Clinical Microbiology and Infection 31 (2025) 2056–2062

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.org

Original article

Key predictors of mortality in Crimean-Congo haemorrhagic fever: a retrospective multicentre cohort study

Deniz Güllü [1, 2, 3, *], Defne Yigci [1, *], Nurcan Baykam [4], Aysel Kocagül Çelikbaş [4], Derya Yapar [4], Özlem Akdoğan [4], Kemalettin Özden [5], Rukiye İnan Sarıkaya [6], İmran Hasanoğlu [7], Rahmet Güner [7], Ebru Doğan [8], Faruk Karakeçili [9], Handan Alay [5], Zeynep Türe Yüce [10], Esma Eryılmaz Eren [11], Ayşe Erbay [12], Şebnem Eren Gök [12], Çiğdem Kader [12], Gamze Ünüvar Kalın [10], Azize Yetişgen [13], Müge Özgüler [14], Arzu Şenol [14], Ömür Gündağ [14], Merve Çağlar Özer [15], Firuze Soyak [16], Büşra Tanır [14], Işıl Deniz Alıravcı [17], Güle Çınar [18], Barçın Öztürk [19], Esra Gürbüz [20], Bahadır Orkun Özbay [21], Fatihan Pınarlık [2, 3], Mert Kuşkucu [3, 22], Önder Ergönül [3, 23, *]

[1] School of Medicine, Koç University, Istanbul, Türkiye
[2] Graduate School of Health Sciences, Koç University, Istanbul, Türkiye
[3] Koç University İşbank Center for Infectious Diseases (KUISCID), Koç University, Istanbul, Türkiye
[4] Department of Infectious Diseases and Clinical Microbiology, Hitit University School of Medicine, Corum, Türkiye
[5] Department of Infectious Diseases and Clinical Microbiology, Atatürk University Faculty of Medicine, Erzurum, Türkiye
[6] Department of Infectious Diseases and Clinical Microbiology, Balıkesir University, School of Medicine, Balıkesir, Türkiye
[7] Department of Infectious Diseases and Clinical Microbiology, Ankara Bilkent City Hospital, Ankara, Türkiye
[8] Department of Infectious Diseases and Clinical Microbiology, Balıkesir Royal Hospital, Balıkesir, Türkiye
[9] Department of Infectious Diseases and Clinical Microbiology, Erzincan Binali Yıldırım University, School of Medicine, Erzincan, Türkiye
[10] Department of Infectious Diseases and Clinical Microbiology, Erciyes University, School of Medicine, Kayseri, Türkiye
[11] Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital, Kayseri, Türkiye
[12] Department of Infectious Diseases and Clinical Microbiology, Bozok University, School of Medicine, Yozgat, Türkiye
[13] Department of Infectious Diseases and Clinical Microbiology, Malatya Training and Research Hospital, Malatya, Türkiye
[14] Department of Infectious Diseases and Clinical Microbiology, Elazığ Fethi Sekin City Hospital, Elazig, Türkiye
[15] Department of Infectious Diseases and Clinical Microbiology, Karabük Training and Research Hospital, Türkiye
[16] Department of Infectious Diseases and Clinical Microbiology, Kastamonu Training and Research Hospital, Kastamonu, Türkiye
[17] Department of Infectious Diseases and Clinical Microbiology, Onsekiz Mart University, School of Medicine, Canakkale, Türkiye
[18] Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Ankara University, Ankara, Türkiye
[19] Department of Infectious Diseases and Clinical Microbiology, Adnan Menderes University, School of Medicine, Aydin, Türkiye
[20] Department of Infectious Diseases and Clinical Microbiology, Van Training and Research Hospital, Van, Türkiye
[21] Department of Infectious Diseases and Clinical Microbiology, Tokat State Hospital, Tokat, Türkiye
[22] Department of Medical Microbiology, Koç University, School of Medicine, Istanbul, Türkiye
[23] Department of Infectious Diseases and Clinical Microbiology, Koç University, School of Medicine, Istanbul, Türkiye

ARTICLE INFO

Article history:
Received 26 June 2025
Received in revised form
7 August 2025
Accepted 11 August 2025
Available online 21 August 2025

Editor: M. Paul

Keywords:
Crimean-Congo haemorrhagic fever (CCHF)

ABSTRACT

Objective: This study aimed to identify key predictors of mortality in patients with Crimean-Congo haemorrhagic fever (CCHF). Our specific goals included characterizing the demographic and clinical features of hospitalized CCHF patients in Türkiye, determining the factors associated with mortality among these patients, and evaluating the impact of early ribavirin administration.
Methods: A retrospective study was conducted on 1103 CCHF patients across 18 hospitals in Türkiye from 1 January 2019 to 20 November 2024. All data were obtained via an online data collection system by the designated physician at each centre. Patients with laboratory-confirmed CCHF infection who were hospitalized were included in the study. Univariate analyses and time-dependent Cox regression were conducted.

* Corresponding author: Önder Ergönül, İşbank Center for Infectious Diseases, Koç University, Topkapı, Koç Üniversitesi Hastanesi, Davutpaşa Cd. Number 4, 34010 Zeytinburnu, İstanbul, Türkiye.
E-mail address: oergonul@ku.edu.tr (Ö. Ergönül).
* These authors contributed equally to this work.

https://doi.org/10.1016/j.cmi.2025.08.009

Disease severity
Mortality
Ribavirin
Risk factors

Results: Of the 1103 patients, 65.7% (725/1102) were men; 87.2% (962/1103) resided in rural areas; and the mean age was 53 years. Ticks were identified as the transmission route in 68.4% (755/1103) of the cases. Comorbidities included diabetes mellitus, chronic heart disease, and hypertension; 4.6% (51/1103) of the patients developed healthcare-related infections. Intensive care unit admission was required in 8.0% (88/1103) of the patients, and the overall mortality rate was 5.1% (56/1103). In univariate analyses, age ≥50 years (odds ratio [OR], 3.1; 95% CI, 1.58–6.08; $p < 0.001$) and diabetes mellitus (OR, 4.49; 95% CI, 2.20–9.18; $p < 0.001$) were associated with increased mortality. Both variables remained statistically significant predictors in the multivariate analysis. Although early ribavirin administration, ≤96 hours from symptom onset, did not reach statistical significance in univariate analysis (OR, 0.52; 95% CI, 0.26–1.05; $p = 0.065$), it was significantly associated with reduced mortality in time-dependent Cox regression (adjusted hazard ratios, 0.21; 95% CI, 0.07–0.69; $p = 0.010$).
Discussion: Key factors such as age and comorbidities can predict mortality in CCHF patients. Timely identification of these predictors, along with early administration of ribavirin, may contribute to improved survival and better clinical outcomes. **Deniz Güllü, Clin Microbiol Infect 2025;31:2056**

Introduction

The World Health Organization estimates that climate-related factors, including vector-borne diseases, will contribute to an additional 250 000 deaths annually in the next decades [1,2]. With climate change driving significant shifts in global vector populations, vector-borne disease outbreaks have been observed in regions previously considered low-risk [3]. One example is Crimean-Congo haemorrhagic fever (CCHF), which has the widest geographic range among clinically significant tick-borne viral infections [4]. Historically, CCHF has been observed in southern and Eastern Europe, North Africa, the Middle East, and West Asia [5]. Recently, CCHF has expanded beyond these higher-risk regions, and cases have been observed in Spain [6] since 2016 and in Portugal [7] since 2024. This broad distribution highlights the growing relevance of CCHF, as rising global temperatures and shifting ecosystems expand the habitat of its vector, the *Hyalomma* tick. Emphasizing the rising global significance of CCHF, *Hyalomma* ticks have also been recorded in Southern France [8], Greece [9], and Sweden [10].

CCHF is caused by the CCHF virus, part of the *Nairovirus* genus in the *Bunyaviridae* family, and is often transmitted by ticks or exposure to bodily fluids of infected individuals or animals [11]. The CCHF often progresses rapidly and severely, typically beginning with nonspecific symptoms such as fever and myalgia, followed by haemorrhagic manifestations [4]. Despite improvements, the mortality rate remains at 10% to 50% [12,13]. Although some studies have suggested the role of ribavirin administration in improving outcomes, current clinical management relies heavily on supportive care with no approved use of antiviral medications. In addition, although several severity scoring systems have been proposed [14–16], findings have been limited by sample size, unicentric study design, and a lack of external validation. Reliable identification of high-risk patients and timely initiation of appropriate treatment, therefore, remains difficult. As CCHF continues to emerge in new regions and clinical severity varies widely, there is a pressing need to identify patients most at risk of developing severe disease.

This study represents one of the largest efforts to date, analysing data from 1103 laboratory-confirmed CCHF patients across 18 centres in Türkiye to identify prognostic indicators for mortality.

Methods

Study design and setting

This retrospective multicentre cohort study aimed to identify factors associated with in-hospital mortality among patients diagnosed with CCHF. Data were collected from 18 hospitals located in endemic regions of Türkiye between January 2019 and November 2024 using a centralized online system completed by designated physicians.

Participants

Eligible patients were those hospitalized with clinical suspicion of CCHF and laboratory-confirmed infection, defined as positive RT-PCR for CCHF virus, performed by the national reference laboratory. All patients who met these criteria during the study period were included.

Variables and outcome

The primary outcome was in-hospital mortality. The primary exposure of interest was the timing of ribavirin initiation. Epidemiological data were obtained through patient or caregiver recall at the time of admission, whereas clinical data were extracted from hospital records by the treating physicians. Data entry was manually verified by hospital physicians and cross-checked centrally for consistency. A complete list of variables, their definitions, collection methods, and measurement units is provided in File S1.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were reported as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQR). Univariate analyses were conducted to identify variables associated with in-hospital mortality, using chi-square or Fisher's exact test for categorical variables, and the Mann–Whitney *U*-test for continuous variables. The association between ribavirin timing and mortality was also assessed across predefined thresholds (e.g. 96 hours from symptom onset) by

categorizing patients into early versus no/late treatment groups. Odds ratio (OR) and 95% CIs were reported.

To address immortal time bias and model treatment timing appropriately, a time-dependent Cox proportional hazards regression analysis was performed using the data set truncated at 30 days of follow-up. Ribavirin was included as a time-varying covariate, with patients contributing unexposed time from symptom onset until ribavirin initiation, and exposed time thereafter. Those who received ribavirin within 96 hours of symptom onset were categorized as early treated, whereas patients receiving it later or not at all comprised the comparison group. Patients who initiated treatment on the day of death were considered exposed, with a minimal survival interval assigned. Variables for the multivariable model were selected a priori based on clinical relevance, not solely on statistical significance. This included age ≥50 years, sex, farmer, and comorbidities including diabetes mellitus (DM), chronic heart disease, and hypertension. The model did not use automatic variable selection procedures. Only patients with complete data for all variables included in the model were analysed. Proportional hazards assumptions were evaluated using Schoenfeld residuals via the Grambsch-Therneau test, whereas ties were handled using the Breslow method. Adjusted hazard ratios (aHRs) with 95% CIs were reported. Statistical significance was defined as a 2-tailed p value < 0.05. Analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp) and Stata 17.0 (StataCorp).

Ethical considerations

The study was approved by the Koç University School of Medicine Ethics Board (IRB: 2023.381.IRB1.134). The requirement for informed consent was waived due to the retrospective study design.

Results

Characteristics of the study population

A total of 1103 hospitalized patients with laboratory-confirmed CCHF were included from 18 hospitals across Türkiye between 2019 and 2024 (Fig. 1A, B). The median age was 53 years (IQR, 41–63.5), and 65.7% (725/1102) were men. Most patients (962/1103, 87.2%) were residents of rural areas, and 76% (838/1103) reported farming or animal husbandry as their occupation.

Transmission and incubation

Most patients (755/1103, 68.4%) reported a recent tick bite as the suspected route of transmission, followed by 15.4% (170/1103) with direct contact with animals. Although no cases of sexual transmission were identified, 8 patients reported exposure through contact with blood or body fluids, and 2 healthcare workers acquired the infection via needlestick injury while managing CCHF patients. Among those with a reported tick bite, the median incubation period was 2 days (IQR, 1–4).

Clinical features and symptom onset

The median time from symptom onset to hospitalization was 3 days. The most common prodromal symptoms were fever (849/1103, 77%), myalgia (793/1103, 71.9%), and fatigue (950/1103, 86.1%). Haemorrhagic manifestations occurred in 15.6% (172/1103) of patients, most frequently presenting as epistaxis followed by gingival bleeding and ecchymosis.

Comorbidities and coinfections

The most frequently reported comorbidity was hypertension, observed in 8% (88/1103) of patients, followed by DM in 5.9% (65/1103) and chronic heart disease in 4.6% (51/1103). Other comorbid conditions were rare, each occurring in fewer than 10 patients. Coinfections were documented in 29 patients, whereas Healthcare related infections (HRIs) developed in 4.6% (51/1103) during hospitalization.

Treatment

Ribavirin was administered to 36.4% (401/1103) of patients, with a median initiation time of 3 days after symptom onset. Blood products and adjunctive therapies such as fresh frozen plasma, platelet transfusion, or plasmapheresis were used in 17.1% (189/1103) of patients.

Outcomes

Among the total cohort, 8.0% (88/1103) were admitted to the intensive care unit (ICU), and 5.1% (56/1103) died during hospitalization (Fig. 1B). The median hospital stay was 7 days (IQR, 5–9), and the median ICU stay among those admitted was 3 days (IQR, 2–6).

Laboratory values

Compared with survivors, patients who died had significantly lower haemoglobin levels, white blood cells, and platelet counts, as well as prolonged activated partial thromboplastin time. Markers of organ damage and inflammation, such as alanine

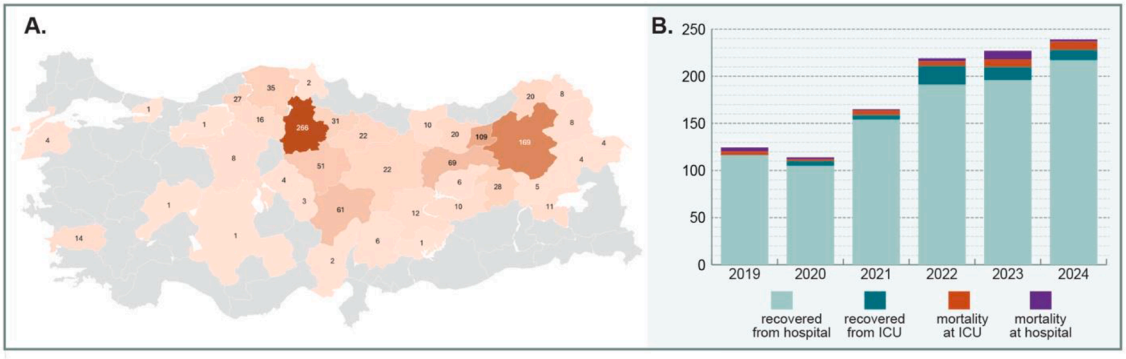

Fig. 1. (A) Heatmap of the geographical distribution of cases across 18 centres in Türkiye. (B) Distribution of cases across 18 centres in Türkiye between years 2019 and 2024 illustrating cases recovered from hospital (without ICU admission), recovered from ICU, mortality at ICU, and mortality at hospital (without ICU admission). ICU, intensive care unit.

aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and creatine kinase, were all significantly elevated among nonsurvivors. Additionally, serum creatinine and blood urea nitrogen levels were higher in patients who died. The full comparison of laboratory findings between survivors and nonsurvivors is presented in Table 1.

Risk factors for mortality

In univariate analysis, patients aged ≥50 years had significantly higher odds of mortality compared with younger individuals (OR, 3.1; 95% CI, 1.58–6.08; p < 0.001). Those working in agriculture were less likely to experience fatal outcomes than individuals in other occupations (OR, 0.55; 95% CI, 0.31–0.97; p = 0.036). Although early initiation of ribavirin at all tested thresholds was associated with reduced odds of death, none of the time cutoffs reached statistical significance; initiation within 72 and 96 hours demonstrated the strongest protective trends (p = 0.060 and p = 0.065, respectively). Additional results on clinical manifestations, comorbid conditions, and therapeutic interventions are summarized in Table 2.

In the multivariable Cox regression model, a total of 1044 patients were included, with 50 mortality events. After adjustment for covariates, ribavirin administration within ≤96 hours from symptom onset was independently associated with a significantly lower risk of in-hospital mortality (aHR, 0.21; 95% CI, 0.07–0.69; p = 0.010). Increased age (aHR, 2.56; 95% CI, 1.24–5.30; p = 0.011) and DM (aHR, 2.71; 95% CI, 1.28–5.74; p = 0.009) were also significantly associated with higher mortality (Table 3). No violation of the global proportional hazards assumption was detected. The unadjusted Kaplan–Meier survival curves comparing early ribavirin administration versus no or late treatment are presented in Fig. 2.

Discussion

In this large multicentre study of 1103 hospitalized patients with laboratory-confirmed CCHF in Türkiye, we analysed key demographic and clinical characteristics, disease outcomes, and treatment patterns to identify factors associated with mortality. Our results contribute to the growing body of evidence on CCHF severity predictors, particularly in endemic regions, and offer insights into the timing of antiviral treatment.

In the same period, from 2019 to 2024, a total of 6570 laboratory-confirmed patients were reported from the Ministry of Health of Türkiye [17]. Our study included detailed clinical, laboratory, and outcome features of 17% of the cases, and the geographical distributions of the cases were parallel, as presented in Fig. 1A.

The median age of patients was 53 years, with a male predominance (725/1102, 66%), and most residing in rural areas (962/1103, 87%). In Türkiye, CCHF predominantly affects middle-aged males in rural settings due to occupational exposure to ticks and livestock. Comparatively, data from Iraq show a younger mean age of 36 years, with 58.9% males and 45.2% residing in rural areas [18]. Demographic variations may indicate different patterns of urbanization and occupational exposure, underscoring the importance of regional epidemiological factors in CCHF transmission and risk profiles.

Mortality and ICU admission rates in CCHF patients vary widely across countries and studies. The World Health Organization estimates case fatality rates between 10% and 40%, reflecting differences in surveillance quality, diagnostic capacity, healthcare infrastructure, and case reporting patterns across affected regions [19]. In our study, the mortality rate was 5.1% (56/1103), which is compatible with the Ministry of Health report [17], and the ICU admission rate was 8% (88/1103). The fluctuation may stem from study design, better access to care, earlier recognition at high-volume centres, and greater resource availability. Notably, 21 patients in our cohort died without ICU admission (Fig. 1B), likely due to late presentation and critical illness at the time of hospital arrival.

In our cohort, older age was independently associated with higher mortality (p = 0.008), aligning with previous studies that identified age as a strong predictor of poor outcomes [20]. The protective trend observed among farmers may reflect increasing awareness and early presentation in this high-risk population. DM was found to be a risk factor for mortality in univariate analysis (p < 0.001, Table 2), contradicting some studies in the literature that have found no association between DM and CCHF severity [21]. The association between DM and mortality also remained significant after adjustment (p = 0.009, Table 3). This could be

Table 1
Comparison of laboratory findings between patients who died and those who survived

Variables	Survived (n = 1047)	Died (n = 56)	Test statistic (Z)	p value
Haemoglobin level (g/dL)	14.2 (13–15.3; n = 1045)	13.5 (12.5–15; n = 54)	−1.86	0.062
White blood cell count (× 10^3/uL)	2.6 (1.84–3.74; n = 1047)	3.3 (1.78–5.75) (n = 54)	−2.11	**0.035**
Lymphocyte (× 10^3/uL)	0.57 (0.39–0.89; n = 969)	0.68 (0.38–1.26) (n = 50)	−1.35	0.176
Platelet count (× 10^3/μL)	89 (46–127; n = 1046)	39 (21–121; n = 54)	−3.7	**<0.001**
aPTT (s)	32 (28–37; n = 1013)	38 (29–54; n = 52)	−3.2	**0.001**
INR	1.08 (0.98–1.2; n = 1012)	1.1 (0.98–1.4; n = 49)	−1.46	0.143
Fibrinogen (mg/dL)	254 (210–300; n = 620)	230 (145–284; n = 31)	−1.94	0.052
D-Dimer (g/L)	1.8 (0.84–4.56; n = 315)	4.76 (1.08–35.2; n = 22)	−2.1	**0.036**
ALT (U/L)	58 (30–124; n = 1046)	135 (54–397; n = 54)	−4.47	**<0.001**
AST (U/L)	106 (45–251; n = 1046)	222 (77–1161; n = 54)	−3.88	**<0.001**
LDH (U/L)	420 (275–675; n = 996)	766 (383–2836; n = 52)	−5.43	**<0.001**
CK (U/L)	278 (136–680; n = 990)	388 (202–1005; n = 49)	−2.04	**0.041**
BUN (mg/dL)	25 (15.5–38; n = 951)	33 (17.4–47; n = 51)	−2.49	**0.013**
Creatinine (mg/dL)	0.88 (0.7–1.02; n = 1034)	0.94 (0.7–1.53; n = 54)	−2.4	**0.016**
CRP (mg/L)	9.5 (3.3–27; n = 918)	15 (4.3–43.7; n = 48)	−1.8	0.072
PCT (ng/mL)	0.17 (0.1–0.5; n = 511)	0.53 (0.1–1; n = 27)	−2.37	**0.018**
Ferritin (g/mL)	1.65 (0.61–2; n = 282)	1.83 (0.99–2.4; n = 8)	−0.76	0.448

Continuous variables are presented as median (interquartile range). Died and survived group sizes are reported per variable due to missing data. Mann–Whitney U-tests were used to compare distributions between groups; Z-statistics are reported in place of U due to large sample sizes. p values < 0.05 were considered statistically significant and are shown in bold and underlined.
aPTT, activated partial thromboplastin time; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, blood urea nitrogen; CRP, C-reactive protein; PCT, procalcitonin.

Table 2
Univariate analysis of factors associated with in-hospital mortality

Variable	*N* = survived (%)	*N* = died (%)	OR	CI (95%)	p value
Sex					
Female	354 (34.3)	18 (32.1)			
Male	687 (65.7)	38 (67.9)	1.103	0.621–1.961	0.738
Age					
<50 y	456 (44.2)	11 (20.4)			
≥50 y	575 (55.8)	43 (79.6)	3.100	1.581–6.080	**<0.001**
Occupation					
Others	245 (23.4)	20 (35.7)			
Farmer	802 (76.6)	36 (64.3)	0.550	0.313–0.967	**0.036**
Hospitalization after symptom onset					
<4 d	627 (61.5)	32 (59.3)			
≥4 d	392 (38.5)	22 (40.7)	1.100	0.630–1.920	0.738
Clinical symptoms					
Fever	811 (77.5)	38 (67.9)	0.614	0.344–1.096	0.096
Myalgia	755 (72.1)	38 (67.9)	0.816	0.459–1.454	0.490
Abdominal pain	246 (23.5)	22 (39.3)	2.107	1.210–3.670	**0.007**
Vomiting	428 (40.9)	25 (44.6)	1.166	0.679–2.004	0.577
Diarrhoea	270 (25.8)	23 (41.1)	2.006	1.157–3.477	**0.012**
Headache	539 (51.5)	29 (51.8)	1.012	0.591–1.734	0.964
Conjunctivitis	169 (16.1)	5 (8.9)	0.509	0.200–1.295	0.149
Rash	153 (14.6)	8 (14.3)	0.974	0.452–2.099	0.946
Haemorrhage	154 (14.7)	18 (32.1)	2.747	1.528–4.937	**<0.001**
Fatigue	908 (86.7)	42 (75)	0.459	0.244–0.863	**0.013**
Loss of appetite	357 (34.1)	19 (33.9)	0.993	0.563–1.751	0.979
Haemorrhage type					
No haemorrhage	904 (86.3)	39 (69.6)	1 (ref)		
Petechiae	39 (3.7)	2 (3.6)	1.189	0.277–5.102	0.816
Ecchymosis	15 (1.4)	4 (7.1)	2.865	1.417–5.790	**0.003**
Haemorrhage	89 (8.5)	11 (19.6)	6.181	1.960–19.49	**0.002**
Haemorrhage site					
Gingival	40 (3.8)	4 (7.1)	1.937	0.668–5.617	0.276
Epistaxis	47 (4.5)	6 (10.7)	2.553	1.042–6.254	**0.047**
Vaginal	31 (3.0)	1 (1.8)	0.596	0.080–4.446	0.919
Rectal	15 (1.4)	5 (8.9)	6.745	2.359–19.28	**0.002**
Comorbidities					
Diabetes mellitus	54 (5.2)	11 (19.6)	4.495	2.201–9.178	**<0.001**
Chronic heart disease	46 (4.4)	5 (8.9)	2.133	0.813–5.599	0.177
Hypertension	81 (7.7)	7 (12.5)	1.704	0.748–3.883	0.203
Healthcare-related Infections					
No	1003 (95.8)	49 (87.5)			
Yes	44 (4.2)	7 (12.5)	3.256	1.395–7.600	**0.012**
Treatment					
Ribavirin	382 (36.5)	19 (33.9)	0.894	0.507–1.576	0.698
Vitamin K	8 (0.8)	8 (14.8)	22.06	7.928–61.41	**<0.001**
Plasmapheresis	25 (2.4)	9 (17.3)	8.355	3.677–18.99	**<0.001**
Fresh Frozen Plasma	146 (14.2)	43 (76.8)	20.03	10.51–38.16	**<0.001**
Dexamethasone	146 (14.2)	43 (76.8)	20.03	10.51–38.16	**<0.001**
Prednisolone	57 (5.6)	4 (7.4)	1.354	0.473–3.882	0.541
Thrombocyte	289 (28)	46 (82.1)	11.84	5.897–23.78	**<0.001**
Erythrocyte Suspension	35 (3.5)	13 (23.2)	8.456	4.174–17.13	**<0.001**
Ribavirin treatment initiation					
≤24 h	88 (8.4)	1 (1.8)	0.198	0.027–1.449	0.080
≤48 h	169 (16.1)	5 (8.9)	0.509	0.200–1.295	0.149
≤72 h	244 (23.3)	7 (12.5)	0.470	0.210–1.051	0.060
≤96 h	307 (29.3)	10 (17.9)	0.524	0.261–1.052	0.065

p values were considered statistically significant and are shown in bold and underlined.
OR, odds ratio.

Table 3
Time-dependent Cox regression model evaluating the effect of early ribavirin administration on in-hospital mortality truncated at 30 days

Variables	aHR	95% CI	p value
Being a female	0.611	0.323–1.153	0.128
Age (≥50 y)	2.565	1.241–5.301	**0.011**
Being a farmer	0.604	0.328–1.114	0.106
Diabetes mellitus	2.708	1.278–5.739	**0.009**
Chronic heart disease	1.242	0.481–3.208	0.654
Hypertension	0.951	0.404–2.239	0.909
Ribavirin initiation within ≤96 h	0.214	0.066–0.694	**0.010**

p values were considered statistically significant and are shown in bold.
aHR, adjusted hazard ratio.

attributed to the endothelial dysfunction frequently observed in patients with DM [22]. Since endothelial dysfunction plays a key role in CCHF pathogenesis, preexisting comorbidities that impair endothelial function could worsen disease progression in affected patients [23].

HRIs significantly impact hospitalized patients, especially those with preexisting infections. In our cohort, 51 patients developed secondary infections, most commonly soft tissue infections (phlebitis, $n = 14$), followed by catheter-related bloodstream infections ($n = 12$), pneumonia ($n = 8$), and urinary tract infections ($n = 6$). These complications necessitate broad-spectrum antibiotics and supportive care, complicating care and outcomes. HRIs were significantly associated with in-hospital mortality

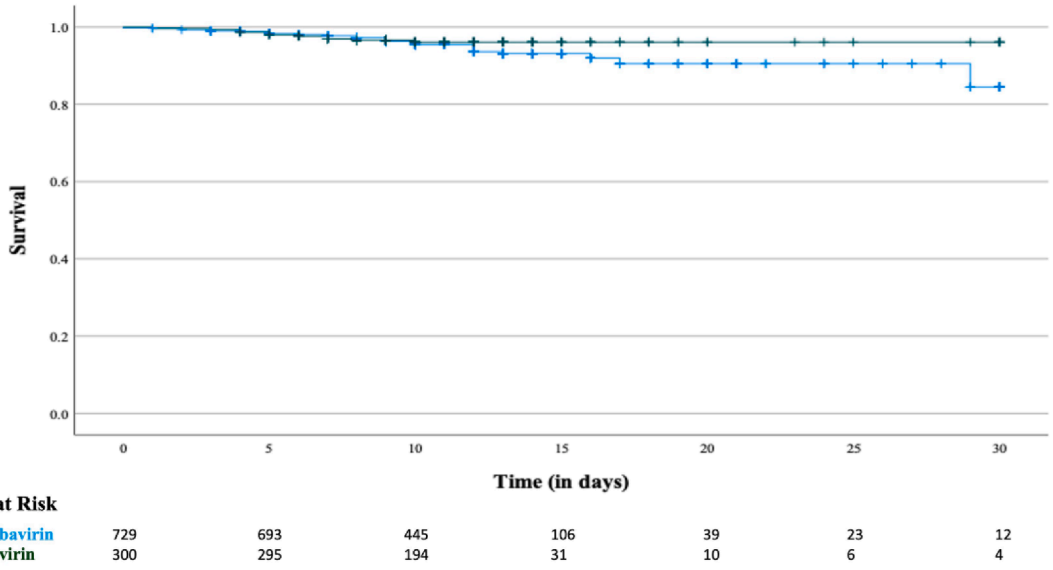

Fig. 2. Kaplan–Meier survival curves comparing early ribavirin administration (within 96 hours of symptom onset) versus no or late treatment truncated at 30 days. The green line represents patients who received ribavirin within 96 hours of symptom onset. The blue line represents those who received ribavirin later or not at all. Survival probabilities were estimated using unadjusted Kaplan–Meier analysis.

($p = 0.012$). This association is likely bidirectional, as many HRIs are acquired during hospital stays, reflecting the risks of prolonged hospitalization and invasive interventions.

An association with mortality was observed for several treatment options relevant to the haemorrhagic phase, including those aimed at addressing coagulation issues and supporting blood volume (Table 2). This inverse association, where more treatment correlates with higher mortality, is likely due to confounding by indication. This means patients who were more severely ill receive more intensive interventions as a last resort. Hence, the observed links probably reflect illness severity, not a direct negative effect of the treatments themselves.

The role of ribavirin administration in the management of CCHF has remained an important topic of debate. Several studies have suggested that ribavirin has great potential in reducing adverse outcomes [13,24,25], whereas others have found no significant benefit of ribavirin use [26–28]. In our study, although early ribavirin administration showed no statistically significant association with mortality in univariate analysis (Table 2), this likely reflects methodological limitations such as immortal time bias. In contrast, the time-dependent Cox regression model, which accounted for treatment timing, demonstrated a statistically significant protective effect of early ribavirin use on survival (Table 3). Additionally, ribavirin use was determined by individual clinicians at participating centres in the absence of standardized national guidelines, resulting in variations in treatment timing. In some cases, ribavirin may have been administered too late, particularly in patients with severe haemorrhagic symptoms, reducing its potential to alter the disease course [13].

This study has several limitations inherent to its retrospective observational design. First, the reliance on clinical documentation and patient or family recall introduces the potential for recall bias, particularly regarding symptom onset and tick bite history. Second, in the absence of a national treatment guideline for ribavirin use in CCHF, treatment decisions were made at the discretion of local clinicians, possibly introducing variability in indications for initiation. Although we applied time-dependent modelling to minimize immortal time bias and adjusted for key clinical covariates, the possibility of residual confounding remains. Unmeasured factors, such as disease severity not fully captured by available variables, could partially explain the observed association between ribavirin administration and improved survival. Other potential confounders, including differences in supportive care, clinical decision-making, or timing of hospital admission, may also have contributed to the observed outcomes. Finally, as only the oral formulation of ribavirin is available in Türkiye, its use may have been restricted in patients with gastrointestinal bleeding, including gingival or oral mucosal haemorrhage. Despite these limitations, this study offers important observational evidence regarding the potential role of ribavirin and other risk factors in influencing mortality.

Conclusion

Our findings suggest a potential clinical benefit of early ribavirin administration in patients with CCHF. In this observational cohort, initiation of ribavirin within 96 hours of symptom onset was independently associated with a reduced risk of in-hospital mortality. Although this supports the plausibility of a time-sensitive antiviral effect, the absence of standardized treatment protocols, the retrospective design, and the exclusion of non-hospitalized cases limit the generalizability and causal interpretation of these results. Future studies should aim to establish clear criteria for initiation timing and integrate patient demographics, laboratory trends, and treatment responses to better define ribavirin's role and contribute to the development of unified clinical management guidelines for CCHF. The findings of this study may serve as a basis for generating hypotheses and informing the design of such prospective investigations.

CRediT authorship contribution statement

Önder Ergönül, Mert Kuşkucu, and Fatihan Pınarlık: Conception and design. **Nurcan Baykam, Aysel Kocagül Çelikbaş;, Derya Yapar, Özlem Akdoğan, Kemalettin Özden, Rukiye İnan Sarıkaya, İmran Hasanoğlu, Rahmet Güner, Ebru Doğan, Faruk Karakeçili, Handan Alay, Zeynep Türe Yüce, Esma Eryılmaz Eren, Ayşe Erbay, Şebnem Eren Gök, Çiğdem Kader, Gamze Ünüvar Kalın, Azize Yetişgen, Müge Özgüler, Arzu Şenol, Ömür Gündağ;, Merve Çağlar Özer, Firuze Soyak, Büşra Tanır, Işıl Deniz**

Alıravcı;, Güle Çınar, Barçın Öztürk, Esra Gürbüz, and Bahadır Orkun Özbay: Data acquisition. Deniz Güllü;, **Defne Yigci, and Önder Ergönül**: Data analysis and interpretation. **Deniz Güllü; and Defne Yigci**: Drafting the manuscript. **Deniz Güllü;, Defne Yigci, and Önder Ergönül**: Critical revision of the manuscript. **Önder Ergönül**: Supervision.

Transparency declaration

Potential conflict of interest

The authors declare no conflict of interest.

Financial report

The authors declare that no funding was received for this study.

A portion of this work was presented at European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Global 2025, Vienna, Austria, 11 April 2025 to 15 April 2025.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.08.009.

References

[1] George AM, Ansumana R, de Souza DK, Niyas VKM, Zumla A, Bockarie MJ. Climate change and the rising incidence of vector-borne diseases globally. Int J Infect Dis 2024;139:143–5. https://doi.org/10.1016/j.ijid.2023.12.004.
[2] Orkun O, Karaer Z, Cakmak A, Nalbantoglu S. Crimean-Congo hemorrhagic fever virus in ticks in Turkey: A broad range tick surveillance study. Infect Genet Evol 2017;52:59–66. https://doi.org/10.1016/j.meegid.2017.04.017.
[3] Rocklöv J, Dubrow R. Climate change: An enduring challenge for vector-borne disease prevention and control. Nat Immunol 2020;21:479–83. https://doi.org/10.1038/s41590-020-0648-y.
[4] Ergönül Ö. Crimean-Congo haemorrhagic fever. Lancet Infect Dis 2006;6:203–14. https://doi.org/10.1016/S1473-3099(06)70435-2.
[5] Messina JP, Pigott DM, Golding N, Duda KA, Brownstein JS, Weiss DJ, et al. The global distribution of Crimean-Congo hemorrhagic fever. Trans R Soc Trop Med Hyg 2015;109:503–13. https://doi.org/10.1093/trstmh/trv050.
[6] Eslava M, Carlos S, Reina G. Crimean-Congo hemorrhagic fever virus: An emerging threat in Europe with a focus on epidemiology in Spain. Pathogens 2024;13:770. https://doi.org/10.3390/pathogens13090770.
[7] Zé-Zé L, Nunes C, Sousa M, de Sousa R, Gomes C, Santos AS, et al. Fatal case of Crimean-Congo hemorrhagic fever, Portugal, 2024. Emerg Infect Dis 2025;31:139. https://doi.org/10.3201/eid3101.241264.
[8] Bernard C, Kukla CJ, Rakotoarivony I, Duhayon M, Stachurski F, Huber K, et al. Detection of Crimean-Congo haemorrhagic fever virus in *Hyalomma marginatum* ticks, southern France, May 2022 and April 2023. Eurosurveillance 2024;29:2400023. https://doi.org/10.2807/1560-7917.ES.2024.29.6.2400023.
[9] Saratsis A, Ligda P, Aal F, Jelicic M, Polgar J, de Vries M, et al. The scenario of ticks and tick-borne pathogens of sheep on a mediterranean Island. Microorganisms 2022;10:1551. https://doi.org/10.3390/microorganisms10081551.
[10] Grandi G., Chitimia-Dobler L., Choklikitumnuey P., Strube C., Springer A., Albihn A., et al. First records of adult *Hyalomma marginatum* and H. rufipes ticks (Acari: Ixodidae) in Sweden. Ticks and tick-borne diseases, vol. 11; 2020. 101403. https://doi.org/10.1016/j.ttbdis.2020.101403.
[11] Ergonul O. Crimean-Congo hemorrhagic fever virus: New outbreaks, new discoveries. Curr Opin Virol 2012;2:215–20. https://doi.org/10.1016/j.coviro.2012.03.001.
[12] Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antivir Res 2013;100:159–89. https://doi.org/10.1016/j.antiviral.2013.07.006.
[13] Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. Antivir Res 2008;78:125–31. https://doi.org/10.1016/j.antiviral.2007.11.002.
[14] Akinci E, Bodur H, Sunbul M, Leblebicioglu H. Prognostic factors, pathophysiology and novel biomarkers in Crimean-Congo hemorrhagic fever. Antivir Res 2016;132:233–43. https://doi.org/10.1016/j.antiviral.2016.06.011.
[15] Bakır M, Gözel M, Köksal I, Aşık Z, Günal Ö, Yılmaz H, et al. Validation of a severity grading score (SGS) system for predicting the course of disease and mortality in patients with Crimean-Congo hemorrhagic fever (CCHF). Eur J Clin Microbiol Infect Dis 2015;34:325–30. https://doi.org/10.1007/s10096-014-2238-0.
[16] Dokuzoguz B, Celikbas AK, Gök ŞE, Baykam N, Eroglu MN, Ergönül Ö. Severity scoring index for Crimean-Congo hemorrhagic fever and the impact of ribavirin and corticosteroids on fatality. Clin Infect Dis 2013;57:1270–4. https://doi.org/10.1093/cid/cit527.
[17] Republic of Türkiye MoH. Guideline for management of Crimean-Congo hemorrhagic fever patients. Ankara: Republic of Türkiye Ministry of Health; 2025.
[18] Baghdadi GA, Aakef IR, Mahdi SG, Khaleel RI. Crimean-Congo haemorrhagic fever in Iraq. East Mediterr Health J 2024;30:570–6. https://doi.org/10.26719/2024.30.8.570.
[19] WHO. Crimean-Congo haemorrhagic fever WHO website. 2025. Acceded 20 February 2025, https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever.
[20] Sethi SM, Zahid S, Nasir N. Predictors of mortality in Crimean-Congo hemorrhagic fever patients admitted at a tertiary care hospital in Pakistan over the last 10 years: a case-control study. Am J Trop Med Hyg 2024;111:416–20. https://doi.org/10.4269/ajtmh.23-0630.
[21] Turkdogan KA, Zorlu A, Engin A, Guven FMK, Polat MM, Turgut OO, et al. C-type natriuretic peptide is associated with the severity of Crimean-Congo hemorrhagic fever. Int J Infect Dis 2012;16:e616–20. https://doi.org/10.1016/j.ijid.2012.04.009.
[22] De Vriese AS, Verbeuren TJ, Van de Voorde J, Lameire NH, Vanhoutte PM. Endothelial dysfunction in diabetes. Br J Pharmacol 2000;130:963–74. https://doi.org/10.1038/sj.bjp.0703393.
[23] Doğan HO, Büyüktuna SA, Kapancik S, Bakir S. Evaluation of the associations between endothelial dysfunction, inflammation and coagulation in Crimean-Congo hemorrhagic fever patients. Arch Virol 2018;163:609–16. https://doi.org/10.1007/s00705-017-3653-1.
[24] Tasdelen Fisgin N, Ergonul O, Doganci L, Tulek N. The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: Early use is promising. Eur J Clin Microbiol Infect Dis 2009;28:929–33. https://doi.org/10.1007/s10096-009-0728-2.
[25] Ergonul O. Evidence supports ribavirin use in Crimean-Congo hemorrhagic fever. Int J Infect Dis 2014;29:296. https://doi.org/10.1016/j.ijid.2014.08.016.
[26] Soares-Weiser K, Thomas S, G GT, Garner P. Ribavirin for Crimean-Congo hemorrhagic fever: Systematic review and meta-analysis. BMC Infect Dis 2010;10:207. https://doi.org/10.1186/1471-2334-10-207.
[27] Ascioglu S, Leblebicioglu H, Vahaboglu H, Chan KA. Ribavirin for patients with Crimean-Congo haemorrhagic fever: A systematic review and meta-analysis. J Antimicrob Chemother 2011;66:1215–22. https://doi.org/10.1093/jac/dkr136.
[28] Ceylan B, Calıca A, Ak O, Akkoyunlu Y, Turhan V. Ribavirin is not effective against Crimean-Congo hemorrhagic fever: Observations from the Turkish experience. Int J Infect Dis 2013;17:e799–801. https://doi.org/10.1016/j.ijid.2013.02.030.