	2000–2016	2005–2013	2008–2011	2012–2013
Number	46	81	67	161	26	54	41
Male (*n*, %)	39 (85)	71 (87.7)	54 (80.6)	114 (71)	18 (69.2)	34 (63)	30 (73)
Age median (min–max) years	14 (2–17)	15 (IQR 11.5–17)	15.5 (8–18)	Mean 15.5 (±3.6)	Mean 10.5 ± 4 (2.5–16.7)	Mean 12.8 (±3.3) (6–17.3)	12.8 (4–17)
Days between first symptoms and hospital admission Median (min–max)	3 (1–10)	3 (IQR 2–4)	4.7 (2–9)	NR	NR	Mean 3.6 (+/- 2.4) (1–15)	NR
Tick exposure history (*n*, %)	31 (66)	52 (64.2)	NR	8 (5)	19 (73.0)	49 (90.7)	35 (88)
Fever (*n*, %)	46 (98)	75 (92.6)	63 (94)	160 (99)	NR	53 (98)	38 (93)
Loss of appetite (*n*, %)	31 (66)	NR	NR	NR	NR	NR	NR
Nausea (*n*, %)	31 (66)	41 (50.6)	NR	17 (11)	NR	21 (39)	17 (42)
Vomiting (*n*, %)	30 (64)	41 (50.6)	30 (44.8)	16 (10)	NR	32 (59)	16 (39)
Abdominal pain (*n*, %)	30 (64)	21 (25.9)	25 (37.3)	NR	NR	12 (22)	NR
Headache (*n*, %)	14 (30)	55 (67.9)	30 (44.8)	6 (4)	NR	21 (39)	NR
Skin rash (*n*, %)	13 (28)	NR	38 (56.7)	NR	NR	11 (20)	5 (12.2)
Diarrhea (*n*, %)	11 (23)	13 (16)	21 (31.8)	5 (3)	NR	12 (22)	NR
Bleeding (*n*, %)	7 (15)	3 (3.7)	Mucosal bleeding 29 (43.3) petechiae 27 (40.3)	36 (22)	NR	12 (22)	3 (7)
Joint/muscle pain (*n*, %)	6 (13)	43 (53.1)	48 (71.6)	38 (24)	NR	NR	NR
Lethargy (*n*, %)	5 (11)	70 (86.4)	60 (89.6)	NR	NR	26 (48.1)	NR
Sore throat (*n*, %)	0 (0)	NR	NR	NR	NR	NR	19 (46)
Conjunctival injection/facial hyperemia (*n*, %)	15 (32)	NR	NR	NR	NR	NR	10 (24.4)
Received blood products (*n*, %)	26 (55)	11 (13.6) plts Eleven (13.6) FFP	NR	NR	20 (76.9)	20 (37)	NR
Ribavirin use (*n*, %)	46 (98)	15 (18.5)	33 (49.2)	161 (100)	18 (69.2)	39 (72)	NR
Length of stay Median (min–max) days	10 (3–18)	7 (IQR 5–8.5)	Mean 7.1 (3–13)	NR	Mean 10 (5–15)	11 (3–23)	NR
Fatal cases and case fatality rate (*n*, %)	1 (2)	1 (1.2)	0	19 (12)	0	1 (1.9)	0

TABLE 5. (*CONTINUED*)

First author, year, reference	*Oflaz et al. 2014*	*Deveci et al. 2013*	*Tuygun et al. 2012*	*Gul et al. 2011*	*Tezer et al. 2010*	*Dilber et al. 2009*	*Sharifi-Mood et al. (2008)*
Country	Türkiye	Türkiye	Türkiye	Türkiye	Türkiye	Türkiye	Iran
Region	Sivas	Sivas	Ankara	Sivas	Ankara	Karadeniz	Systan-Baluchestan
Years	NR	2010–2011	2005–2010	NR	2008–2009	2008	1999 – 2006
Number	121	44	50	23	31	21	34
Male (*n*, %)	84 (69)	30 (68)	31 (62)	17 (74)	19 (61)	15 (71.4)	23 (67.6)
Age median (min–max) years	Mean 11.4 (±3.9)	14 (4–17)	Mean9 (±4)	Mean 12 (±2)	Mean 9.4 (±4.8) (1–16)	Mean 10.3 (±3.9)	Mean 13.3 (5–18)
Days between first symptoms and hospital admission Median (min–max)	6	NR	Mean 3.5 (SD 2.1)	5 (3–7)	2 (1–6)	2 (9.5)	3 (2–6)
Tick exposure history (*n*, %)	NR	NR	41 (82)	14 (60)	27 (87.0)	15 (71)	8 (23.5)
Fever (*n*, %)	112 (93)	NR	50 (100)	18 (78)	31 (100)	17 (81)	30 (88.2)
Loss of appetite (*n*, %)	NR	NR	NR	NR	NR	5 (24)	NR
Nausea (*n*, %)	55 (46)	18 (41)	30 (60)	NR	21 (67.7)	11 (52)	21 (61.8)
Vomiting (*n*, %)	55 (46)	18 (41)	30 (60	NR	21 (67.7)	11 (52)	NR
Abdominal pain (*n*, %)	NR	10 (23)	13 (26)	NR	NR	6 (29)	NR
Headache (*n*, %)	60 (49)	12 (27.2)	15 (30)	8 (35)	14 (45.1)	7 (33)	22 (64.7)
Skin rash (*n*, %)	NR	NR	12 (24)	3 (13)	5 (16.1)	5 (23.8)	NR
Diarrhea (*n*, %)	20 (17)	10 (23)	10 (20)	8 (35)	12 (38.7)	4 (19)	12 (35.3)
Bleeding (*n*, %)	20 (17)	4 (9)	38 (76)	3 (13)	6 (19.3)	3 (14)	24 (70.6)
Joint/muscle pain (*n*, %)	87 (72)	NR	23 (46)	20 (87)	11 (35.5)	5 (24)	24 (70.6)
Lethargy (*n*, %)	NR	NR	25 (50)	NR	29 (93.5)	10 (48)	NR
Sore throat (*n*, %)	85 (70)	22 (50)	25 (50)	14 (60)	23 (74.1)	NR	NR
Conjunctival injection/facial hyperemia (*n*, %)	NR	10 (22.7)	14 (28)	5 (22)	NR	6 (28.5)	NR
Received blood products (*n*, %)	NR	NR	NR	NR	NR	13 plts (61.9) 5 FFP (23.8) 6 RBC (28.6)	NR
Ribavirin use (*n*, %)	115 (95)	NR	23 (46)	21 (91)	17 (54.8)	0	34 (100)
Length of stay Median (min–max) days	9 (7–10)	NR	NR	8 (7–10)	10 (3–19)	9 (3–22)	8 (5–14)
Fatal cases and case fatality rate (*n*, %)	0	0	1 (2)	0	0	1 (5)	9 (26.5)

FFP, fresh frozen plasma transfusion; IQR, interquartile range; NR, not reported; plts, platelets (platelet transfusion); RBC, red blood cells (red blood cell transfusion).

Authors' Contributions

I.B.: Conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft, reviewing, and editing. E.H.E.: Resources, investigation, and methodology. M.J.R.: Resources, investigation, and methodology. L.Ş.: Resources, investigation, and methodology. N.J.B.: Writing, supervision, reviewing, and editing. S.A.: Resources and methodology. H.L.: Supervision, reviewing, and editing. G.K.: Supervision, reviewing, and editing. T.E.F.: Funding acquisition, writing, supervision, reviewing, and editing.

Ethical Approval

Ethical approval for the study was provided by Ondokus Mayis Research Ethics Committee (OMU KAEK 2023/186), which confirmed that informed consent from participants was not required for this retrospective analysis of routinely collected clinical data.

Author Disclosure Statement

No conflicting financial interests exist.

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