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*Original Article*

# Evaluation of cytokines as Th1/Th2 markers in pathogenesis of children with Crimean-Congo hemorrhagic fever

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**Abstract:** Cytokine networks play a key role in the pathogenesis of the disease in Crimean-Congo Hemorrhagic Fever (CCHF) patients. Therefore, our aim was to study the effects of cytokine levels on the pathogenesis and severity of the disease in children with CCHF. Fifty-two patients diagnosed with CCHF and 34 healthy controls (HC) were included in the study. The patients with CCHF were divided into two groups (severe and non-severe). The levels of the Interleukin-10 (IL-10), IL-12, IL-6, Endothelin-1 (ET-1) and tumor necrosis factor-α (TNF-α) were measured in all groups. IL-12 levels did not show any difference between the CCHF and HC groups and among the severe, non-severe and HC groups. IL-10 and ET-1 levels were significantly higher in the severe group when compared to the non-severe group and the HC group. Moreover, IL-10 and ET-1 levels were significantly higher in the non-severe group when compared to the HC group. In terms of IL-6 and TNF-α levels, there was no difference between the severe and non-severe groups while the said levels were significantly higher in the severe group when compared to the HC group. The results of the present study showing significantly higher IL-10 and ET-1 levels in the severe group suggest that Th2-mediated humoral immunity is more effective in the pathogenesis and severity of CCHF in children.

**Keywords:** Crimean-Congo hemorrhagic fever, IL-10, IL-12, ET-1, Th2

## Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a viral disease that infects humans via Hyalomma ticks or direct contact with the blood of infected animals (including domestic animals) and CCHF viruse belongs to the genus Nairovirus in the family Bunyaviridae. It is a viral hemorrhagic fever (VHF) and causes the severe human disease CCHF. Patients' symptoms include fever, generalized pain, myalgia, fatigue, nausea, or vomiting, while severe cases exhibit hemorrhagic manifestations (epistaxis, hematemesis, melena, petechiae, or ecchymosis) and increased vascular permeability accompanied by severe thrombocytopenia and shock [1].

The pathogenesis of CCHF is poorly understood. The endothelium is supposedly a major target in CCHF, as indicated by clinical features, such as hemorrhage and increased vascular permeability [2]. Although the parameters of host factors have not been fully evaluated yet, recently the role of soluble mediators of the immune system, including inflammatory cytokines, are implicated in the pathogenesis of the disease [3-5]. Recent studies on cytokine profiles in CCHF patients suggest that pro-inflammatory and anti-inflammatory cytokines play a role in the pathogenesis and severity of the disease [4-7]. Elevated levels of Endothelin-1 (ET-1) synthesized from the endothelial cell is associated with the endothelial damage [8-10]. The role of Interleukin-10 (IL-10) in CCHF disease severity is also unclear. In an Albanian study, IL-10 level was high in a patient dying because of the disease [11]. However, in a Turkish study, IL-10 was found to be negatively correlated with disseminated intravascular coagulopathy [6]. Elevated serum levels of the cytokines IL-6,

**Table 1.** Demographic, clinical and laboratory characteristics of patients with CCHF

| Characteristics | Severe group (n=25) | Non-severe group (n=27) |
|---|---|---|
| Age (years) | 12.7±3.1 | 12.0±4.1 |
| Gender (male/female) | 12/13 | 19/8 |
| Days from symptoms to admission | 5.4 (2.0-12.0) | 5.5 (0.0-15.0) |
| Hospitalization days | 10.6±3.8 | 8.6±2.2* |
| Symptoms (n, %) and Clinical findings (n, %) | | |
| Myalgia | 5 (21%) | 0 (0%)* |
| Headache | 11 (44%) | 6 (23%) |
| Nausea or vomiting | 20 (80%) | 12 (44%) |
| Fever (>38°C) | 9 (36%) | 7 (26%) |
| Tonsillopharyngitis | 13 (52%) | 11 (41%) |
| Fatigue/weakness | 10 (42%) | 3 (12%)* |
| Diarrhea | 8 (33%) | 3 (11%) |
| Abdominal pain | 7 (29%) | 3 (11%) |
| Bleeding (Epistaxis or Haemoptysis) | 2 (8%) | 0 (0%) |
| Melaena | 2 (8%) | 0 (0%) |
| Petechiae, purpura or ecchymosis | 6 (24%) | 2 (7%) |
| Facial-conjunctival hyperemia | 11 (46%) | 1 (4%)** |
| Hepatomegaly | 3 (13%) | 1 (4%) |
| Splenomegaly | 2 (8%) | 1 (4%) |
| Somnolence | 2 (8%) | 0 (0%) |
| Selected laboratory findings | | |
| PLT ($x10^9$/L) | 69.4 (8.0-177.0) | 131.2 (69.0-203.0)** |
| WBC ($x10^9$/L) | 2.9 (0.7-14.0) | 3.3 (1.5-7.0) |
| Hb (g/dL) | 13.3 (11.8-16.8) | 13.5 (8.3-15.8) |
| PT (s) | 14.9 (9.6-26.1) | 13.7 (9.6-23.0) |
| aPTT (s) | 42.8 (23.8-65.1) | 35.6 (16.0-49.7)* |
| INR | 1.4 (0.9-2.3) | 1.2 (0.9-2.1) |
| AST (IU/L) | 190.6 (26-557.0) | 59.9 (18.0-166.0)** |
| ALT (IU/L) | 91.1 (12.0-329.0) | 27.1 (9.0-96.0)** |
| LDH (IU/L) | 582.0 (140.0-1435.0) | 272.7 (128.0-454.0)** |
| D-dimer ($x10^3$) | 7.7 (0.6-39.8) | 1.3 (0.1-5.1)* |
| Fibrinogen (mg/dL) | 212.3 (96.0-261.0) | 246.9 (136.0-303.0)* |

PLT, platelet; WBC, white blood cell; Hb, hemoglobin; PT, prothrombin time; s, second; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase. *$p<0.05$, **$p<0.001$.

ET-1 and tumour necrosis factor-α (TNF-α) were correlated with CCHF disease severity in several patient studies [4, 6, 10, 12].

Therefore, the aim of the present study was to identify the possible role of IL-6, IL-10, IL-12, TNF-α and ET-1 in the severity and pathogenesis of CCHF in children.

## Material and methods

The patients diagnosed with CCHF at Cumhuriyet University Faculty of Medicine were included in the study. The diagnosis was based on detection of viral RNA by real time-polymerase chain reaction (RT-PCR). The RT-PCR of viral RNA analysis was carried out at Refik Saydam Hygiene Center, which is a reference laboratory for CCHF diagnosis in Turkey. The first 7 days after the onset of disease was considered to be the acute phase. Serum samples of 52 (mean age 12.4±3.6 years, 31 male) patients were obtained in the acute phase and stored at -80°C. Patient's baseline characteristics were recorded and baseline complete

**Table 2.** Comparison cytokine levels between in CCHF patient and HC groups

| | CCHF Patient (n=52) | HC (n=34) | *p* Value |
|---|---|---|---|
| IL-12 (pg/mL) | 2.8 (0.0-47.6) | 2.3 (0.4-6.1) | 0.601 |
| IL-10 (pg/mL) | 33.9 (1.6-127.1) | 7.0 (0.5-23.1) | <0.001 |
| TNF-α (pg/mL) | 11.4 (2.2-57.0) | 6.4 (3.1-9.7) | <0.001 |
| IL-6 (pg/mL) | 37.0 (15.4-83.8) | 27.2 (9.1-54.4) | 0.012 |
| ET-1 (pg/mL) | 6.4 (0.5-21.3) | 3.8 (0.2-10.6) | 0.001 |

blood count, biochemical parameters and homeostasis parameters were determined at Clinical Laboratory of Cumhuriyet University Medical Faculty Hospital (**Table 1**). The healthy control (HC) group consisted of 34 age and gender matched healthy children free of the inflammatory disease (mean age 11.2±3.0 years, 18 male). The severity criterion defined in the previous studies [13-15] was not suitable for children as the primary endpoints were mortality but none of the patients died in our study. Therefore, we divided the patients with CCHF into two groups as severe and non-severe based on the severity criteria defined for children with CCHF by Deveci et al. [10].

IL-6, IL-10, IL-12, TNF-α and ET-1 serum levels were checked in all CCHF patients and HC groups, and all results were compared with healthy control group. Serum ET-1 levels were measured by Big Endothelin-1, an EIA kit (Enzo Life Sciences GmbH, Lorrach, Germany). Serum IL-10, IL-12 and TNF-α levels (Bender MedSystems GmbH, eBioscience, Vienna, Austria), and serum IL-6 levels (Boster Biological Technology, Fremont, CA) were measured by ELISA as described in the content of the kit.

In descriptive analysis, the mean±SD was used for the homogeneous parameters while the arithmetic median (min.-max.) was used for the non-homogeneous parameters. In intergroup comparisons, the Student-T test, which is a parametric test, and the Man-Whitney U test and Kruskal-wallis test, which is a non-parametric test, were used. The difference between the categorical variables was assessed using the Chi-square test. $p<0.05$ was regarded as significant.

## Results

Demographic and clinical characteristics of the children with CCHF are shown in **Table 1**. In terms of age and gender, there was no significant difference among the severe, non-severe and HC groups. Nausea/vomiting, tonsillopharyngitis, headache and facial-conjunctival hyperemia (80%, 52%, 44%, and 46%, respectively) were the most frequently detected signs in the severe group; however, there was no significant difference between the severe and non-severe groups in terms of the frequency of the said signs. Other significant clinical symptoms were fever (36%), diarrhea (33%), petechiae, purpura or ecchymosis (24%), and abdominal pain (29%). Bleeding, melaena, and somnolence were observed in only 2 (8%) patients in the severe groups while there was no significant difference between the severe and non-severe groups in terms of the frequency of the said clinical symptoms. There was a significant difference between the severe and non-severe groups in terms of facial-conjunctival hyperemia, myalgia and fatigue/weakness. Biochemical parameters, namely AST, ALT and LDH levels were significantly higher in the severe group when compared to the non-severe group. Furthermore, compared with the non-severe group, PLT and fibrinogen levels were significantly decreased and D-dimer and aPTT levels were significantly increased in the severe group.

While ET-1, TNF-α and IL-10 were all negatively correlated with WBC and PLT, they were negatively correlated with AST. Moreover, ET-1 and IL-10 were negatively correlated with fibrinogen, they were positively correlated with LDH. ET-1 and TNF-α were positively correlated with ALT and there was a negative correlation between Hb and IL-10. In addition, IL-10 was positively correlated with IL-12, ET-1 and TNF-α and there was a positive correlation between IL-12 and ET-1 (**Table 4**).

Compared with the HC group, increased serum IL-10, TNF-α, IL-6 and ET-1 levels were significant in the CCHF group while there was no significant difference between the groups in terms of IL-12 levels (**Table 2**). Moreover, when we compared the cytokine levels of the severe and non-severe groups with those of the HC group, cytokine IL-12 levels did not show a significant difference between the groups while IL-10, ET-1, TNF-α and IL-6 levels were significantly higher in the severe group. Serum IL-10 and ET-1 levels were statistically significantly higher in the severe group when compared to the non-severe and HC groups. There was no significant

**Table 3.** Comparison of Cytokine levels between in study groups

| | Severe Groups (n=25) | Non-Severe Groups (n=27) | HC Groups (n=34) | *p* Value |
|---|---|---|---|---|
| IL-12 | 3.6 (0.0-47.6) | 2.1 (0.4-4.9) | 2.3 (0.4-6.1) | 0.777 |
| IL-10 | 46.7 (9.2-127.1)[a,b] | 22.2 (1.6-126.2)[c] | 7.0 (0.5-23.1) | <0.001 |
| TNF-α | 12.9 (3.7-48.6)[b] | 10.0 (2.2-57.0) | 6.4 (3.1-9.7) | <0.001 |
| IL-6 | 43.1 (22.0-83.8)[b] | 33.2 (15.4-75.9) | 27.2 (9.1-54.4) | 0.008 |
| ET-1 | 8.6 (1.3-21.3)[a,b] | 5.5 (0.5-12.6)[c] | 3.8 (0.2-10.6) | 0.001 |

[a]Significantly different from Non-severe CCHF at p<0.05 level. [b]Significantly different from HC at p<0.05 level. [c]Significantly different from HC at p<0.05 level.

**Table 4.** Correlation analysis between the study markers and the rutin parameters in patients with CCHF

| | IL-12 | ET-1 | TNF-α | IL-10 |
|---|---|---|---|---|
| Continuous variables | Correlation Coefficient | Correlation Coefficient | Correlation Coefficient | Correlation Coefficient |
| WBC | 0.004 | -0.425** | -0.387* | -0.501** |
| LT | 0.023 | -0.529** | -0.415** | -0.630** |
| Hb | -0.223 | -0.059 | -0.060 | -0.029** |
| Fibrinogen | -0.138 | -0.549** | -0.008 | -0.373* |
| INR | 0.140 | 0.194 | 0.062 | 0.037* |
| ALT | 0.0004 | 0.331* | 0.279* | 0.553 |
| AST | -0.087 | 0.433** | 0.261* | 0.619** |
| LDH | 0.000 | 0.393* | 0.196 | 0.493** |
| IL-10 | 0.347* | 0.545** | 0.555** | - |
| ET-1 | 0.245* | - | - | - |

*p<0.05. **p<0.001.

difference between the non-severe group and severe groups in terms of serum TNF-α and IL-6 levels while the said levels showed a significant difference between the severe group and HC group. There was no difference between the non-severe and HC groups in terms of TNF-α and IL-6 levels while IL-10 and ET-1 levels were significantly higher in the non-severe group (**Table 3**).

## Discussion

The main characteristics of VHF is the impairment of endothelial cell function leading to changes in vascular permeability and haemorrhage. However, the endothelial damage is most likely not a result of the direct effects of virus replication but rather a result of multiple host-induced mechanisms, including cytokines [5]. Therefore we wanted to investigate the role of cytokine (IL-6, IL-10, IL-12, TNF-α and ET-1) levels in children with CCHF.

The most major symptoms in VHFs is bleeding indicating endothelial dysfunction. Very similar findings, with overproduction of both proinflammatory cytokines, such as TNF-α and anti-inflammatory cytokines (IL-10 and IL-6) and relatively low levels of IL-12 have been observed in patients with dengue virus infection, another viral illness characterized by plasma leakage and an increase in microvascular permeability [16-19].

In previous studies conducted on CCHF patients [4-6, 20], there are contradictory results regarding the IL-6 and TNF-α levels. While IL-6 and TNF-α levels are significantly higher in fatal patients when compared to non-fatal patients in some studies [4, 6], there is no difference between fatal and non-fatal patients in other studies [5, 20]. These studies were conducted on adult patient groups and the severity criteria used was the fatality. Our study was conducted on children having CCHF and fatality was observed in none of our patients. On the other hand, in a study on an infected murine model, Bente et al. [7] reported that increased TNF-α, IL-6 and IL-10 levels played an important role in the pathogenesis of CCHF.

In our study, TNF-α and IL-6 levels were significantly higher in the CCHF and severe groups when compared to the HC group, but not significant compared with non-severe group, and between the non-severe group and HC groups. While the said results are consistent with the results obtained by some studies [4, 6], they are not consistent with the results obtained by the other studies [5, 20]. The reason of obtaining inconsistent results could be related with having a severity criteria related with fatality and having no severity based classification in children.

Elevated production of IL-6 contributes to the pathogenesis of various autoimmune and inflammatory diseases [21]. Moreover, increased TNF-α levels causes an increase in vascular permeability by damaging the stability of the endothelial cells [22]. According to the results we obtained, there is no correlation between serum TNF-α and IL-6 levels while there exist a strong positive correlation between ET-1 and TNF-α. Therefore, it is possible that increased TNF-α and IL-6 levels are not the markers of severity but important cytokines in the pathogenesis of CCHF in children with CCHF.

In our study, serum IL-10 and ET-1 levels were significantly higher in CCHF patients when compared to the HC group. Moreover, serum IL-10 and ET-1 levels were significantly higher in the severe group when compared to the non-severe group and HC group and significantly higher in the non-severe group when compared to the HC group. Our finding regarding significantly higher serum IL-10 level in the severe group when compared to the non-severe and HC groups was consistent with the studies [4, 5] but not consistent with the other studies [6, 20]. This could be related with the number of the patients in the fatal group [6] and having insufficient severity criteria in children patients [20].

While serum IL-12 level was lower in the CCHF group when compared to the HC group in a study conducted by Saksida et al. [5], there was no significant difference between the CCHF and HC groups or between the severe and non-severe groups in terms of IL-12 levels in our study. Having no difference between the groups in terms of IL-12 levels can be interpreted as non-activation of the Th1-mediated cellular immunity which is consistent with the results obtained by Ozsurekci et al. in pediatrics patients [20] and Saksida et al. in adult patients [5].

Moreover, observing higher serum ET-1 levels in the severe group when compared to the non-severe and HC groups with a significant difference between the severe and non-severe groups was consistent with the findings obtained in the previous studies [10]. This shows us that vascular endothelial plays a significant role in the pathogenesis of CCHF [3, 5]. Serum ET-1 had a positive correlation with IL-12, IL-10, WBC and PLT, and a negative correlation with ALT and AST, which are well known to increase depending on severity of the disease. However, the correlation between ET-1 and IL-10 was more significant when compared to the correlation between ET-1 and IL-12 ($p<0.05$ vs $p<0.001$). This suggests us that Th2-mediated humoral immunity due to IL-10 activation is more important in the endothelial damage observed in the pathogenesis of CCHF [5, 23].

Cytokines, namely IL-6, IL-10 and IL-12 are involved in the proliferation and differentiation of helper T-cells. CD4+ helper T-cells have been classified as Th1 and Th2 cells on the basis of their cytokine production profiles, and IL-6 promotes IL-4-induced Th2 differentiation and inhibits IL-12-induced Th1 differentiation [5, 21]. Furthermore IL-12 is one of the main inductors of cell-mediated immunity for against intracellular pathogens [5]. The major actions of IL-12 are on T and NK cells and induces proliferation cytotoxic activity of these cells. Conversely, IL-12 production is inhibited by IL-10 [24]. Thereby, hampering the development of Th1 immunity. IL-10 production is mainly secreted by Th2 cells, and it is expressed by cells of the innate and the adaptive immune system. Direct effects on these populations explains the major immunological impact of this cytokine, including the regulation of the Th1/Th2 balance [25].

In conclusion, serum levels of IL-10 and ET-1 were increased in children with CCHF, and this increase was related to the severity of the disease in the present study. We concluded that endothelial damage occurring in the pathogenesis of the paediatric CCHF patients is caused

not by TH1-mediated cell immunity but Th2-mediated humoral immunity.

## Disclosure of conflict of interest

None.

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