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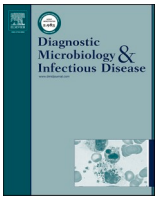

A non-fatal Crimean-Congo hemorrhagic fever virus infection; The balanced cytokine responses on the outcome of the clinical disease

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ABSTRACT

Crimean-Congo Hemorrhagic Fever (CCHF) is a neglected tick-borne viral disease with high pathogenicity and mortality in humans. This study reports clinical, virological, and immunological findings of a non-fatal severe CCHF case with tick-bite history and active melena. Laboratory results showed thrombocytopenia, elevated liver enzymes (AST, ALT), and prolonged aPTT. During the first four days of illness and recovery phase, viral RNA load, anti-CCHFV IgG/IgM levels, and cytokine profiles were analyzed by RT-qPCR and EIA. This enabled assessment of key immune responses against CCHFV. The patient had a high viral load and was seropositive. A marked increase in IFN-γ and IL-10 after day two suggests that the immune system was not only fighting the virus, but also modulating inflammation. This immune balance may contribute to recovery by lowering viral load and limiting tissue damage.

1. Introduction

CCHF is an important tick-borne viral zoonosis with an increasing incidence and mortality rate. The causative agent of the disease, Crimean-Congo Hemorrhagic Fever Virus (CCHFV-*Orthonairovirus haemorrhagiae*), is an orthonairovirus within the *Bunyavirales* order. CCHFV, an RNA virus, possesses a segmented genome with a single-stranded negative polarity [1]. Clinical manifestations of CCHF include hemorrhage, increased vascular permeability, and prolonged high fever, indicative of viral involvement. CCHF typically progresses through four distinct phases: incubation; 1-7 days, pre-hemorrhagic; fever, fatigue, muscle pain, nausea, hemorrhagic; severe bleeding, liver damage, intense inflammation, risk of death, and convalescence; recovery begins 10-20 days post-infection, with symptoms gradually returning to normal [2].

The increasing global burden of CCHF has been linked to several factors, including ecological changes, global warming, expansion of agriculture, and human encroachment into tick-infested habitats. Due to its epidemic potential, lack of specific antiviral therapy, and relatively high case fatality rates, CCHF poses a significant public health challenge. Geographically, CCHF is distributed across more than 30 countries, with significant presence in the Middle East, Asia, Eastern Europe, and Africa. Case fatality ratio of the disease varies between 5 to 40% and this is a puzzling aspect of the clinical picture where the real cause of fatality remains elusive. Since the first cases were identified in 2002, the disease has been most commonly reported in Türkiye, with approximately 1,000 confirmed cases annually and a case fatality ratio of 5% [3]. The pathogenesis of the disease is known to involve not only direct viral effects but also the host immune response. In particular, the uncontrolled release of inflammatory cytokines has emerged as a key determinant of immune dysregulation and tissue damage seen in severe cases. Therefore, evaluating cytokine profiles according to the stages of the disease is of great importance for understanding the pathogenesis and determining potential therapeutic approaches. This report examines the time-dependent changes in inflammatory and regulatory cytokines in a non-fatal CCHFV case, addressing the immune dynamics of CCHFV infection. In this context, the study aims to highlight both the potential prognostic value of immune markers and contribute to the development of future immunotherapeutic strategies.

In this report, a 46-year-old male patient who presented to the

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emergency department of Bezmialem Vakif University Hospital in Istanbul, Türkiye, on day 0 of hospitalization, with a history of a tick-bite six days prior, high fever, and complaints of melena is reported. The patient's coagulation, hemogram, and biochemical parameters, as shown in Table 1, indicated severe thrombocytopenia ($7 \times 10^3/\mu L$), leukopenia, elevated liver enzymes (AST, ALT), and prolonged aPTT. The data obtained suggest that the patient's clinical characteristics and findings are largely consistent with the severe CCHF criteria described by Swanepoel et al. [4]. He was admitted to ICU on day 1 of hospitalization and managed with supportive therapy, including platelet and erythrocyte transfusions and broad-spectrum antibiotics. Ribavirin was not administered. Following a 6-day treatment period, clinical stability was achieved, the patient was transferred to the infectious diseases department for continued care and was discharged in good health 4 days later (Fig. 1).

2. Results

To determine viral kinetics, serum samples from the first 4 days of disease and the convalescent period were tested for CCHFV RNA. RT-qPCR analysis [5] showed a high viral load ($\sim 10^{10}$ copies/mL) on day 1, which declined progressively, reaching minimal levels during convalescence (Fig. 2A). Humoral immune responses were assessed by measuring anti-CCHFV antibodies using CCHFV rNP-based IgG/IgM EIA tests. Humoral immune profiling showed early anti-CCHFV IgM positivity on day-1, peaking on day-3, while IgG seroconversion occurred only during the recovery phase (Fig. 2B-C).

In this case, cytokine levels were measured in daily serum samples of the non-fatal CCHF patient, twice at different times, to assess the prominent immune responses against the infection. The cytokine and chemokine concentrations in the serially collected serum samples were tested using the commercial Q-Plex™ Array Human Cytokine Stripwells (Quansys Biosciences, 16-plex, Ref#10333HU) ELISA kit, following the manufacturer's instructions. These cytokines include interleukin-1α (IL-1α), IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8 (CXCL8), IL-10, IL-12p70, IL-13, IL-15, IL-17A, IL-23, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and TNF-β. The analysis showed that the IL-12p70 level was below the detection threshold, and the cytokines IL-1α, IL-1β, IL-13, IL-17A, IL-23, and TNF-β showed no statistically significant differences compared to the control group (Undetected and non-significant data were not shown). The analysis revealed that IL-2 levels were significantly elevated during the first three days (Fig. 3). Also, other cytokines/chemokines, such as TNF-α, IL-4, IL-6, IL-8, and IL-15 were increased significantly from day-1 onwards. Notably, during the convalescent period, while others returned to baseline level, only IL-4 remained elevated. Moreover, the levels of IL-10 and IFN-γ showed a strikingly increased concentrations from day-2 onward, which was particularly noteworthy.

3. Discussion

Here, in order to better understand the potential role of inflammatory responses in controlling viral pathogenesis, we describe a balanced cytokine response in a non-fatal CCHF patient, where the CCHF viral load decreased over time depending on the day of illness, severity, and outcome, and CCHFV infection-related seropositivity was detected. One of the most striking observations of the study was the remarkable concentrations of IFN-γ and IL-10 reached early on during the clinical phase. The prominence of this seemingly counter effective cytokines was substantial and thus could not be disregarded.

Crimean-Congo Hemorrhagic Fever (CCHF) is one of the viral hemorrhagic fevers with high mortality rates, accompanied by severe inflammatory responses. The limited current treatment options and the absence of an effective vaccine make understanding the immune response and pathogenesis mechanisms of CCHFV crucial. The increasingly recognized role of the host immune response in the pathogenesis of the disease, especially the influence of cytokine profiles on the course of the disease, has become a central point of focus. Cytokine analyses conducted in a non-fatal CCHF case examined in this study demonstrate that the balanced activation of the immune system might be critically important for controlling viral load and aiding the recovery process.

CCHFV primarily targets vascular endothelial cells and hepatocytes [3]. The endothelial damage observed in CCHFV pathogenesis is a result of several mechanisms, including the direct viral effects through viral replication in endothelial cells and/or the indirect effects of excessive and uncontrolled inflammatory responses triggered by the host, such as cytokine/chemokine storms [6]. Studies conducted in immunocompromised animal models have shown that CCHFV infections trigger robust pro- and anti-inflammatory cytokine responses, including TNF-α, IL-6, IL-10, and IFN-γ [7,8]. Earlier, blocking TNF-α signaling, either by knocking out the TNF-α receptor or using TNF-α neutralizing antibodies, provided a survival advantage in CCHFV-infected mouse models [9]. Studies conducted in Türkiye and Albania also support this finding, reporting significantly higher TNF-α levels in severe and fatal cases [10,11]. However, the prognostic value of IL-6 varies across studies, with some indicating similar levels in both mild and severe cases, while others report a significant increase in fatal cases. Moreover, IL-6 and TNF-α are thought to increase endothelial permeability through the protein kinase C pathway, leading to alterations in tight junction distribution and disruptions in intracellular actin organization [12,13]. Specifically, it has been emphasized that excessive activation of monocytes, as a result of high TNF-α and IL-6 production, leads to hemophagocytosis, which correlates with the severity of hemorrhagic fevers [14]. Additionally, the role of IL-8 in CCHF pathogenesis is characterized by neutrophil infiltration observed in infected individuals and elevated concentrations in fatal CCHF cases [15]. In the patient studied here, an early increase in IL-6, IL-8, and TNF-α levels was observed. It is thought that high levels of these cytokines may impair endothelial cell

Table 1
Clinical laboratory findings of the patient. Data are mean (range) of values. WBC, leukocyte; PLT, platelet; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; Hgb, hemoglobin. *dph*, day post-hospitalization; *Conv.* convalescent sample taken at 25 days post-discharge; *NC*, reference values range.

	1dph	2dph	3dph	4dph	Conv.	NC	Swanepoel's Criteria for Severe CCHF[4]
WBC ($10^3/\mu L$)	6,15 (5,88-6,41)	4,36 (3,85-4,79)	4,68 (4,10-5,42)	7,22 (9,05-5,97)	11,49	**4,6-10,2**	**≥10**
PLT ($10^3/\mu L$)	12 (7-16)	25 (18-37)	26 (22-39)	38 (31-52)	351	**142-424**	**<20**
aPTT (s)	45,4 (45,3-45,4)	44,6 (41,8-49,8)	47,4	47,8		**20-32,1**	**≥60**
Fibrinogen (mg/dL)	134,4	193,6	221,2	288,7		**200-400**	**≥110**
AST(U/L)	489	584	2296	3218	22	**0-34**	**≥200**
ALT(U/L)	241	290	971	1222	26	**10-49**	**≥150**
CRP (mg/L)	47,99	45,22	57,16	61,22	<0,20	**0-5**	
Hgb (g/dL)	11,65 (10,8-12,5)	7,78 (7,1-8,2)	8,68 (8,5-9,0)	7,8 (7,5-8,1)	11,9	**13-17,5**	

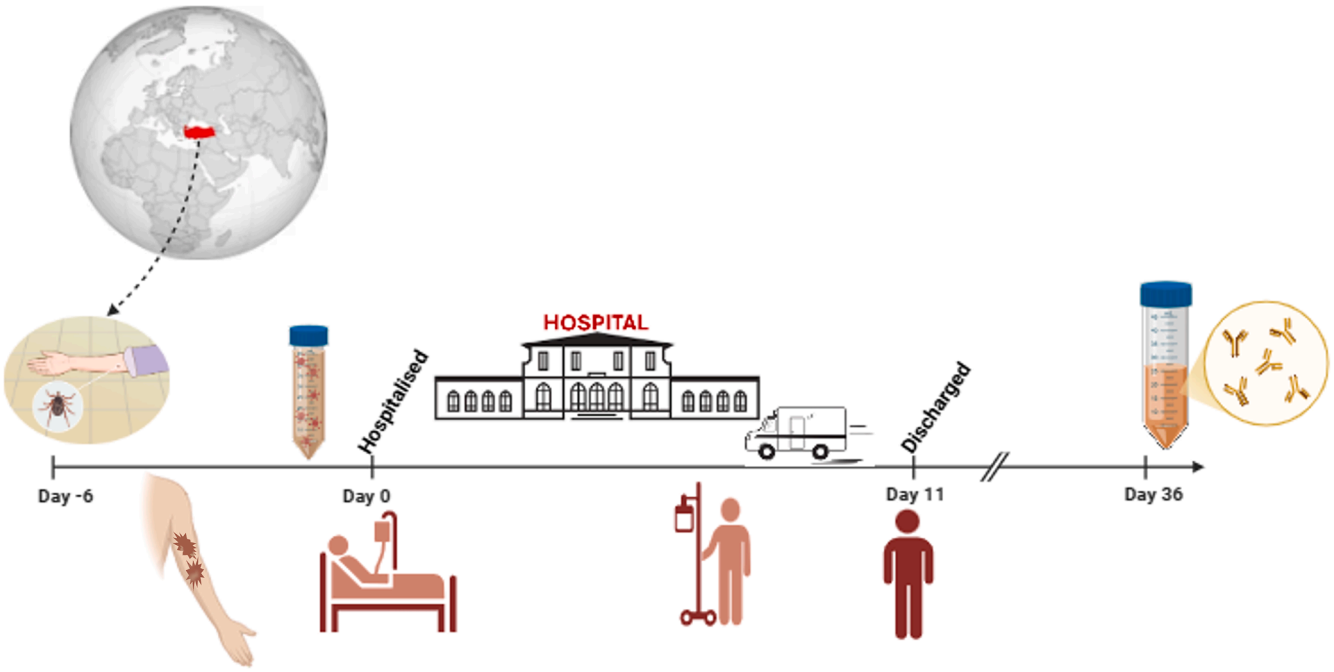

Fig. 1. Clinical timeline of the CCHF case. In Türkiye, a 46-year-old male patient with a history of a tick bite 6 days earlier (day 6) presented to the hospital with high fever and ecchymoses at the venous access sites (day 0). The patient, who had active melena and a platelet count of 7×10^3/μL, was admitted to the intensive care unit with a suspected diagnosis of CCHF (day 1). After six days of intensive care treatment, he was transferred to the infectious diseases department and was discharged in good health following a 4 day observation period (day 11). Figure created in BioRender.com (https://biorender.com/).

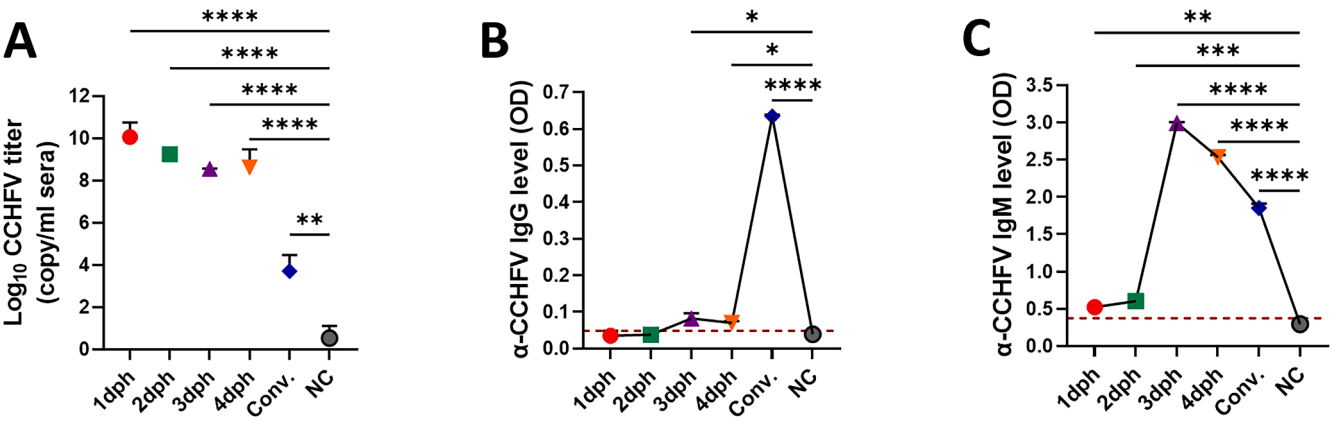

Fig. 2. Daily kinetics of CCHF viral RNA, anti-CCHFV IgG and anti-CCHFV IgM in the CCHF case. ***A.*** Viral load was measured as viral RNA copy number/ml sera by RT-qPCR. The amount of viral RNA was determined using *Ct* values based on a standard curve generated from known concentrations of CCHFV-NP plasmid DNA. ***B-C.*** IgG/M antibodies to CCHFV were detected by a CCHFV recombinant NP based IgG/M EIA. EIA plates were coated with 1μg/well CCHFV rNP and analyzed using 100-fold diluted CCHF patient or healthy human sera and 1/10,000 dilution of HRP-conjugated goat anti-human IgG (Bio-Rad Laboratories, 5172-2504) or HRP-conjugated goat anti-human IgM (Abcam, ab97205). Cutoff values for IgG and IgM are indicated by a dotted line. The cutoff value that determined IgG/M positivity or negativity was calculated as the average plus two standard deviations of serum samples collected from the person with no history of CCHFV infection. All data are presented as standard error about the mean and analyzed by one-way ANOVA with the Bonferroni post-test, compared with uninfected negative control; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. *dph*, day post-hospitalization; *Conv.,* convalescent sample taken at 25 days post-discharge; *NC*, negative control grup.

stability and increase vascular permeability, a view that is also supported by the current literature [16]. Elevated levels of IL-6, IL-8, and IL-10, as well as poor outcomes, have also been reported in other viral hemorrhagic fevers, such as Ebola, Rift Valley, and Lassa fevers [17,18]. As observed in this case, the early elevation of IL-6 and IL-8 similarly suggests that these cytokines may have potential as biomarkers for early diagnosis and prognosis of the disease [19]. Furthermore, the similarly marked increase in IL-6 and IL-8 levels has also been observed in other viral hemorrhagic fevers, which is noteworthy [20].

IL-2 plays a crucial role in activating natural killer (NK) cells, $CD8^+$ T cells, and other lymphocyte subgroups [21]. The significant elevation of IL-2 levels during the first three days of the disease may be a strong indicator of early T cell activation. This increase may demonstrates the rapid engagement of cellular immunity, which plays a vital role in the early phase of antiviral defense, and might suggest that the transition between innate and adaptive immunity occurred in a timely and effective manner. When considered in conjunction with the rise in IFN-γ, this finding supports the activation of the Th1 cell response and the suppression of viral replication. Similarly, the increase in IL-15 levels, particularly in terms of NK cell activation and the long-term $CD8^+$ T cell

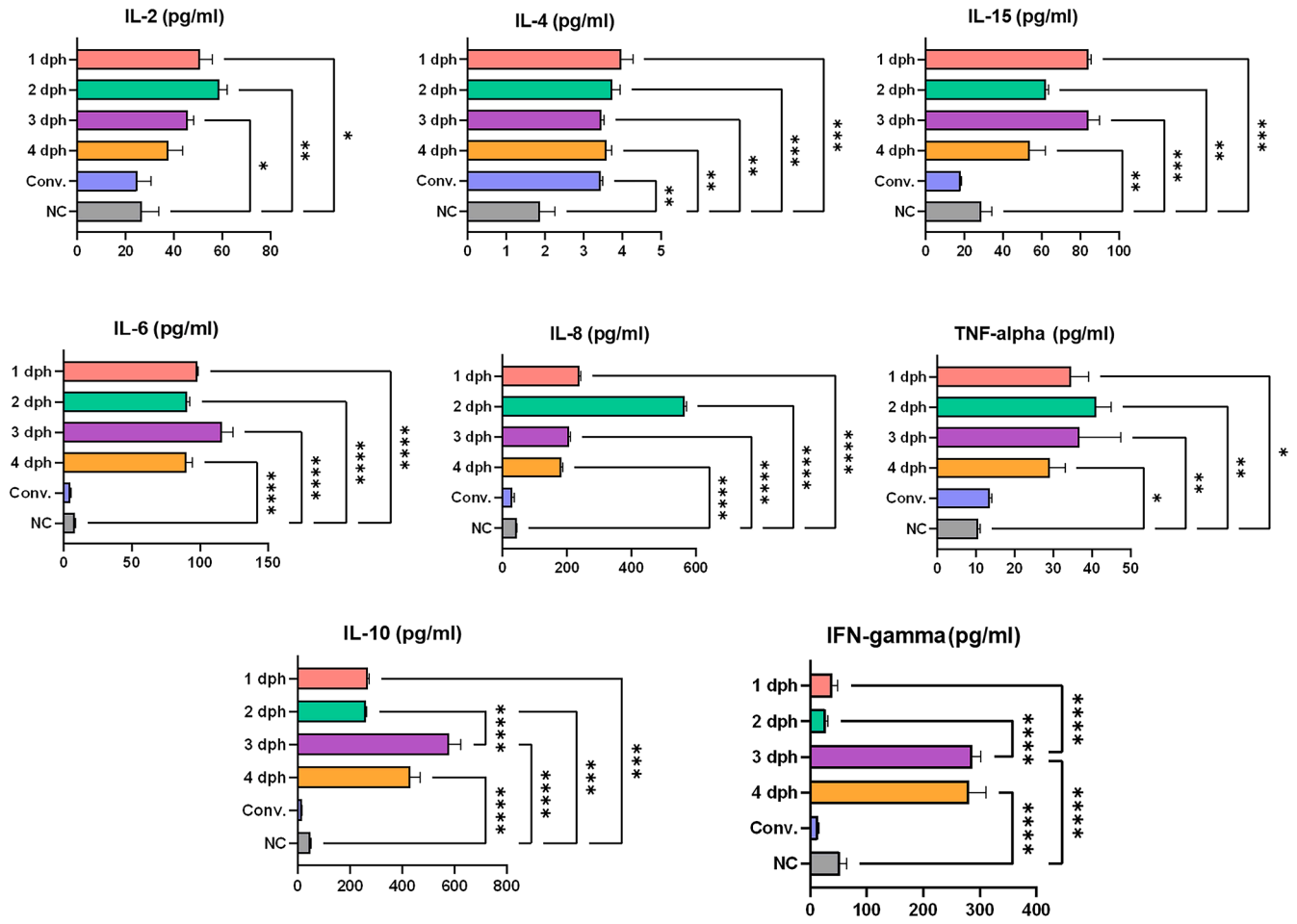

Fig. 3. Daily kinetics of serum cytokine/chemokines concentrations in the CCHF case. Quantitative levels of cytokines/chemokines were measured by 16-plex ELISA. Data were analyzed between groups by the one-way ANOVA followed by the with the Bonferroni's correction test. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. Undetected and non-significant data were not shown. *dph*, day post-hospitalization; *Conv.,* convalescent sample taken at 25 days post-discharge; *NC*, negative control grup.

memory, is an important marker [22]. Literature reports that IL-15 plays a bridging role in both innate and adaptive immunity and is crucial during CCHFV infections [23]. In this context, the concurrent elevation of IL-2 and IL-15 supports the notion that cellular immunity might have been strongly activated during the initial phase of the antiviral response.

The sustained high levels of IL-4 during the convalescent phase may indicate a shift of the immune response toward a different direction. IL-4, a cytokine that supports Th2 responses and enhances humoral immunity, suggests that the immune system has transitioned toward Th2 dominance during the suppression of inflammation and tissue repair [24]. The continued expression of IL-4 during the recovery phase may be seen as a regulatory mechanism that contributes to tissue repair and the resolution of inflammation [25,26].

As an anti-inflammatory cytokine, IL-10 plays a critical role in preventing the excessive activation of inflammation and protecting tissues. Studies conducted in CCHF and other viral hemorrhagic fever, such as Hantavirus fevers, have found that serum IL-10 levels are elevated and correlate with viral load and the clinical course of the disease [27]. Literature has shown that delayed and inadequate activation of IL-10 is associated with fatal CCHFV cases [28]. In this case, the significant increase in IL-10 levels, particularly from the second day onward, suggests that the immune system developed a response to balance inflammation, thereby limiting immunopathological damage. Another important cytokine, IFN-γ, is known for its role in inhibiting viral replication as a component of the Th1 cell response [29]. IFN-γ also plays an important role as a major proliferator of cytotoxic T cells [30]. Studies in mice lacking IFN-α/β receptors have demonstrated that an early rise in IFN-γ levels supports survival [8]. It has also been reported that fatal CCHF patients exhibit markedly elevated concentrations of IFN-γ, TNF-α, and IL-10 [28]. In this study, the increase in IFN-γ levels from the second day onward indicates that innate immunity was activated and contributed to viral control. We interpret the significant increases in IFN-γ and IL-10 levels after the second day as the indication that immune system is both effectively combating the virus and attempting to balance the excessive inflammatory responses. This balance may ensure the patient's recovery by reducing viral load while simultaneously preventing or limiting tissue damage.

In conclusion, we interpret the significant increases in IFN-γ and IL-10 levels after the second day of the disease as the indication that immune system is both effectively combating the virus and attempting to balance the excessive inflammatory responses. This balance may ensure the patient's recovery by reducing viral load while simultaneously preventing or limiting tissue damage. Thus, immune dynamics contribute to the recovery process and to the outcome of the non-fatal CCHFV infection. Undoubtedly, further clarification of the effects of these cytokines and their potential roles in CCHFV pathogenesis is essential. In this context, comprehensive studies are necessary to better understand the disease mechanisms and to develop potential therapeutic strategies.

Author statement

As corresponding author for the above-named manuscript I declare and take legal responsibility for stating that each person named as an author of the manuscript:

- has made substantial contributions to the conception or design of the work; or to the acquisition, analysis, or interpretation of data for the work; AND
- has drafted the work or revised it critically for important intellectual content; AND
- has approved the final version to be published; AND
- agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

Data is available from the corresponding author on reasonable request; code availability is not applicable.

CRediT authorship contribution statement

Aysegul Pirincal: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Nesibe Selma Guler Cetin:** Investigation, Conceptualization. **Bilge Sumbul:** Investigation. **Hayrettin Daskaya:** Investigation. **Bulent Durdu:** Investigation. **Mehmet Z. Doymaz:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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