



Comparison of Blood Parameters in Crimean-Congo Hemorrhagic Fever and Upper Respiratory Infection Patients with Similar Complaints

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Abstract

Background: Crimean-Congo Hemorrhagic Fever (CCHF) often presents with non-specific flu-like symptoms that resemble upper respiratory tract infections (URTI), especially in endemic areas. We aimed to evaluate whether complete blood count (CBC) parameters could distinguish between CCHF and URTI in emergency settings.

Methods: We conducted a retrospective comparative analysis of 503 patients: 203 confirmed CCHF cases and 300 URTI cases. The study was carried out at Erzurum City Hospital, Erzurum, Turkey, between 2023 and 2024. Hematological parameters including WBC, PLT, RDW, MPV, and others were analyzed. ROC analysis was used to evaluate the prognostic value in CCHF patients.

Results: Significant differences in multiple CBC parameters were observed between the two groups. CCHF patients had significantly lower WBC, PLT, and lymphocyte counts, and higher MPV and RDW values compared to URTI patients (P -value<0.001). Among CCHF cases, 40.4% were initially misdiagnosed as URTI. ROC analysis indicated moderate prognostic power for HGB and PLT in predicting mortality.

Conclusion: CBC parameters can assist in distinguishing CCHF from URTI in endemic areas, especially when RT-PCR is unavailable. Emergency physicians should consider CCHF in differential diagnosis when specific hematological abnormalities are present.

Keywords: Complete blood count; Crimean-Congo hemorrhagic fever; Upper respiratory tract infection

Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a viral zoonosis transmitted primarily by Hyalomma ticks and characterized by sudden-onset fever, myalgia, and in some cases, bleeding diathesis. The disease is caused by a Nairovirus in the Bun-

yaviridae family, and its transmission to humans occurs via tick bites or direct contact with the blood or tissues of infected animals or humans (1). CCHF is endemic in over 50 countries across Europe, Asia, the Middle East, and Africa.



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Among these, Turkey reports the highest number of confirmed cases annually, particularly during the spring and summer seasons. Since the disease was first identified in Turkey in 2002, over 12,000 confirmed cases and nearly 600 deaths have been reported, with a case fatality rate ranging from 5% to 30% depending on the clinical severity and timing of diagnosis (2,3).

The global health burden of CCHF continues to grow due to increasing tick populations, climate change, and expanding geographic distribution. The disease poses not only a public health threat due to its high mortality but also an occupational hazard for farmers, veterinarians, and healthcare workers. Early and accurate diagnosis is essential to prevent complications, reduce mortality, and limit nosocomial transmission. However, in the early stages of infection, CCHF presents with non-specific symptoms such as fever, headache, fatigue, nausea, and myalgia, which are also commonly seen in upper respiratory tract infections (URTIs) (4,5).

Especially in endemic regions, patients presenting with flu-like symptoms during tick season may initially be misdiagnosed as having URTI, leading to inappropriate management and delayed antiviral therapy. According to Turkish Ministry of Health surveillance data, a significant portion of CCHF cases are initially misclassified as benign viral infections on first admission to emergency departments (6).

Several hematological abnormalities have been associated with CCHF pathophysiology, including leukopenia, thrombocytopenia, and elevated mean platelet volume (MPV). On the other hand, URTIs typically exhibit mild leukocytosis or lymphocytosis, depending on the viral etiology. Therefore, complete blood count (CBC) parameters may help differentiate CCHF from other viral infections with overlapping symptoms in resource-limited emergency settings where molecular testing is not immediately available (7,8).

The aim of this study was to evaluate whether there are statistically significant differences in CBC parameters between patients diagnosed with CCHF and those with URTIs. By identifying distinct hematological profiles, we aim to assist

emergency physicians in suspecting CCHF earlier, particularly in cases without a known tick exposure. This could improve triage decisions and timely RT-PCR testing, ultimately leading to better patient outcomes.

Methods

Study Design

This study was conducted with the approval of the Ethics Committee of Erzurum Faculty of Medicine, Health Sciences University, Erzurum, Turkey (Meeting No: 7, Decision No: 1, Date: 28.08.2023). Since the patient data were obtained by retrospectively reviewing the hospital information system, the need for an informed consent form was not required.

Patients who presented to the Emergency Medicine Clinic of Erzurum City Hospital between March 1, 2019, and August 30, 2023, and were diagnosed with CCHF based on a positive RT-PCR test, were retrospectively evaluated. Additionally, patients who presented to the same clinic between December 1, 2022, and February 28, 2023, and were diagnosed with URTI with a requested CBC test were included in the study.

The parameters used in our study were routinely evaluated in patient groups, and no research-specific parameters were included.

Patient Selection

Patients were identified through the hospital information system using the International Classification of Diseases (ICD) code A98.0. Out of 565 patients, 15 were under 18 years old, 249 had a history of tick exposure at the time of emergency admission, 18 exhibited hemorrhagic findings upon admission, and 80 had chronic diseases and/or were on chronic medication that could affect CBC parameters; these patients were excluded from the study. The remaining 203 patients were included in the study, and their initial symptoms and CBC parameters (WBC, RBC, HGB, MCV, RDW-CV, PLT, MPV, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Baso-

phils, P-LCR) were recorded for comparison with URTI patients.

Since no CCHF cases had been previously observed in Erzurum during December, January, or February, the control group consisted of URTI patients who presented between December 2022 and February 2023. The hospital information system was used to identify patients diagnosed with URTI using the ICD codes J06, J06.8, and J06.9. Patients were reviewed in order of admission. A total of 290 patients under 18 years old, 282 with chronic diseases and/or chronic medication use, 153 whose complaints could not be accessed in the system, and 501 without a CBC request were excluded from the study. The remaining 300 patients had their initial symptoms and CBC parameters recorded for comparison with CCHF patients.

Statistical Methods

All statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA). Prior to analysis, the dataset was reviewed for missing values, outliers, and data entry errors.

Missing values were examined on a case-by-case basis. Patients with missing values in critical hematological parameters were excluded from the analysis to ensure the reliability of results and avoid imputation-related bias.

Outlier values were initially identified using box-plots, z-scores (± 3.0), and interquartile range (IQR) methods. If an outlier was confirmed to be an accurate and clinically plausible value based on a review of original patient records, it was retained in the analysis. To assess the potential impact of these extreme values, sensitivity analyses were performed by comparing key results with and without the inclusion of these outliers. No significant changes in statistical significance or direction of associations were observed.

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test, histograms, and skewness/kurtosis Z-values. As

most variables did not follow a normal distribution, non-parametric tests were employed.

Categorical variables were expressed as frequencies and percentages and compared using Pearson's chi-square test. Continuous variables were presented as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test.

A *P*-value of <0.05 was considered statistically significant.

Additionally, a Receiver Operating Characteristic (ROC) curve analysis was performed to assess the prognostic ability of WBC, HGB, and PLT in predicting mortality among CCHF patients. Area Under the Curve (AUC), sensitivity, specificity, and optimal cut-off values were reported using Youden's index.

Results

Demographic characteristics

A total of 503 cases, including 203 CCHF and 300 URTI cases, were included in the study. The mean age of CCHF patients was 49.0 ± 17.8 years, while the mean age of URTI patients was 32.0 ± 14.8 years. Among CCHF cases, 62.1% ($n=126$) were male, and 37.9% ($n=77$) were female, whereas, in the URTI group, 47.0% ($n=141$) were male, and 53.0% ($n=159$) were female.

Symptoms

The distribution of symptoms in both patient groups is presented in Table 1.

Laboratory findings

In the statistical analysis of hematological parameters, there were no differences in MCV, RBC, and HGB values between the two patient groups. However, significant differences were found in WBC, RDW, PLT, MPV, NEU, LYM, MON, EOS, BAS, and PLCR distributions. The distribution of hematological parameters in both groups is shown in Table 2.

Table 1: Distribution of Symptoms in CCHF and URTI Patients

Symptoms	CCHF (n=203) N(%)	URTI (n=300) N(%)
Fever	107 (52.7)	144 (48.0)
No Fever	96 (47.3)	156 (52.0)
Fatigue	126 (62.1)	270 (90.0)
No Fatigue	77 (37.9)	30 (10.0)
Headache	53 (26.1)	162 (54.0)
No Headache	150 (73.9)	138 (46.0)
Nausea-Vomiting	52 (25.6)	40 (13.3)
No Nausea-Vomiting	151 (74.4)	260 (86.7)
Myalgia	95 (46.8)	260 (86.7)
No Myalgia	108 (53.2)	40 (13.3)
Diarrhea	22 (10.8)	14 (4.7)
No Diarrhea	181 (89.2)	286 (95.3)

CCHF: Crimean Congo Hemorrhagic Fever, URTI: Upper respiratory tract infection

Table 2: Comparison of Hematological Parameters in CCHF and URTI Patients

Parameters	CCHF	URTI	P-value
	Median (IQR)	Median (IQR)	
WBC	3.98 (2.97)	9.32 (3.69)	<0.001
RBC	4.95 (0.70)	5.08 (0.77)	0,288
HGB	14.27 (2.20)	14.56 (2.70)	0,162
MCV	83.67 (5.60)	84.64 (5.85)	0,442
RDW	13.44 (1.20)	13.12 (1.05)	<0.001
PLT	126.84 (84.00)	258.68 (78.00)	<0.001
MPV	10.44 (1.40)	10.36 (1.10)	<0.001
NEU	2.84 (2.92)	6.36 (3.44)	<0.001
LYM	0.82 (0.60)	2.04 (1.21)	<0.001
MON	0.33 (0.27)	0.79 (0.38)	<0.001
EOS	0.07 (0.05)	0.14 (0.16)	<0.001
BAS	0.02 (0.01)	0.04 (0.03)	<0.001
PLCR	28.65 (11.70)	25.75 (9.10)	<0.001

BAS: Basophil count, CCHF: Crimean Congo Hemorrhagic Fever, EOS: Eosinophil count, HGB: Hemoglobin, IQR: Inter quartile range, LYM: Lymphocyte count MCV: Mean red blood cell volume, MON: Monocyte count, MPV: Mean platelet volume, NEU: Neutrophil count, PLCR: Platelet large cell ratio, PLT: Platelet count, RBC: Red blood cell, RDW: Red cell distribution width, URTI: Upper respiratory tract infection WBC: White blood cell

Prognostic findings in cchf cases

A significant difference was observed in the age distribution between surviving and deceased CCHF patients (P -value<0.001). In terms of

gender, 9.5% of male and 3.9% of female patients had died, with no significant difference in mortality rates by gender (P -value=0.137) (Table 3).

Table 3: Age and Gender Distribution of CCHF Cases by Prognosis

Variables	Survived (n=188)	Deceased (n=15)	P-value
	Median (IQR) / Number (Per-cent)	Median (IQR) / Number (Per-cent)	
Age (years)	48.5 (28.0)	68.0 (17.0)	<0.001
Gender			
Male	114 (90.5)	12 (9.5)	0.137
Female	74 (96.1)	3 (3.9)	

IQR: Inter quartil range

Survivors and deceased patients showed significant differences in WBC, RBC, HGB, PLT, and NEU values (P -value<0.05 for all). The distribu-

tion of laboratory parameters by prognosis is presented in Table 4.

Table 4: Distribution of Laboratory Parameters by Prognosis in CCHF Patients

Parameters	Survived (n=188)	Deceased (n=15)	P-value
	Median (IQR)	Median (IQR)	
WBC	3.9 (2.5)	5.8 (3.8)	0.046
RBC	5.0 (0.7)	4.3 (1.3)	0.006
HGB	14.4 (2.1)	13.1 (2.9)	0.021
MCV	83.6 (5.8)	84.6 (3.9)	0.473
RDW	13.4 (1.1)	13.8 (1.5)	0.258
PLT	130.2 (79.5)	85.3 (111.0)	0.015
MPV	10.4 (1.4)	10.9 (1.5)	0.096
NEU	2.7 (2.7)	4.5 (2.7)	0.043
LYM	0.8 (0.6)	0.9 (0.7)	0.789
MON	0.3 (0.3)	0.3 (0.2)	0.196
EOS	0.1 (0.1)	0.0 (0.1)	0.910
BAS	0.0 (0.0)	0.0 (0.0)	0.097
PLCR	28.4 (11.3)	32.3 (10.2)	0.076

BAS: Basophil count, CCHF: Crimean Congo Hemorrhagic Fever, EOS: Eosinophil count, HGB: Hemoglobin, IQR: Inter quartile range, LYM: Lymphocyte count, MCV: Mean red blood cell volume, MON: Monocyte count, MPV: Mean platelet volume, NEU: Neutrophil count, PLCR: Platelet large cell ratio, PLT: Platelet count, RBC: Red blood cell, RDW: Red cell distribution width, URTI: Upper respiratory tract infection WBC: White blood cell

To determine the prognosis of CCHF cases, ROC analysis was performed for WBC, HGB, and PLT values. Statistically significant AUC values were found for HGB and PLT (P -

value=0.033 and P -value=0.016, respectively). The results of the ROC analysis for WBC, HGB, and PLT are shown in Table 5, and their ROC curves are illustrated in Fig. 1.

Table 5: ROC Analysis Results for WBC, HGB, and PLT

Parameters	AUC	%95 GI	Cut-off Point	Sensitivity	Specificity	P-value
WBC	0.66	0.4- 0.82	-	-	-	0.061
HGB	0.68	0.52- 0.85	13.05	82.4	53.3	0.033
PLT	0.69	0.54- 0.84	73.0	81.4	53.3	0.016

AUC: Area under curve, CI: Confidence interval, HGB: Hemoglobin, PLT: Platelet count, WBC: White blood cell

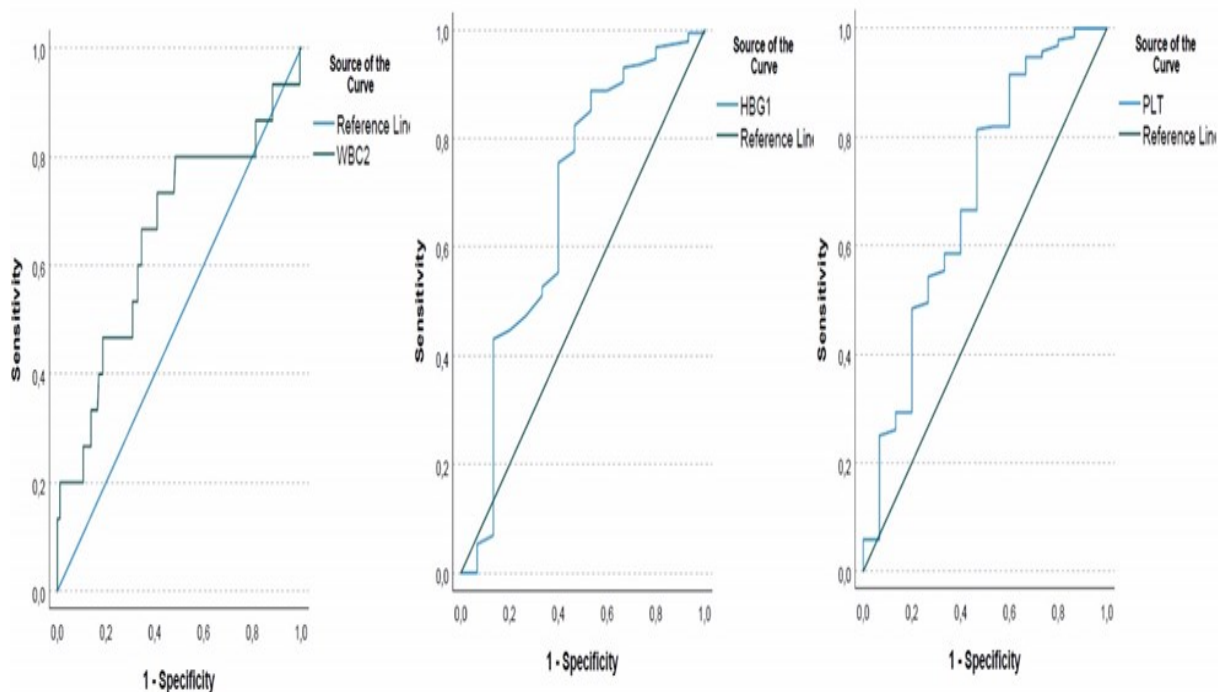


Fig. 1: ROC Curves for WBC, HGB, PLT in CCHF Cases

Re-evaluation of cCHF patients' emergency department visits

A total of 82 CCHF patients (40.4%) were initially misdiagnosed as URTI and discharged after their first emergency department visit. These pa-

tients returned within 1–5 days, at which point RT-PCR testing confirmed the diagnosis of CCHF. The most frequent re-admission occurred within one day (Table 6).

Table 6: Re-admission Data for CCHF Cases

Re-admission Period (Days)	Count (Percentage)
1	55 (27.1)
2	16 (7.9)
3	5 (2.5)
4	2 (1.0)
5	4 (2.0)

The most common initial URTI sub-diagnosis among CCHF patients at the first visit was tonsillitis, coded as J02 ICD, in 51% of cases.

Discussion

While numerous studies have previously investigated hematological parameters in CCHF, most of them have focused on either isolated patient

groups or on mortality prediction only. In contrast, our study provides a comparative analysis between CCHF and URTI patients who presented with similar nonspecific complaints in an emergency setting. This approach reflects a real-world diagnostic challenge and distinguishes our work from previous research that often lacked a differential comparison group. Moreover, we evaluated the misdiagnosis rate and timing of re-

admissions, which are rarely reported in earlier studies. These aspects contribute to the originality and clinical relevance of our study.

In the early stages of the disease, patients may present to the hospital with non-specific symptoms that can be confused with other illnesses, making an initial diagnosis of CCHF challenging for physicians. Particularly in the absence of a history of tick exposure or clinical findings, patients may not be considered as having CCHF, even in endemic regions. Approximately 50-60% of CCHF patients have a history of tick exposure, while nearly half do not report such exposure at the time of admission (5). In our study, 249 patients (44%) had a history of tick exposure. However, 203 CCHF patients included in the study did not report tick exposure. This situation may complicate the diagnosis of CCHF in endemic regions, especially during the spring and summer seasons when the disease is prevalent, and may further hinder its differentiation from other conditions with similar symptoms, such as URTIs. In our study, 82 CCHF patients (40.4%) were initially misdiagnosed with URTI during their first emergency department visit and were discharged. The pathophysiology of CCHF has not been fully elucidated. However, the most significant known feature of the virus is its ability to evade the immune response by targeting host cells, particularly macrophages and endothelial cells (6). Proinflammatory cytokines released in response to viral activity lead to an inflammatory immune response in the vascular endothelium, target cells, and tissues. Activation of lymphocytes, monocytes, and macrophages, along with excessive cytokine secretion, results in the proliferation of hemophagocytic macrophages. In a study (7), reactive hemophagocytosis was detected in seven of 14 patients (50%), suggesting a contribution of hemophagocytosis to cytopenia in CCHF infection. Simultaneously, platelet aggregation and degranulation occur, leading to a rapid decline in leukocyte, lymphocyte, and platelet counts (8). In our study, the mean WBC, PLT, and LYM values in CCHF patients were below the normal range and were significantly lower compared to those in URTI patients (P -value=0.000). Similarly, alt-

hough the mean MON, NEU, EOS, and BASO values in CCHF patients were within normal ranges, they were significantly lower than those in URTI patients (P -value=0.000). These findings suggest that these changes are related to disease pathogenesis, immune response activation, and alterations in bone marrow activity.

Mean platelet volume (MPV) is a cost-effective marker derived from complete blood counts that reflects platelet function and activation (9). Recent studies have demonstrated that MPV may serve as an inflammatory marker. In a study (10), MPV levels were found to be significantly higher in CCHF patients compared to the control group. Similarly, in our study, MPV values were significantly higher in CCHF patients than in URTI patients (P -value=0.000).

Red cell distribution width (RDW) is a quantitative test used to assess variations in erythrocyte size and volume. Although previous studies have established associations between RDW levels and inflammatory conditions such as pulmonary embolism, celiac disease, coronary artery disease, and sepsis, limited research has examined the relationship between CCHF and RDW levels (11-12). In a study (13), RDW levels were higher in CCHF patients than in the control group. Consistent with these findings, our study showed that mean RDW values were significantly higher in CCHF patients than in URTI patients (P -value=0.000).

Platelet-large cell ratio (P-LCR) is a hematological parameter that represents the proportion of large platelets relative to normal platelets. Studies have shown that P-LCR is associated with platelet activation and function and that it is affected in diseases impacting vascular structures, such as CCHF. It has also been suggested as a useful prognostic marker (14-15). In another study (16) on mice infected with Dengue virus, which causes viral hemorrhagic fever, an increase in P-LCR values was observed, particularly during the early days of the disease. In our study, mean P-LCR values were significantly higher in CCHF patients than in URTI patients (P -value =0.000), likely due to the role of platelets in CCHF pathogenesis.

HGB, MCV, and RBC are three interrelated parameters included in hematological tests. Previous studies have indicated that anemia may be observed in hemorrhagic diseases such as CCHF, with these parameters displaying lower values (17-18). However, in our study, both CCHF and URTI patients had HGB, MCV, and RBC values within normal ranges, with no significant differences between the two groups. This may be attributed to the exclusion of patients with bleeding manifestations and chronic diseases associated with anemia.

Several studies in the literature have identified hematological parameters contributing to mortality in CCHF, highlighting the roles of thrombocytopenia, leukocytosis, and anemia in disease outcomes (19). In a study (20), neutrophil and leukocyte counts were found to be significantly higher in the fatal group than in the surviving group, whereas platelet levels were significantly lower. Reductions in monocyte and lymphocyte counts and increases in neutrophil counts were associated with poor outcomes in CCHF. In our study, of the 203 CCHF cases analyzed, 15 resulted in mortality (21). The WBC and NEU values of deceased patients were significantly higher than those of survivors, whereas HGB, RBC, and PLT values were significantly lower. ROC analysis of WBC, HGB, and PLT for prognostic evaluation revealed AUC values of 0.66, 0.68, and 0.69, respectively.

This study has several strengths. To our knowledge, it is one of the few comparative studies evaluating hematological differences between CCHF and URTI patients with similar presenting complaints in an emergency setting. The relatively large sample size and strict exclusion of patients with confounding chronic conditions enhance the internal validity of our findings. Moreover, the inclusion of re-evaluation data on misdiagnosed cases provides real-world insight into clinical challenges.

However, there are also limitations to consider. First, the retrospective design limits our ability to establish causal relationships and is dependent on the accuracy of medical records. Second, demographic differences between the groups, particu-

larly in age and sex, may have influenced some of the hematological parameters, although we attempted to minimize this by excluding confounding conditions. Third, the study was conducted at a single center in an endemic region, which may limit the generalizability of our results. Finally, the absence of advanced inflammatory markers or cytokine profiles may limit a more in-depth understanding of the underlying pathophysiology.

Conclusion

CCHF is a multisystemic disease with a potentially fatal course. Turkey is an endemic region for CCHF, and case numbers have been steadily increasing since 2002. During the early phase of the disease, CCHF cases exhibit non-specific clinical symptoms that resemble other illnesses, particularly URTIs, and tend to increase during spring and summer. This presents diagnostic challenges, particularly in emergency departments with high patient volumes, where cases may be misdiagnosed as URTIs. Additionally, the high cost and time-consuming nature of RT-PCR, the gold standard diagnostic method for CCHF, further complicate the timely diagnosis of CCHF patients.

We recommend performing CBC tests in patients presenting to emergency departments in endemic regions, particularly during summer, with non-specific symptoms such as fever, headache, fatigue, joint-muscle pain, nausea-vomiting, and diarrhea. The presence of low WBC, PLT, NEU, LYM, MON, EOS, and BAS levels, along with high P-LCR, RDW, and MPV values, may serve as indicators prompting emergency physicians to consider CCHF as a potential diagnosis.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

Non-declared

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