

Cytokine release syndrome in Crimean-Congo hemorrhagic fever: can IL-1 receptor antagonist levels be a guide in its treatment?

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Abstract. – **OBJECTIVE:** Crimean-Congo Hemorrhagic Fever (CCHF) is a potentially fatal zoonotic viral disease involving fever and hemorrhage. Our aim was to investigate the relationship between interleukin (IL)-1 and IL-1 receptor antagonist (RA) levels in patients with CCHF and the course of the disease and mortality, as well as to contribute to the literature at a time when new therapeutic protocols are being investigated.

PATIENTS AND METHODS: Sixty-one patients with CCHF were admitted to our hospital's infectious diseases ward between March and September 2022, and 40 healthy people were included in the control group in our study. The patients were divided into mild/moderate (n=35) and severe (n=26) CCHF groups depending on the clinical course. The patients with CCHF were also divided into surviving and exitus groups. IL-1 and IL-1RA levels were measured from blood specimens using the ELISA method.

RESULTS: Significant elevation in IL-1 and IL-1RA levels was observed in CCHF cases with a severe manifestation compared to those with moderate disease. Both patient groups' IL-1 and IL-1RA levels were also significantly higher than those of the control group. In addition, IL-1 and IL-1RA levels were significantly higher among the exitus patients compared to the surviving CCHF patients. The laboratory values of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase (CK), platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were also significantly higher among the patients with severe manifestations compared to the moderate severity patient group, and in the exitus patients compared to the survivors. However, platelet count and fibrinogen levels were lower in the patients with a severe manifestation compared to the moderate severity group and in the exitus patients compared to the survivors. White blood cells (WBC) were higher in exitus patients than in survivors.

CONCLUSIONS: IL-1 and IL-1RA levels were elevated in all the CCHF patients, while the higher values in patients with a fatal course suggest that the inflammatory process is very severe and that IL-1 receptor antagonists may be needed in the treatment.

Key Words:

CCHF, IL-1, IL-1RA, Mortality.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute, severe viral hemorrhagic febrile disease that can be fatal in patients with a severe manifestation^{1,2}.

The disease is generally transmitted by a tick carrying the virus. However, it can also be transmitted by contact with the blood, body fluids, and tissues of viremic humans and animals through skin or mucosa with impaired integrity³.

The clinical course of the disease is associated with uncontrolled viral replication and high cytokine levels in the host tissues; it, therefore, probably results both directly from virus-mediated pathology and indirectly from immune-mediated pathologies capable of leading to vascular dysfunction and, in severe cases, death⁴.

Recent studies⁵ have shown that pro- and anti-inflammatory cytokines play an important role in the pathogenesis of CCHF. As with other viral hemorrhagic fevers, the course of the disease depends on the viral load and the balance between immune response mediators and is even thought⁶ to be capable of exhibiting a fatal course as a result of the cytokine storm.

Cytokines mediate immune resistance against microorganisms by regulating the onset and continuation of the immune response and also determining the shape of that response. However, they can also induce pathogenesis when over-synthesized⁷.

A series of inflammatory molecules, including interleukin-1 (IL-1), are involved in these processes. The *IL-1* gene family consists of three proteins, IL-1 α , IL-1 β , and IL-1 receptor antagonist (IL-1RA). IL-1 α and IL-1 β exhibit similar effects by binding to the IL-1 type I receptor⁸.

IL-1RA inhibits IL-1 receptor binding in a competitive manner, while intracellular IL-1RA not only inhibits IL-1 binding but also regulates IL-1 functions⁹.

The purpose of this study was to determine the applicability of serum IL-1 and IL-1RA levels in predicting the clinical course and mortality in order to contribute to the treatment of patients with severe disease.

Patients and Methods

Sixty-one patients with CCHF were admitted to our hospital's infectious diseases ward between March and September 2022, and 40 healthy individuals with no tick contact or symptoms were included in the study. Patients aged over 18 were included. Patients with acute or chronic disease, hematological pathology, malignancy, or systemic drug use were excluded. The control group consisted of 40 healthy individuals.

CCHF patient group consisted of patients with a history of tick bites, with a positive transcriptase (RT)-PCR test in blood samples sent from patients with concomitant high fever, elevated liver enzymes, leukopenia, and thrombocytopenia.

Blood specimens collected from the CCHF patients and control group were centrifuged for 15 min at 4,000 rpm for serum separation. The sera obtained were stored at -80°C in Eppendorf tubes. IL-1 and IL-1RA parameters were subsequently investigated and recorded from the same specimens. CCHF patient group laboratory values including serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase (CK), fibrinogen, white blood cells (WBC), platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were also recorded.

The 103 individuals enrolled in the study were divided into three groups. The first group consist-

ed of healthy individuals consenting to take part in the study (n=40). The CCHF cases were classified as moderate or severe disease manifestations based on their LDH, AST, ALT, CK, WBC, PT, aPTT, platelet count, and fibrinogen values. The patients were evaluated using the Swanepoel system, based on platelet counts <20x10⁹/l, AST>200 U/l, ALT>150 U/l, aPTT>60 s, and fibrinogen <110 mg/dl².

The second, CCHF PCR (+) group, consisted of patients with a moderate disease manifestation (n=35), and the third, CCHF PCR (+), group consisted of patients with a severe disease manifestation (n=26). The CCHF PCR (+) patients were also subdivided into surviving and fatal groups.

Blood Specimens and Analyte Assay Techniques

The patients' IL-1 and IL-1RA levels were investigated using the enzyme-linked immunosorbent assay (ELISA) method (BT LAB, Shanghai, China). Serum LDH, AST, ALT, and CK levels were determined using commercial kits on a Beckman Coulter AU5821 device (Tokyo, Japan) housed in the laboratory. Ferritin levels were measured using commercial kits on a Beckman Coulter DxI800 device. WBC and platelet counts were measured with a Sysmex XN-9000 device (Cobe, Japan) and were recorded as cells/ μ L. PT, aPTT, and fibrinogen tests were conducted on a Stago STAR Max device (Paris, France).

Statistical Analysis

Data were recorded and analyzed using SPSS software for Windows (version 20.0; IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, and numerical variables as mean \pm standard deviation. Visual (histogram) and analytical methods (Kolmogorov-Smirnov or Shapiro-Wilk tests) were used to evaluate the normality of the distribution of variables. The Chi-square test was applied to compare categorical variables, and the *t*-test or One-Way Analysis of Variance, as appropriate, in the comparison of continuous variables. The significance of differences between groups was assessed using the post-hoc Tukey test. Pearson's correlation coefficient was applied for linear correlation analysis. The receiver operating characteristic curve (ROC) technique, which indicates the predictive power of a specific method, was employed to determine sensitivity, specificity, area under the curve (AUC), and cut-off values. Statistical significance was set at $p < 0.05$.

Table I. Comparison of laboratory parameters at admission in patients with moderate and severe Crimean-Congo hemorrhagic fever.

Parameter	Moderate (n=35)	Severe (n=26)	p
WBC (/ μ L)	2,950.2 \pm 1,120.3	3,890.5 \pm 3,519.3	0.397
Platelet count (cells/ μ L)	72.66 \pm 37.73	11.23 \pm 5.57	<0.001
AST (U/L)	216.57 \pm 99.59	1,028.08 \pm 294.13	<0.001
ALT (U/L)	289.57 \pm 134.53	2,197.31 \pm 1,563.74	<0.001
LDH (U/L)	546.29 \pm 180.52	2,907.69 \pm 1,893.76	<0.001
CK (U/L)	371.71 \pm 197.27	1,207.69 \pm 476.27	<0.001
PT(s)	13.43 \pm 2.48	26.35 \pm 6.01	<0.001
aPTT (sec)	43.71 \pm 6.21	71.35 \pm 7.94	<0.001
Fibrinogen (ng/mL)	4.85 \pm 0.87	2.24 \pm 1.07	<0.001

Values are expressed as mean \pm standard deviation. WBC: white blood cell, CK: Creatine kinase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: Lactate dehydrogenase, PT: prothrombin time, aPTT: activated partial thromboplastin time.

Results

Mean ages were 47.51 \pm 14.04 years in the CCHF patients with moderate disease severity and 53.27 \pm 14.62 in those with severe manifestations. The mean age of the control group was 52.78 \pm 13.72 years. No significant age difference was determined between the patient and control groups ($p=0.183$).

The mean age of the exitus CCHF patients was 63.20 \pm 13.19 years, compared to 47.37 \pm 13.33 in the surviving patients. The difference between these two groups was statistically significant ($p=0.001$).

No significant gender difference was observed between the three groups ($p=0.151$).

Eight (19.5%) of the exitus CCHF patients were men, and two (10.0%) were women, while 33 (80.5%) of the surviving patients were men,

and 18 (90.0%) were women. There was no significant gender difference between the two groups ($p=0.346$).

A comparison of the total patient group laboratory data is shown in Table I. LDH, AST, ALT, CK, PT, and aPTT values were significantly higher in the patients with severe disease than in the group with moderate disease ($p<0.001$ for all), while platelet count and fibrinogen values were lower ($p<0.001$ for all). The two groups had no statistically significant difference in WBC values ($p<0.397$).

IL-1 and IL-1RA levels were significantly higher in the CCHF patients with severe disease manifestations than in those with moderate disease and were also significantly higher in both patient groups than in the control group (Figure 1).

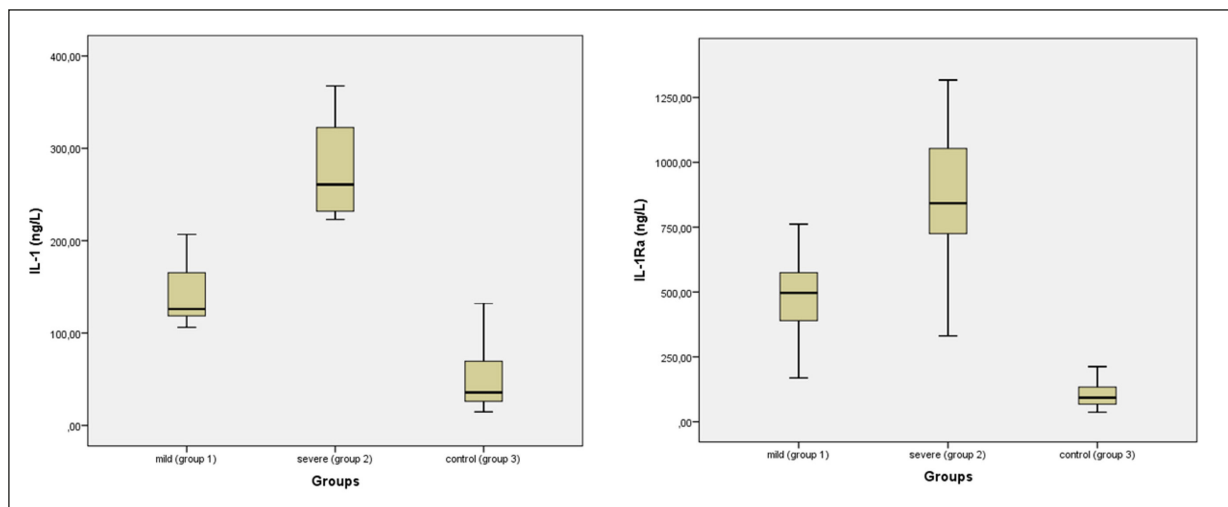


Figure 1. Box plots showing the groups' serum IL-1 and IL-1RA levels.

Table II. Comparison of IL-1 and IL-1RA levels in patients with Crimean-Congo hemorrhagic fever between severe and non-severe disease and patients who survived and died.

Parameter	Moderate (n=35) mean±SD	Severe (n=26) mean±SD	Survivor (n=51) mean±SD	Non-survivor (n=10) mean±SD	Control (n=40) mean±SD	p
IL-1 (ng/L)	139.02±29.89	277.78±49.72	172.93±57.78	326.82±40.198	53.02±38.73	<0.001 ^{a,b,c}
IL-1RA (ng/L)	473.59±143.68	874.73±226.66	568.97±196.21	1,030.08±275.66	104.59±54.75	<0.001 ^{a,b,c}

^a=Comparison of moderate and severe patients, ^b=Comparison of survivor and non-survivor patients, ^c=Comparison of patients and controls.

The patients were divided into two groups on the basis of mortality, survival, and exitus. The exitus patients consisted of individuals who developed macrophage activation syndrome (MAS) during follow-up. IL-1 and IL-1RA levels were significantly higher in the exitus patients than in the surviving group (Table II). In addition, WBC, LDH, AST, ALT, CK, PT, and aPTT values were also significantly higher in the exitus patients (respectively $p < 0.004$, for others $p < 0.001$). Platelet count and fibrinogen values were all significantly lower in the exitus group ($p < 0.001$ for all) (Table III).

IL-1 levels exhibited significant, high positive correlation with IL-1RA, longest PT, longest aPTT, highest AST, highest ALT, highest LDH, and highest CK, and significant, low negative correlation with lowest platelet count, and lowest fibrinogen levels.

IL-1RA levels exhibited significant, high positive correlation with IL-1, longest PT, longest aPTT, highest AST, highest ALT, highest LDH, and highest CK, and significant, moderate negative correlation with lowest platelet count, lowest fibrinogen levels (Table IV).

At a cut-off value of 210.85 ng/L, serum IL-1RA levels exhibited 97% sensitivity and 95% specificity in differentiating CCHF cases from healthy individuals [AUC=0.995, $p < 0.001$, 95% Confidence Interval (CI) 0.988-1.00]. Additionally, at a cut-off value of 107.67 ng/L serum IL-1 levels exhibited 95% sensitivity and 90% specificity in differentiating CCHF cases from healthy individuals (AUC=0.963, $p < 0.001$, 95% CI 0.925-1.00) (Figure 2).

Discussion

Inflammation is an inseparable part of immune reactions to infections. However, a number of highly pathogenic viruses result in high morbidity and mortality, causing an excessive and prolonged inflammatory response on the part of cytokines and chemokines, known as ‘cytokine release syndrome’¹⁰.

CCHF is a potentially severe disease caused by the virus⁶. After entering the body, the CCHF virus produces viremia and leads to inflammation in tissues and organs, particularly mononuclear cells and neutrophils¹¹.

Table III. A comparison of laboratory results between the fatal and non-fatal cases.

Parameter	Non-survivors mean±SD n=10	Survivors mean±SD n=51	p
Age	63.20±13.19	47.37±13.33	<0.001
WBC (/μL)	2,601.34±1,143.39	4,933.64±3,204.99	<0.004
Highest alanine transferase level (U/L)	3,819.00±1,152.81	570.10±562.67	<0.001
Highest aspartate transferase level (U/L)	1,329.00±212.94	412.16±312.66	<0.001
Highest lactic dehydrogenase level (U/L)	5,020.00±1,283.91	872.94±553.70	<0.001
Highest creatinine phosphokinase level (U/L)	1,740.00±217.05	529.61±308.117	<0.001
Lowest fibrinogen level (g/L)	1.17±0.22	4.24±1.24	<0.001
Lowest platelet count (1x10 ⁹ cells/L)	5.40±2.06	54.53±41.29	<0.001
Longest prothrombin time (s)	32.20±5.35	16.33±4.97	<0.001
Longest activated partial thromboplastin time (s)	77.10±8.98	51.25±12.62	<0.001

WBC: white blood cell.

Table IV. Correlation analysis of IL-1 and IL-1RA laboratory parameters.

	IL-1		IL-1RA	
	Correlation coefficient (r)	p	Correlation coefficient (r)	p
IL-1			0.862	<0.001
IL-1RA	0.862	<0.001		
Longest PT	0.858	<0.001	0.697	<0.001
Longest aPTT	0.834	<0.001	0.710	<0.001
Lowest PLT	-0.668	<0.001	-0.495	<0.001
High ALT	0.787	<0.001	0.702	<0.001
High AST	0.883	<0.001	0.822	<0.001
High LDH	0.822	<0.001	0.697	<0.001
High CK	0.837	<0.001	0.713	<0.001
Lowest fibrinogen	-0.820	<0.001	-0.644	<0.001

IL-1: interleukin-1, IL-1RA: IL-1 receptor antagonist, CK: Creatine kinase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: Lactate dehydrogenase, PT: prothrombin time, aPTT: activated partial thromboplastin time, PLT: platelets.

An insufficient antibody response is reported in fatal cases of CCHF. Inflammatory mediators play an important role in these cases, and shock, together with a fulminant course, is observed¹².

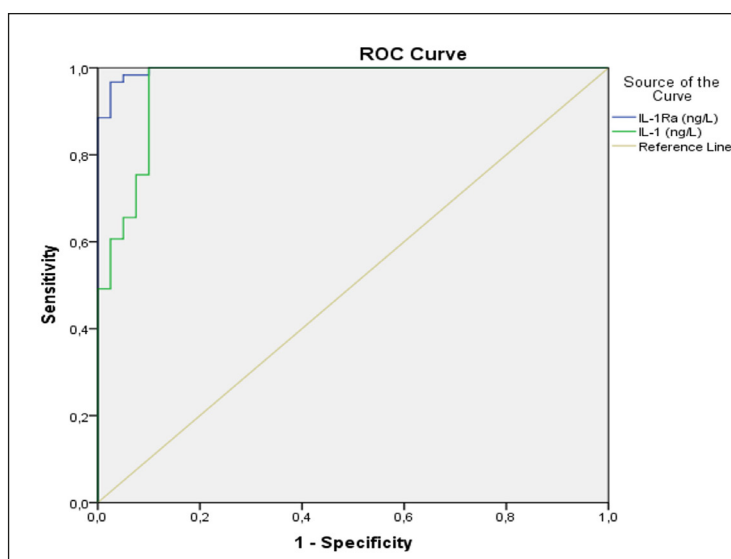
Severe or irregular (uncontrolled) inflammation contributes to the pathogenesis of numerous acute and chronic conditions. Cytokines, generally known as interleukins, are proteins that regulate the inflammatory response by transmitting pro- and anti-inflammatory signals. IL-1 is an important proinflammatory cytokine involved in the innate immune response¹³. It is also involved in the pathogenesis of various inflammatory diseases, including viral infections¹⁴.

Both IL-1 and IL-1RA are produced by endothelial cells, smooth muscle cells, and macrophages⁸.

The binding of IL-1 to its receptor results in several inflammatory effects, including leukocyte extravasation, protease, and prostaglandin production, and T-cell activation. Long-term inflammation is harmful to surrounding tissues and must be controlled in order to reduce collateral tissue damage¹⁵.

Secreted IL-1RA inhibits IL-1 receptor binding in a competitive manner, while intracellular IL-1RA not only inhibits IL-1 binding but also modulates the effects of IL-1 beyond the receptor⁹.

Figure 2. Determination of the diagnostic sensitivity and specificity of serum IL-1 and IL-1RA levels in patients diagnosed with Crimean-Congo hemorrhagic fever using ROC curve analysis. ROC: receiver-operating characteristic curve.



MAS emerges as a result of a fulminant cytokine storm and is associated with pancytopenia, tissue hemophagocytosis, hepatic function disorder, coagulopathy, and/or central nervous system dysfunction. MAS is a cause of fatal multiple organ dysfunction syndrome, which generally emerges as a complication of infection, malignancies, and autoimmune disorders¹⁶.

Intensive care requirements were developed in 10 of our patients with CCHF during follow-up. Patients with thrombocytopenia, leukopenia, blurred consciousness, hepatic enzyme elevation, and hemorrhage problems were followed up as MAS. Mortality rates as high as 60% have been reported in adult MAS in some studies^{17,18}. All the cases that developed MAS in this study were fatal. Serum IL-1 levels in the CCHF patients were significantly higher than those in the healthy control group. They were also significantly higher in the CCHF patients with severe manifestations compared to those in the moderate disease group. Moreover, IL-1 was significantly higher in the exitus CCHF patients than among the survivors.

Since IL-1RA prevents proinflammatory signals and blocks the effects of IL-1 by bindings to IL-1 receptors, it is a natural anti-inflammatory marker that should be present at high levels in the body¹⁵. In the present study, IL-1RA levels were statistically significantly higher in the CCHF patients than in the healthy control group. In addition, IL-1RA levels were significantly higher in the patients with manifestations of MAS and in the exitus patients compared to the surviving patients.

Significant IL-1 and IL-1RA elevation in patients with CCHF may be interpreted as indicating intense inflammatory/anti-inflammatory warfare.

Inflammation is thought to be very severe in patients with severe CCHF manifestations, and the release of natural IL-1RA increases in order to cope with the inflammation resulting from cytokine release. The increase in IL-1RA levels, in addition to IL-1 in exitus patients developing MAS, suggests that it may be beneficial to support these patients by means of external IL-1RA therapy.

Studies¹⁹⁻²¹ have documented that IL-1 plays a critical role in the pathogenesis of acute and chronic inflammation. IL-1 receptor blockage is one of the strategies currently employed in the treatment of conditions deriving from IL-1²².

IL-1RA has been used in the antagonization of IL-1, with its important role in cytokine storm syndrome²³.

IL1RA levels have been investigated in various infectious diseases and have been found to be high^{24,25}.

IL-1RA elevation has been linked to fatal cases of human Ebola virus (EBOV) infection. It has been suggested²⁶ that elevated IL-1RA may contribute to host protection against EBOV infection, possibly by suppressing an overactive proinflammatory immune response as a last-ditch effort.

IL-1 elevation is regarded as an early diagnostic marker in sepsis, and increasing levels may serve as a biomarker allowing septic patients to be identified among poor prognostic markers²⁷.

Elevated IL-1RA has also been shown^{28,29} to be associated with high survival rates following septic shock. Another study³⁰ described high IL-1RA levels as a marker of fatal sepsis.

Considering the cycle from these two distinct perspectives, IL-1RA levels rise significantly during the hottest part of the inflammatory war but may not reach sufficiently high levels actually to win that war in some cases. We proposed this idea in the context of patients with CCHF. Further confirmatory studies are, of course, required. This requires urgent investigation, especially in cases that develop severe MAS, and prompt action should be taken for external support if necessary.

Higher IL-1RA levels have been reported³¹ in severe COVID-19 cases compared to patients with milder manifestations. Another study³² reported significantly higher IL-1RA levels in COVID-19 patients who developed MAS compared to cases without MAS.

Suppression of members of the proinflammatory IL-1 family has been shown¹⁴ to exhibit a therapeutic effect in several inflammatory diseases, also including viral infections.

A previous study³³ showed improved pulmonary functions and a decreased risk of mortality in COVID-19 patients treated with IL-1R drugs and developing MAS compared to patients who were not given IL-1RA medications.

Another study³⁴ showed that treatment with IL-1RA drugs can prevent hemodynamic alterations, septic shock, and organ infection by exhibiting novel therapeutic effectiveness on COVID-19.

Similarly, the high levels of IL-1 and IL-1RA in CCHF patients, especially in patients with MAS and in fatal cases, suggest that the fight against inflammation is quite severe. It can be thought that although the body increases the level of IL1RA in suppressing the inflammation caused by IL1, it cannot reach a sufficient level. We think that the idea of increasing the effect of IL1 receptor

antagonists in the fight against patients with MAS will shed light on the studies to be done in CCHF.

Laboratory changes that can be seen in the course of CCHF disease include anemia, leukopenia, thrombocytopenia, increase in AST and ALT levels, prolongation of PT and aPTT times, increase in fibrin degradation products and decrease in fibrinogen³⁵. In addition, leukocytosis can be seen as an indicator of poor prognosis^{2,36}.

In our study, the laboratory parameters of the patients who showed signs of serious disease were at a level that supports these studies^{2,35,36}. A significant association was observed with disease severity. AST, ALT, CK, LDH, PT, and PTT values were significantly higher in severe disease manifestations. Thrombocytopenia and low fibrinogen levels were also detected in these patients. While WBC values were low in both patient groups with moderate and severe clinical courses, the WBC values of the patients who died were higher than the surviving patients.

In addition, IL-1 and IL-1RA exhibited significant positive correlations with the highest AST, ALT, CK, LDH, PT, and PTT values, and significant negative correlations with low platelet and fibrinogen levels.

A significant positive correlation was determined between IL-1 and the highest AST, highest ALT, highest LDH, highest CK, longest PT, longest PTT, and IL-1RA levels, while a significant negative correlation was observed with the lowest platelet count and lowest fibrinogen.

IL-1RA exhibited a significant positive correlation with the highest AST, highest ALT, highest LDH, highest CK, longest PT, and longest PTT values and a significant moderate negative correlation with the lowest platelet count and lowest fibrinogen level.

The results of this study also suggested that high IL-1 and IL-1RA levels may be regarded as poor prognostic laboratory parameters in terms of showing the severity of inflammatory warfare.

At a cut-off value of 210.85 ng/L, serum IL-1RA levels differentiated cases of CCHF from healthy individuals with 97% sensitivity and 95% specificity (AUC=0.995, $p<0.001$, 95% confidence interval 0.988-1.00). In addition, at a cut-off value of 107.67 ng/L, IL-1 levels differentiated cases of CCHF from healthy individuals with 95% sensitivity and 90% specificity (AUC=0.963, $p<0.001$, 95% confidence interval 0.925-1.00) (Figure 2). This suggests that IL-1 and IL1RA levels may be effective in determining the disease course in patients with CCHF.

Supportive therapy represents the primary treatment in CCHF. The antiviral agent ribavirin has also been used³⁷ in human CCHF cases, although the clinical evidence is inconsistent, and this led to debates among clinicians. Novel antiviral therapeutics against CCHF now need to be developed on an urgent basis in order to manage the growing threat to public health posed by this highly infectious pathogen.

Limitations

The principal limitation of this study was the small sample size. Further studies involving larger patient numbers are now needed to confirm the role of IL-1-RA in treating CCHF patients.

Conclusions

It is, therefore, of great importance to determine the mechanism responsible for the pathology and focus on treating it accordingly. Significant elevation in IL-1, which we think may constitute one of the cytokines responsible for the clinical manifestation in patients with CCHF, was determined in the present study. We also think that an increase in IL-1RA levels can be a useful guide in determining the severity of inflammatory warfare. New supportive studies on this subject are now needed. We believe that the effects of IL-1 can be suppressed by increasing the level of IL-1RA in the body to change the course of severe inflammation, especially in patients with MAS. In this case, as in many other diseases, we found that external IL-1RA support may be beneficial to reduce the effects of inflammation.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Informed Consent

Consent was obtained from the families of the patients participating in the study.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ataturk University Medical Faculty Ethical Committee (No. B.30.2. Ata.0.01.00/209).

Authors' Contributions

Each Author has contributed substantially to the research, preparation, and production of the paper and approves of its submission to the Journal.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

- 1) Whitehouse CA. Crimean-Congo haemorrhagic fever. *Antiviral Res* 2004; 64: 145-160.
- 2) Swanepoel R, Gill DE, Shepherd AJ, Leman PA, Mynhardt JH, Harvey S. The clinical pathology of Crimean-Congo Hemorrhagic fever. *Rev Infect Dis* 1989; 11: 794-800.
- 3) Çeviker SA, Günel Ö, Kılıç SS. Retrospective Analysis of Crimean-Congo Haemorrhagic Fever Cases. *Klinik Journal* 2019; 32: 275-280.
- 4) Rodriguez SE, Hawman DW, Sorvillo TE, O'Neal TJ, Bird BH, Luis L, Rodriguez LL, Bergeron E, Nichol ST, Montgomery JM, Spiropoulou CF, Spengler JR. Immunobiology of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2022; 199: 105244.
- 5) Parlak E, Ertürk A, Çağ Y, Sebin E, Gümüştöre M. The effect of inflammatory cytokines and the level of vitamin D on prognosis in Crimean-Congo hemorrhagic fever. *Int J Clin Exp Med* 2015; 8: 18302-18310.
- 6) Papa A, Tsergouli K, Çağlayık DY, Bino S, Como N, Uyar Y, Korukluoğlu G. Cytokines as biomarkers of Crimean-Congo hemorrhagic fever. *J Med Virol* 2016; 88: 21-27.
- 7) Kılıçturgay K. Sitokinler. In: *İmmünoloji*. Nobel Tıp Kitabevi, İstanbul 2000; 175-215.
- 8) Fearon WF, Fearon DT. Inflammation and Cardiovascular Disease Role of the Interleukin-1 Receptor Antagonist. *Circulation* 2008; 117: 2577-2579.
- 9) Klueh U, Antar O, Qiao Y, Kreutzer, DL. Role of Interleukin-1/Interleukin-1 Receptor Antagonist Family of Cytokines in Long-Term Continuous Glucose Monitoring In Vivo. *J Diabetes Sci Technol* 2013; 7: 1538-1546.
- 10) Que Y, Hu C, Wan K, Hu P, Wang R, Luo J, Li T, Ping R, Hu Q, Sun Y, Wu X, Tu L, Du Y, Chang C, Xu G. Cytokine release syndrome in COVID-19: a major mechanism of morbidity and mortality. *Int Rev Immunol* 2022; 41: 217-230.
- 11) Topçu AW, Söyletir G, Doğanay M. *İnfeksiyon Hastalıkları ve Mikrobiyolojisi*. Nobel Tıp Kitapları 2008; 1251-1264.
- 12) Ardalan MR, Tubbs RS, Chinikar S, Shoja MM. Crimean-Congo hemorrhagic fever presenting as thrombotic microangiopathy and acute renal failure. *Nephrol Dial Transplant* 2006; 21: 2304-2307.
- 13) Abbate A, Toldo S, Marchetti C, Kron J, VanTassel BW, Dinarello CA. Interleukin-1 and the Inflammation as Therapeutic Targets in Cardiovascular Disease. *Circ Res* 2020; 126: 1260-1280.
- 14) Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I, Kritas S. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020; 34: 327-331.
- 15) Luotola K. IL-1 Receptor Antagonist (IL-1Ra) Levels and Management of Metabolic Disorders. *Nutrients* 2022; 14: 3422.
- 16) Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial. *Crit Care Med* 2016; 44: 275-281.
- 17) Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, Fardet L. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med* 2014; 127: 1118-1125.
- 18) Shabbir M, Lucas J, Lazarchick J, Shirai K. Secondary hemophagocytic syndrome in adults: a case series of 18 patients in a single institution and a review of literature. *Hematol Oncol* 2011; 29: 100-106.
- 19) Arend WP. The balance between IL-1 and IL-1Ra in disease. *Cytokine Growth Factor Rev* 2002; 13: 323-340.
- 20) Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat Rev Immunol* 2005; 5: 629-640.
- 21) Sims JE, Smith DE. The IL-1 family: regulators of immunity. *Nat Rev Immunol* 2010; 10: 89-102.
- 22) Klementiev B, Li S, Korshunova I, Dmytriyeva O, Pankratova S, Walmod PS, Kjær LK, Dahllöf MS, Lundh M, Christensen DP, Mandrup-Poulsen T, Bock E, Berezin V. Anti-inflammatory properties of a novel peptide interleukin 1 receptor antagonist. *J Neuroinflammation* 2014; 11: 27.
- 23) Vaninov N. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol* 2020; 20: 277.
- 24) Kreuzer KA, Dayer JM, Rockstroh JK, Sauerbruch T, Spengler U. The IL-1 system in HIV infection: peripheral concentrations of IL-1beta, IL-1 receptor antagonist and soluble IL-1 receptor type II. *Clin Exp Immunol* 1997; 109: 54-58.
- 25) de-Oliveira-Pinto LM, Gandini M, Freitas LP, Siqueira MM, Marinho CF, Setúbal S, Kubelka CF, Cruz OG, de Oliveira SA. Profile of circulating levels of IL-1Ra, CXCL10/IP-10, CCL4/MIP-1beta

- and CCL2/MCP-1 in dengue fever and parvovirus. *Mem Inst Oswaldo Cruz* 2012; 107: 48-56.
- 26) Batorski LH, Halfmann P, Marzi A, Lopes TJS, Neumann G, Feldmann H, Kawaoka Y. Loss of Interleukin 1 Receptor Antagonist Enhances Susceptibility to Ebola Virus Infection. *J Infect Dis* 2015; 212: 329-335.
- 27) Ge Y, Huang M, Yaob Y. Recent advances in the biology of IL-1 family cytokines and their potential roles in development of sepsis. *Cytokine Growth Factor Rev* 2019; 45: 24-34.
- 28) Arnalich F, Lopez-Maderuelo D, Codoceo R, Lopez J, Garrido LM, Capiscol C, Fernandez-Capitán C, Madero R, Montiel C. Interleukin-1 receptor antagonist gene polymorphism and mortality in patients with severe sepsis. *Clin Exp Immunol* 2002; 127: 331-336.
- 29) Meyer NJ, Ferguson JF, Feng R, Wang F, Patel PN, Li M, Xue C, Qu L, Liu Y, Boyd JH, Russell JA, Christie JD, Walley KR, Reilly MP. A functional synonymous coding variant in the IL-1RN gene is associated with survival in septic shock. *Am J Respir Crit Care Med* 2014; 190: 656-664.
- 30) Endo S, Inada K, Yamada Y, Kasai T, Takakawa T, Nakae H, Kamei Y, Shimamura T, Suzuki T, Taniguchi S, Yoshida M. Plasma levels of interleukin-1 receptor antagonist (IL-1ra) and severity of illness in patients with burns. *J Med* 1996; 27: 57-71.
- 31) Zhao Y, Qin L, Zhang P, Li K 1, Liang L, Sun J, Xu B, Dai Y, Li X, Zhang C, Peng Y, Feng Y, Li A, Hu Z, Xiang H, Ogg G, Ho LP, McMichael A, Jin R, Knight JC, Dong T, Zhang Y. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. *JCI Insight* 2020; 5: e139834.
- 32) Kerget B, Kerget F, Aksakal A, Aşkın S, Sağlam L, Akgün M. Evaluation of alpha defensin, IL-1 receptor antagonist, and IL-18 levels in COVID-19 patients with macrophage activation syndrome and acute respiratory distress syndrome. *J Med Virol* 2021; 93: 2090-2098.
- 33) Kooistra EJ, Waalders NJB, Grondman I, Jansen NAF, Nooijer AH, Netea MG, Veerdonk FL, Ewalds E, Hoeven JG, Kox M, Pickkers P. RCI-COVID-19 Study Group. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care* 2020; 24: 688.
- 34) Conti P, Caraffa A, Gallenga CE, Ross R, Kritas SK, Frydas B, Younes A, Emidio PD, Ronconi G, Toniato E. IL-1 induces thromboxane-A₂(TxA₂) in COVID-19 causing inflammation and micro-thrombi: inhibitory effect of the IL-1 receptor antagonist (IL-1Ra). *J Biol Regul Homeost Agents* 2020; 34: 1623-1627.
- 35) Tartar AS, Akbulut A, Demirdağ K, Balin ŞÖ. Crimean-Congo Hemorrhagic Fever in Differential Diagnosis During the Coronavirus Disease-2019 Pandemic. *Turkiye Parazitoloj Derg* 2022; 46: 50-53.
- 36) Ahmeti S, Berisha L, Halili B, Ahmeti F, Possel RV, Thomé-Bolduan C, Michel A, Priesnitz S, Reisinger EC, Günther S, Krüger A, Sherifi K, Jakupi X, Hemmer CJ, Emmerich P. Crimean Congo hemorrhagic fever, Kosovo, 2013-2016. *Emerg Infect Dis* 2019; 25: 321-324.
- 37) Dai S, Deng F, Wang H, Ning Y. Crimean-Congo Hemorrhagic Fever Virus: Current Advances and Future Prospects of Antiviral Strategies. *Viruses* 2021; 13: 1195.