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ORIGINAL ARTICLE

Blood Group: One of the Indicators of Poor Prognosis in Crimean-Congo Hemorrhagic Fever?

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Abstract

Introduction: Crimean-Congo Hemorrhagic Fever (CCHF) is a severe zoonotic disease characterized by a spectrum of clinical manifestations, including fever and organ bleeding. Specific endemic regions, such as Türkiye's Kelkit Valley, have established prognostic classification systems that notably exclude considerations of blood groups. This study aims to contribute to this evolving field by assessing whether blood groups play a significant role in the course of CCHF.

Methods: The study involves 368 patients who were followed up at our clinic between 2011-2023. Statistical analyses were conducted to evaluate the relationships between demographic characteristics, blood groups, severe case presentations, and mortality rates. The relationships between blood group, gender, age, severe case status, and death status were assessed.

Results: Our findings indicate that individuals with blood group A (+) exhibited a significantly higher rate of severe CCHF cases. However, blood group did not significantly affect mortality rates. Notably, advancing age was identified as a risk factor for mortality.

Discussion and Conclusion: This study contributes valuable insights into the interplay between blood groups and CCHF outcomes, suggesting that blood group A (+) may be associated with an elevated risk of severe disease. Understanding the role of blood groups in CCHF may inform risk assessment and potential personalized therapeutic interventions in the future.

Keywords: Blood group; CCHF; mortality; prognosis.

Crimean-Congo Hemorrhagic Fever (CCHF) is a formidable viral zoonotic disease caused by the Crimean-Congo Hemorrhagic Fever Virus (CCHFV). The clinical presentation of this illness typically commences with fever and may progress to involve various manifestations, including organ bleeding.[1-4] The clinical course of CCHF exhibits a wide spectrum, manifesting significant heterogeneity among affected individuals. The disease has a broad geographical distribution spanning regions from Europe to Asia and Africa.[5-9] While isolated cases of CCHF have been reported globally, certain regions remain endemic to this disease, such as the Kelkit Valley in Türkiye. In this particular region, two prognostic classification systems have been established, one of which was derived from a study conducted within the Kelkit Valley region.[10,11] Remarkably, neither of these classification systems incorporates considerations related to blood groups. The disease still presents a significant public health challenge due to its potential for nosocomial transmission and high case fatality rates.[12] As efforts intensify to comprehend the intricacies of CCHF, researchers have sought to explore various factors influencing the disease's clinical course, one of which is an individual's blood group.

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Blood group, classified by the ABO and Rh (D) systems, has long intrigued investigators studying infectious diseases. Recent research endeavors have attempted to unravel the potential relationship between blood group and susceptibility to, as well as the severity of, various infections, including those caused by CCHFV.[13-17] This emerging area of investigation stems from the recognition that blood group antigens may play a role in viral entry, immune responses, and disease progression.[18-21]

This study aims to contribute to the evolving body of knowledge regarding the interplay between blood groups and CCHF. The objective is to assess whether blood groups might emerge as a significant parameter influencing disease progression. The insights gained from this study could have implications for the incorporation of blood group information into scoring systems for risk assessment or other clinical considerations.

Materials and Methods

Study Design

The data pertaining to patients diagnosed with CCHF and under observation from 2011 to 2023 within the inpatient facility of our Infectious Diseases and Clinical Microbiology Department were retrospectively retrieved from the hospital information management system and the Ministry of Health Public Health Directorate's patient monitoring database. These data were subsequently compiled and stored in an Excel file. Demographic information, including age, gender, blood group, and clinical categorizations (mild-moderate and severe), constituted the dataset for this investigation. The study encompassed a cohort of 368 patients, whose blood group data were obtainable from a total of 569 patients monitored during the specified timeframe. Statistical analyses were conducted to assess the correlations between patients' demographic characteristics, blood groups, severe case presentations, and mortality rates. In studies conducted to predict disease severity and mortality in CCHF patients, patients were defined as mild-moderate and severe cases according to the mortality scoring criteria defined by Swanepoel et al.[22] in 1989, Bakır et al.[23] in 2015 and validated in 2022.[24] Accordingly, cases with bleeding in the first five days of the disease, leukocytosis (>10000/mm^3), or thrombocytopenia (<20000/mm^3), or aspartate aminotransferase ≥200 U/L, or alanine aminotransferase≥150 U/L, or activated partial thromboplastin time ≥60 seconds, or fibrinogen ≤110 mg/dL were defined as severe. Other cases were evaluated as mild-moderate cases.

Statistical Analysis

Descriptive statistics for the measurements were calculated based on variable type and distribution. The relationships between blood groups, gender, age, severe case status, and death status were initially assessed through univariate tests (including Pearson's chi-square test or the Fisher-Freeman-Halton exact test, as well as independent samples t-test). Subsequently, the associations between these three factors and the likelihood of severe cases and fatalities were evaluated through multivariate logistic regression analysis. A significance level of $p \leq 0.05$ was accepted, and calculations were performed using SPSS version 23.

Ethical approval from the local Ethics Committee (Erzincan Binali Yıldırım University, Clinical Research Ethics Committee, Date: March 03, 2023/Decision No: 05/5) was secured for the study. Informed consent was not obtained as the study was planned as a retrospective study.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, as revised in subsequent amendments.

Results

A total of 368 individuals, comprising 141 females and 227 males, with a mean age of 49.7±15.9 years (ranging from 17 to 89 years), were enrolled in the study. Among the patients, 96 (26.1%) were classified as severe cases, and 7 (1.9%) experienced fatalities. Furthermore, the distribution of patients with respect to blood groups is presented in Table 1.

Examination of the table reveals that the highest proportion (42.1%) of participants had blood group A (+), followed by the 0 (+) group. Conversely, the incidence of AB (-) and B (-) blood groups was notably low.

Table 1. Distribution of the patients according to the blood groups

Blood groups*	n	%
0 (-)	25	6.8
0 (+)	88	23.9
A (-)	25	6.8
A (+)	155	42.1
AB (-)	2	0.5
AB (+)	25	6.8
B (-)	6	1.6
B (+)	42	11.4
Total	368	100.0

*Rh groups are shown in brackets.

According to the results of the univariate tests, the rate of severe cases in the A (+) blood group was significantly higher compared to AB (-), AB (+), 0 (-), 0 (+), and B (+) groups. Additionally, the severe case rate in AB (-) and AB (+) blood groups was significantly lower than in all other blood groups. No other statistically significant differences were observed. Severe case rates according to blood groups are presented in Table 2.

In the column displaying the frequency of severe cases (%), groups with differing letters were found to be significantly distinct from each other (p=0.002).

The distribution of mortality rates according to blood groups is detailed in Table 3.

Table 2. Severe case rates according to the blood groups.

	Severe Case		Total, n
	Yes, n	%+	
Blood Groups*			
0 (-)	4	16.0[a]	25
0 (+)	19	21.6[b]	88
A (-)	8	32.0[ab]	25
A (+)	54	34.8[a]	155
AB (-)	0	0.0[c]	2
AB (+)	0	0.0[c]	25
B (-)	2	33.3[ab]	6
B (+)	9	21.4[b]	42
Total	96	26.1	368

*Rh groups are shown in brackets; +Fisher-Freeman-Halton exact test was performed; [a, b, c, ab]: Explains whether the compared parameters show significant differences or not (While parameters with different letters show a significant difference, those with the same letter or a common letter do not show a significant difference).

Table 3. Mortality rates according to blood groups.

	Mortality		Total, n
	Yes, n	%+	
Blood Groups*			
0 (-)	0	0.0	25
0 (+)	2	2.3	88
A (-)	0	0.0	25
A (+)	4	2.6	155
AB (-)	0	0.0	2
AB (+)	0	0.0	25
B (-)	0	0.0	6
B (+)	1	2.4	42
Total	7	1.9	368

*Rh groups are shown in brackets; +Fisher-Freeman-Halton exact test.

Upon examination of the table, it becomes apparent that there was no significant variation in mortality rates between blood groups (p=0.956). However, it is worth noting that out of the 7 total deaths, 4 occurred in the A (+) group, 2 in the 0 (+) group, and 1 in the B (+) group (Table 3). The limited number of fatalities restricts the ability to draw definitive conclusions regarding mortality rates.

When assessing the differences in severe case rates and mortality rates between genders, it was determined that the severe case rate and mortality rate were comparable for both genders. There was no significant difference.

The comparison of mean ages between the groups of severe and mild/moderate cases showed no significant difference.

The comparison showed that the mean age of deceased individuals was significantly higher than survivors (p=0.003).

In the multivariate model evaluation, no significant associations were observed between severe case status and blood group (p=0.300), gender (p=0.100), and age (p=0.958). However, it was noted that the risk of death increased by a factor of 1.095 with advancing age alone (p=0.007). Furthermore, no significant relationships were identified between gender (p=0.547) or blood groups (p=0.998) and mortality.

Discussion

CCHF is one of the haemorrhagic fevers which may result in death and has increasingly become a significant public health concern in various geographical regions, including Europe, in recent years.[8,25-27] Recognizing the disease and assessing poor prognostic factors at the time of diagnosis are crucial for monitoring the disease. Although various factors have been identified, blood type is not among them. It is important to determine the role of blood types in the development, progression, or containment of infections.[18-21] In this sense, the investigation of the potential relationship between blood groups and infections such as CCHF has gained momentum in recent years.[13,15]

Our study indicates a predominance of the male gender. We know that the majority of these patients are individuals engaged in farming and livestock activities. In this context, the higher prevalence of the male gender, similar to other studies, is not surprising.[28-31] However, our analysis did not identify significant associations between gender and disease severity or mortality rates, consistent with prior studies.[13,15] This suggests that, in the context of CCHF, both genders may exhibit similar disease outcomes.

In a study conducted in our region, it was observed that the majority of individuals engaged in livestock farming were in the 41-50 age range.[32] Similarly, the mean age in our study was found to be consistent with the literature.[33-35] The lack of a significant age difference between severe and mild/moderate cases is consistent with the literature.[36] However, in our multivariate model, we uncovered that age was a significant factor associated with an increased risk of death, with a 1.095-fold increase in mortality risk for each year of advancing age. To our knowledge, this finding presents only in our study, expressing that older individuals may be more susceptible to severe CCHF outcomes.

The mortality rate is similar to that reported in studies conducted within Türkiye but has been found to be significantly lower than the rates observed in studies conducted in Europe.[9,36-38] The increase in the number of mild/moderate cases, especially in recent years, may be responsible for this situation.

According to data from Türkiye, the most common blood type in our country is A, while the least common is AB.[39] Similar results were found in a study conducted in a neighboring province.[40]

In our study, the distribution of blood groups among CCHF patients demonstrated notable variability, with blood group A (+) being the most prevalent, which is consistent with the data from our country. Our observation of a significantly higher rate of severe cases among individuals with blood group A (+) aligns with the findings of the previous investigation by Duygu et al.,[15] but differs from the study of the childhood population reported by Güven et al.[13] Amin et al.[31] also reported group B as the most prevalent. We believe that the distribution of blood types in our country may have influenced the outcomes of studies reported from Türkiye, including our own. However, it cannot be overlooked that patients with blood type A (+) might have an increased risk of experiencing more severe cases of CCHF.

Notably, no severe cases were identified among patients with blood type AB. While this is likely due to the smaller number of patients in this group, it also raises the question of whether AB might be a protective blood type against CCHF. However, Duygu et al.[15] found an association between group AB (-) and mortality.

It is essential to recognize that our study did not establish a significant difference in mortality rates among different blood groups, corroborating the results reported by Güven et al.[13] Our findings imply that although blood group A (+) appears linked to increased disease severity, it may not substantially influence the likelihood of survival. Nevertheless, the limited number of fatalities in our study should be acknowledged as it may have impacted our ability to detect statistically significant differences in mortality rates.

Although our study is the largest conducted to date with the most extensive patient population contributing to understanding the interplay between blood groups and CCHF outcomes, it is important to acknowledge certain limitations. The retrospective design of our study and the relatively small number of fatalities may have constrained the robustness of our conclusions. We believe that multi-center, comprehensive studies are needed to eliminate the effects of regional and nationwide blood group distribution to further elucidate the associations between blood groups and CCHF severity and mortality.

Conclusion

A deeper understanding of the role of blood groups in CCHF could potentially inform risk assessment and guide the development of tailored therapeutic interventions. However, continued research is essential to fully unravel the underlying mechanisms and clinical implications of these associations.

Ethics Committee Approval: Ethical approval from the local Ethics Committee (Erzincan Binali Yıldırım University, Clinical Research Ethics Committee, Date: March 03, 2023/Decision No: 05/5) was secured for the study. Informed consent was not obtained as the study was planned as a retrospective study.

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