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Original article

Hitit Index to distinguish patients with and without Crimean-Congo hemorrhagic fever

Huseyin Kayadibi[a,*], Derya Yapar[b], Ozlem Akdogan[b], Nuray N Ulusu[c], Nurcan Baykam[b]

[a] Hitit University School of Medicine, Department of Medical Biochemistry, Corum, Turkey
[b] Hitit University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Corum, Turkey
[c] Koc University School of Medicine, Department of Medical Biochemistry, Istanbul, Turkey

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is fatal. Therefore, it is very important to use an inexpensive, easily accessible, quick and accurate screening index based on clinical signs and laboratory parameters to identify patients suspected of having CCHF.

Laboratory test results on the day of hospitalization for 268 inpatients suspected of having CCHF were used to calculate the laboratory section of the Hitit Index, while 65 of these were also monitored daily during their hospital stay to develop the clinical section of the Hitit Index. Two-hundred CCHF-negative outpatients were also evaluated.

One-hundred and forty-nine inpatients were CCHF-positive and 119 inpatients were CCHF-negative. The Hitit Index is 5.6 − (5.3*lymphocyte) − (0.02*fibrinogen) − (12*direct bilirubin) + (0.04*AST) + (0.32*hematocrit) − (0.5*neutrophil) − (0.07*CKD-EPI) − (0.001*CK) ± conjunctival hyperemia (+1.5 in conjunctival hyperemia presence and −1.5 in conjunctival hyperemia absence). In 65 inpatients monitored daily, Hitit Index results for CCHF-positive and negative inpatients were 6.10(1.90–12.30) and -5.35(−8.83– −1.95), while CCHF-negative outpatients were −10.99(−15.64– −6.95) ($P < 0.001$), respectively. On hospitalization day, just one inpatient was false-negative in 27 CCHF-positive inpatients, while four were false-positive among 38 CCHF-negative inpatients using the Hitit Index. After 24 h, just one inpatient was diagnosed falsely among 27 CCHF-positive and 38 CCHF-negative inpatients, and there was no change after 48 h.

Management of patients living in endemic regions suspected of having CCHF could be achieved within minutes using the Hitit Index. Patients with Hitit Index less than zero can be monitored as outpatients, while patients with Hitit Index results above zero must be hospitalized in infectious diseases wards.

This study was not registered since it was retrospective.

1. Introduction

Crimean-Congo hemorrhagic fever virus (CCHFV), which is a member of the Orthonairovirus genus in the Nairoviridae family, causes Crimean-Congo hemorrhagic fever (CCHF) with an average mortality rate of 3–30% in humans. CCHFV is widespread in many regions of Africa, the Middle East and Eastern Europe to Russia (in more than 30 countries). It is usually transmitted to humans via ticks of the genus *Hyalomma* or by exposure to the blood or other body fluids of an infected animal or CCHF patient. CCHF in humans has clinical symptoms of fever, conjunctival hyperemia, facial hyperemia, headache, myalgia, dizziness, nausea, vomiting, and diarrhea and may affect every site of the body during the hemorrhagic period (Ergonul, 2006; Swanepoel et al., 1989).

The distinguishing medical biochemistry laboratory features of CCHF are elevated liver and muscle enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and creatine kinase (CK); coagulation disorders such as thrombocytopenia, hypofibrinogenemia, prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR); and suppressed complete blood count inflammatory parameters such as leukocyte, lymphocyte, neutrophil and monocyte. Bilirubin may also be an essential biomarker in CCHF due to anti-inflammatory and anti-oxidative effects (Ergonul, 2006; Zhu et al., 2010; Ergonul et al., 2004).

CCHF infection has four distinct phases in humans: an incubation period, prehemorrhagic phase, hemorrhagic phase and the convalescence phase (Ergonul, 2006; Ergonul et al., 2017). In this study,

* Corresponding author at: Hitit University School of Medicine, Department of Medical Biochemistry, Corum, Turkey.
E-mail address: mdkayadibi@yahoo.com (H. Kayadibi).

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we focused on the prehemorrhagic phase to diagnose the patients with CCHF as early as possible, because CCHF is an infectious disease and can be fatal. Diagnosis of CCHF is mainly based on isolation of the virus, identification of the viral genome by molecular techniques such as real-time polymerase chain reaction (PCR), and serological detection of anti − CCHFV antibodies (Vanhomwegen et al., 2012; Tezer and Polat, 2015). PCR is the most important diagnostic tool within the first seven days of CCHF, while Ig M and Ig G antibodies detected by ELISA or immunofluorescence assays can be used after the seventh day of CCHF for the diagnosis of recent CCHFV infection, if paired or consecutive samples are available (Ergonul, 2006). However, these tests are time-consuming, expensive and not easily accessible by most health institutions. Therefore, we need a fast, inexpensive, easily accessible and accurate screening index using routine laboratory tests like complete blood count, coagulation and biochemical analyses, as well as clinical symptoms and physical examination features, to distinguish CCHF patients from others.

In the present study, we aimed to create an index combining the laboratory test results with clinical features to obtain the highest diagnostic accuracy for diagnosis of patients with CCHF on the first day of attendance at health institutions.

2. Materials and methods

2.1. Study design and laboratory parameters

The study group included 308 inpatients who were suspected of CCHF due to their clinical symptoms, as well as early and mostly non-specific signs of CCHF, with or without a tick bite history from 2014 to 2018, but 40 inpatients were excluded due to insufficient laboratory results on the day of hospitalization. Thus, the laboratory section of the Hitit Index was established by using the hospitalization day ALT, AST, LDH, CK, bilirubin direct, bilirubin total, urea, creatinine, CKD-EPI, fibrinogen, PT, INR, aPTT, C-reactive protein, procalcitonine and complete blood count results of 268 inpatients. In addition, clinical symptoms of fever, conjunctival hyperemia, facial hyperemia, headache, myalgia, dizziness, nausea, vomiting, diarrhea, any kind of hemorrhage, as well as history of farming and visiting endemic sites were monitored daily for 67 of these inpatients receiving medical therapy in 2018 until discharge day to establish the clinical section of the Hitit Index. Two of these inpatients were not included due to insufficient hospitalization day laboratory results. These were the first two inpatients with CCHF suspected in 2018. We also tested the specificity of the established Hitit Index in 200 outpatients without any suspicion of CCHF.

Inpatients with positive and negative CCHFV ribonucleic acid (RNA) were categorized as patient and control groups, respectively. All data collected for this study were part of a series of examinations that were routinely performed on these inpatients. The confidentiality of all personal data was protected. The study protocol abided by the ethical guidelines of the Helsinki II Declaration and was approved by the local Ethics Committee of Koc University (2016.146.IRB2.085).

2.2. Statistical analysis

All statistical analyses were performed using the SPSS 22.0 package for Windows (IBM Corp.; Armonk, NY, USA). Demographic and biochemical features were classified as continuous or categorical variables as appropriate. Kolmogorov Smirnov analysis was used to test the normality. The data were expressed as mean ± standard deviation and median (25th–75th interquartile range) for Gaussian-distributed variables and for those variables that did not have Gaussian distribution, respectively. Comparisons between groups were undertaken using the Student`s *t*-test or Mann-Whitney *U*-test, as appropriate. Categorical variables were compared using the chi-square test. Spearman's rank correlation coefficient was used to identify the associations between variables.

The independent effect of each variable was assessed by using univariate logistic regression analysis, and then significant parameters were evaluated with the multivariate logistic regression analysis to create the laboratory and clinical sections of the Hitit Index. The diagnostic accuracy of the Hitit Index was assessed by calculating the areas under the receiver operating characteristic (ROC) curves, accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All reported *P*-values were two-tailed, and those less than 0.05 were considered statistically significant, but for univariate logistic regression analysis *P*-values less than 0.10 were accepted as statistically significant.

Table 1
Comparison of variables between CCHF-positive and negative inpatients.

Variables	CCHF-negative (n = 119)	CCHF-positive (n = 149)	*P* Value
Age, years	49 ± 19	51 ± 16	0.266
Gender, M/F	73/46	101/46	0.209
Hitit Index	−4.86(−8.63–−2.19)	5.88(3.45–12.17)	< 0.001
AST, U/L	33(23–54)	96(45–213)	< 0.001
ALT, U/L	31(17–49)	55(38–116)	< 0.001
LDH, U/L	238(176–327)	330(255–594)	< 0.001
Total Bilirubin, mg/dL	0.75(0.48–1.17)	0.50(0.35–0.60)	< 0.001
Direct Bilirubin, mg/dL	0.18(0.10–0.31)	0.11(0.09–0.19)	< 0.001
Urea, mg/dL	33(26–48)	36(29–48)	0.312
Creatinine, mg/dL	0.80(0.70–1.00)	0.90(0.80–1.10)	0.005
CKD-EPI, mL/min/1.73 m^2	105(82–117)	87(69–101)	< 0.001
Creatine Kinase, U/L	133(76–301)	218(133–614)	< 0.001
Fibrinogen, mg/dL	329(257–400)	209(170–248)	< 0.001
PT, s	14.7 ± 2.94	14.4 ± 3.24	0.396
INR	1.16 ± 0.27	1.10 ± 0.27	0.052
aPTT, s	27.2(24.9–31.5)	31.6(27.8–36.8)	< 0.001
Lymphocytes, 10^3/μL	1.07(0.64–1.58)	0.58(0.39–0.82)	< 0.001
Monocytes, 10^3/μL	0.44(0.26–0.58)	0.21(0.11–0.32)	< 0.001
Leucocytes, 10^3/μL	6.53(3.81–9.63)	2.83(2.00–4.05)	< 0.001
Neutrophils, 10^3/μL	4.36(2.30–7.10)	1.89(1.10–2.91)	< 0.001
Thrombocyte, 10^3/μL	114(86–158)	84(48–121)	< 0.001
Erythrocyte, 10^6/μL	4.71 ± 0.63	4.84 ± 0.55	0.070
Hematocrit, %	41 ± 5.3	42 ± 4.6	0.032

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

3. Results

The demographic and biochemical characteristics of the patients included are summarized in Tables 1 and 2. Associations between the presence of CCHF and evaluated parameters are shown in Table 3. Clinical symptoms, medical history and physical examination features are presented in Table 4. Daily Hitit Index values after patients were hospitalized are presented in Fig. 1. All these inpatients were monitored for at least 48 h. Four CCHF-negative inpatients were discharged after 48 h, while six additional CCHF-negative and one CCHF-positive inpatients were discharged after 72 h. The final diagnosis for CCHF-negative inpatients were hantavirus, leptospirosis, brucellosis, influenza, undiagnosed viral infections, urosepsis, idiopathic thrombocytopenic purpura and pancytopenia. In addition, according to the medical records three and two inpatients died in 2018 and 2017, respectively. Median (25^{th}-75^{th} interquartile range) Hitit Index value for ex inpatients was 18.61 (8.36–67.19). There were statistically significant differences between ex inpatients and only CCHF-positive inpatients, all

Table 2
Demographics and Hitit Index parameters in outpatient group.

Variables	Presumably CCHF-negative (n = 200)
Age, years	48 ± 21
Gender, M/F	95/105
Hitit Index	−10.99(-15.64– -6.95)
Lymphocytes, 10^3/μL	1.93(1.37–2.60)
Fibrinogen, mg/dL	294(225–379)
Direct Bilirubin, mg/dL	0.10(0.10–0.20)
AST, U/L	23(18–35)
Hematocrit, %	39 ± 7.4
Neutrophils, 10^3/μL	5.07(3.50–7.22)
CKD-EPI, mL/min/1.73 m^2	104(84–121)
Creatine Kinase, U/L	86(55–143)

inpatients and all outpatients ($P = 0.011$, $P = 0.002$ and $P < 0.001$, respectively). There was also a statistically significant correlation between Hitit Index and ex status (r = 0.193 and $P = 0.002$).

Conjunctival hyperemia, facial hyperemia, insect bite history and headache were the statistically significant parameters in univariate logistic regression analysis among all evaluated clinical parameters. However, conjunctival hyperemia was the only statistically significant parameter in multivariate logistic regression analysis.

In the presence or absence of conjunctival hyperemia, 1.5 points are added or subtracted to the Hitit Index, respectively, based on the coefficients of conjunctival hyperemia and the regression equation constant. Accordingly, the formula of the Hitit Index is 5.6 − (5.3*lymphocyte) − (0.02*fibrinogen) − (12*direct bilirubin) + (0.04*AST) + (0.32*hematocrit) − (0.5*neutrophil) − (0.07*CKD-EPI) − (0.001*CK) ± conjunctival hyperemia (+1.5 in conjunctival hyperemia presence, -1.5 in conjunctival hyperemia absence) (Table 5). All coefficients used in the Hitit Index were derived from the multivariate logistic regression analysis.

Areas under ROC (AUROC) curve, accuracy, sensitivity, specificity, PPV and NPV for the laboratory section of Hitit Index were 0.992, 96%, 97%, 96%, 91% and 99%, respectively. We could only calculate the AUROC, accuracy, sensitivity, specificity, PPV and NPV of the Hitit Index (0.960, 92%, 96%, 90%, 87% and 97%, respectively) for just 65 inpatients hospitalized in 2018, since we did not have the conjunctival hyperemia results of inpatients from 2014 to 2017.

In sixty-five inpatients with suspected CCHF, 27 inpatients were CCHF-positive and 38 inpatients were CCHF-negative. We especially evaluated the first 48 h of hospital stay for Hitit Index results, since accurate diagnosis in the first 48 h is lifesaving. On hospitalization day, just 1 inpatient was misdiagnosed among 27 CCHF-positive inpatients, while 4 inpatients were misdiagnosed among 38 CCHF-negative inpatients using the Hitit Index. After 24 h, 3 additional false-positive CCHF-negative inpatients were diagnosed correctly using the Hitit Index. As a result, just 1 inpatient was falsely diagnosed among both 27 CCHF-positive and 38 CCHF-negative inpatients. After 48 h, there was no change. Moreover, on hospitalization day, 1 of the 34 inpatients with Hitit Index less than zero was CCHF-positive, while among 31 inpatients with Hitit Index more than zero 5 were CCHF-negative.

In the CCHF-negative 200-outpatient group, the specificity for the laboratory section of the Hitit Index was 98% for a cut-off point of zero. When we subtracted 1.5 due to the absence of conjunctival hyperemia, we obtained 100% specificity for the Hitit Index.

4. Discussion

This is the first study establishing and evaluating an index to distinguish inpatients with suspected CCHF from others. It is important to anticipate the presence of CCHF even at the first admission of a patient. Moreover, hospitalization of any person suspected with CCHF is mandatory because of the fatal prognosis, high rate of transmission, and early medical therapy since early diagnosis is very important for

Table 3
Associations between CCHF and Hitit Index parameters in all inpatients.

CCHF	Hitit Index	Fibrinogen	AST	Neutrophil	Lymphocyte	Direct bilirubin	CKD-EPI	Creatine Kinase	Hematocrit
	r = 0.839, $P < 0.001$	r = −0.585, $P < 0.001$	r = 0.504, $P < 0.001$	r = −0.480, $P < 0.001$	r = −0.432, $P < 0.001$	r = −0.263, $P < 0.001$	r = −0.237, $P = 0.001$	r = 0.246, $P < 0.001$	r = 0.101, $P = 0.099$

Table 4
Clinical symptoms, medical history and physical examination findings of daily monitorized inpatients.

Finding	CCHF-negative (n = 38) Frequency, n (%)	CCHF-positive (n = 27) Frequency, n (%)	*P* Value
Conjunctival hyperemia	5 (13.2)	18 (66.7)	< 0.001
Facial hyperemia	7 (18.4)	18 (66.7)	< 0.001
Insect bite history	10 (26.3)	17 (63.0)	0.003
Headache	9 (23.7)	13 (48.1)	0.040
Diarrhea	6 (15.8)	9 (33.3)	0.098
Farming	28 (73.7)	24 (88.9)	0.131
Nausea	8 (21.1)	10 (37.0)	0.156
Vertigo	3 (7.9)	5 (18.5)	0.199
Bleeding	3 (7.9)	5 (18.5)	0.199
Myalgia	21 (55.3)	19 (70.4)	0.217
Endemic region	34 (89.5)	26 (96.3)	0.309
Vomiting	4 (10.5)	2 (7.4)	0.669
Fever	28 (73.7)	20 (74.1)	0.972
Dizziness	36 (94.7)	26 (96.3)	1.000

efficient ribavirin and/or supportive therapy (Ergonul, 2006; Marroquin et al., 2017; Celikbas et al., 2014). The quantitative PCR reaction is the gold standard diagnostic tool for CCHFV identification, but it is expensive, is not always easily accessible, and takes a long time to get results. For these reasons, we formulated the Hitit Index that can be used to decide which patients must be hospitalized. It is possible to request the PCR test for patients suspected of CCHF in endemic seasons and regions of our country, but in the non-endemic regions when sporadic cases are present, the Hitit Index may be very useful and practical to minimize the number of persons receiving unnecessary clinical isolation.

Although the pathogenesis of CCHF is not clearly understood, endothelial cells, immune cells and hepatocytes are the primary targets. Various kinds of inflammatory markers and cytokines like interleukin (IL)-1, IL-6, IL-8, IL-10 and tumor necrosis factor alpha are secreted when these cells are infected. There are two different theories of direct invasion of the endothelium and immune response-mediated cell damage. In studies conducted about direct cell damage, a cytokine storm develops through mediators released from endothelial cells, the intrinsic coagulation cascade is activated, and hemorrhage is caused, while the toll-like receptors play an important role in the pathogenesis of immune system-mediated cell damage by modulation of adaptive immunity including the regulatory and effector T cells. Accordingly, increased vascular permeability, vasodilatation, hypotension, multiple organ failures, shock, activated coagulation cascade, disseminated intravascular coagulation or consumption coagulopathy and death may develop in these patients (Ergonul, 2006; Akinci et al., 2016; Schnittler and Feldmann, 2003;Kraus and Mirazimi, 2010).

Fibrinogen is essential for blood clot formation. In our study, it was lower in inpatients with CCHF than those without CCHF even in the prehemorrhagic phase. Therefore, we consider that low fibrinogen level may be an important clue for suspicion of CCHF. Levels of fibrinogen in the severity scoring indexes were also significantly lower in patients with CCHF, as in our study (Ergonul, 2006; Swanepoel et al., 1989; Dokuzoguz et al., 2013; Bakir et al., 2015).

Leukocyte, lymphocyte, monocyte and neutrophil counts were significantly lower in CCHF-positive inpatients compared with CCHF-negative inpatients. This reduction may be due to the induction of hemophagocytosis. In addition, reactive hemophagocytosis was detected in 50% of patients (Karti et al., 2004). CCHFV may also cause lymphocytopenia by apoptosis.

It was shown that CCHFV may display hepatotropism and viral replication may occur in the liver on the second day. CCHFV readily passes into hepatocytes through the spaces between liver sinusoids. Hepatic endothelial cell injury occurs, then AST and ALT levels increase as a result of hepatocyte damage (Bente et al., 2010). In the present study, AST, ALT and LDH values were two or three times higher in inpatients with CCHF than those without CCHF. ALT and LDH were statistically significant in the univariate logistic regression analysis, but they were insignificant in multivariate logistic regression analysis. This may be explained by the lower diagnostic power of ALT and LDH compared to the associated laboratory parameters for prediction of patients with CCHF in the early stage of disease.

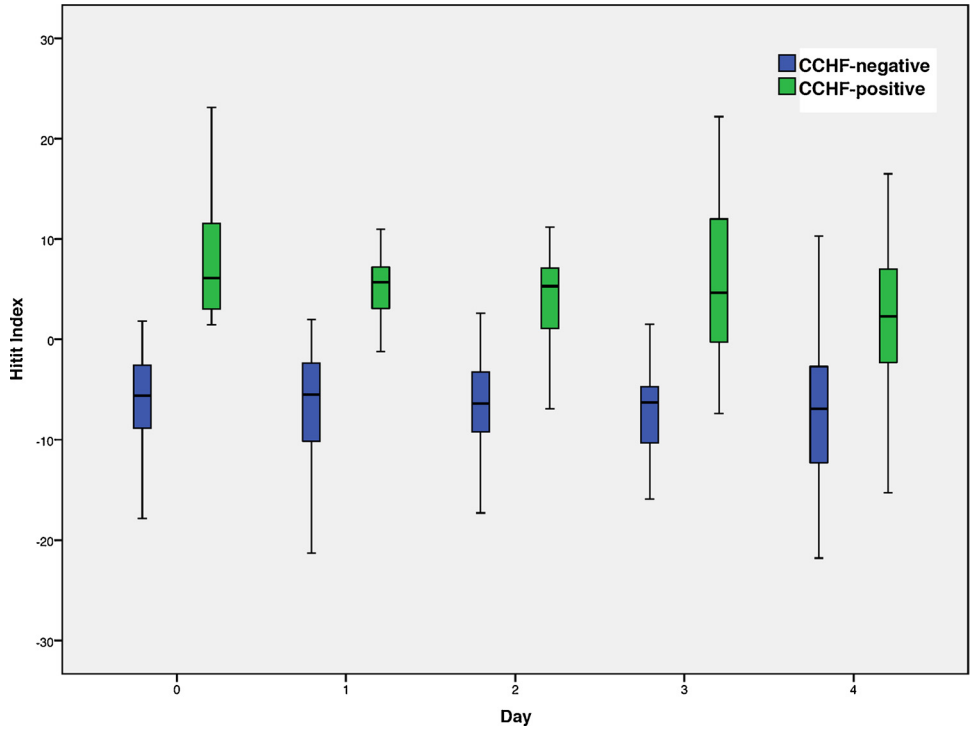

Fig. 1. Daily Hitit Index values after patients were hospitalized.

Table 5
Univariate and multivariate logistic regression analysis of variables associated with the positivity of CCHF on the hospitalization day.

Variables	Univariate analysis			Multivariate analysis		
	OR (95% CI)	Wald	*P* Value	OR (95% CI)	Wald	*P* Value
Direct Bilirubin, mg/dL	0.065(0.013–0.321)	11.3	0.001	< 0.001(< 0.001–0.001)	22.1	< 0.001
Lymphocytes, 10^3/μL	0.128(0.067–0.241)	40.1	< 0.001	0.005(0.001–0.046)	21.8	< 0.001
Fibrinogen, mg/dL	0.983(0.979–0.988)	57.6	< 0.001	0.979(0.970–0.988)	20.1	< 0.001
AST, U/L	1.019(1.012–1.025)	31.9	< 0.001	1.042(1.021–1.064)	15.0	< 0.001
CKD-EPI, mL/min/1.73 m^2	0.989(0.980–0.998)	5.65	0.017	0.931(0.898–0.966)	14.7	< 0.001
Hematocrit, %	1.057(1.005–1.112)	4.65	0.031	1.398(1.173–1.665)	14.0	< 0.001
Neutrophils, 10^3/μL	0.640(0.561–0.731)	43.2	< 0.001	0.588(0.439–0.787)	12.8	< 0.001
Creatine Kinase, U/L	1.001(1.000–1.001)	6.41	0.011	0.999(0.997–1.000)	4.6	0.033
Leukocytes, 10^3/μL	0.644(0.571–0.727)	50.5	< 0.001			
Monocytes, 10^3/μL	0.013(0.003–0.051)	38.3	< 0.001			
ALT, U/L	1.019(1.012–1.027)	24.9	< 0.001			
Total Bilirubin, mg/dL	0.156(0.074–0.329)	23.8	< 0.001			
LDH, U/L	1.004(1.003–1.006)	23.3	< 0.001			
Thrombocyte, 10^3/μL	0.988(0.984–0.993)	23.2	< 0.001			
aPTT, s	1.088(1.045–1.133)	17.0	< 0.001			
INR	0.394(0.148–1.050)	3.47	0.063			
Erythrocyte, 10^6/μL	1.476(0.972–2.240)	3.34	0.068			
Urea, mg/dL	0.993(0.984–1.001)	2.79	0.095			
Creatinine, mg/dL	0.814(0.542–1.233)	0.98	0.322			
PT, s	0.967(0.893–1.046)	0.71	0.400			

Bilirubin, a natural product of the heme catabolism, has anti-inflammatory, anti-oxidative and cell protective properties. It protects grafts against nonspecific inflammation-induced injury via the inhibition of MCP-1, IL-1β, soluble intercellular adhesion molecule 1 and TNF-α synthesis (Ergonul et al., 2017). Bilirubin induces these activities by preventing the vascular cell adhesion molecule 1 mediated migration of leukocytes into the endothelial monolayers (Vogel and Zucker, 2016). It can be proposed from our data that higher bilirubin levels may protect the individuals against CCHFV at the beginning of the pathogenesis of CCHF.

CKD-EPI, an indicator of kidney functions, decreases in patients with renal failure. In the present study, the median value of CKD-EPI was significantly lower, and median creatinine was significantly higher in inpatients with CCHF. However, in univariate logistic regression analysis, only CKD-EPI was statistically significant. This significance continued even in multivariate logistic regression analysis. In the literature, there are few studies explaining renal involvement in CCHF. It was found that intra-renal hemodynamic dysregulation caused by endothelial dysfunction and cytokine storm might be the reason for renal dysfunction in CCHF (Ardalan et al., 2006).

Mild levels of hematocrit elevation in patients with CCHF can be the result of hemoconcentration, which may be caused by dehydration of these patients and the presence of fever. Hematocrit was not statistically significant between patients with and without CCHF at the beginning of the prehemorrhagic phase. However, it was statistically significant in the multivariate logistic regression analysis. After detailed analysis as to whether it should be included or not in the Hitit Index, we faced with the reality that hematocrit is necessary to decrease the false-positive results, especially for those patients with Hitit Index results close to the cut-off point of zero.

Common muscle pain is seen from the first days of CCHF, because rhabdomyolysis or myositis may be seen in the early days of CCHF. Consequently, CK may increase on the first or second day of the disease (Karti et al., 2004). In the present study, there was a statistically significant difference between groups for CK values. CK was also statistically significant both in univariate and multivariate logistic regression analyses.

The earliest and most common symptoms of CCHF are fever, conjunctival hyperemia, rash, headache, weakness, myalgia, anorexia, photophobia, dizziness, nausea and vomiting. It was concluded that CCHF may cause a mild form of ocular disease and must be suspected when superficial or subconjunctival retinal hemorrhages are seen in association with fever in endemic areas (Engin et al., 2009). In our study, conjunctival hyperemia was the only statistically significant parameter among the evaluated clinical features. The addition of conjunctival hyperemia to the Hitit Index decreases the false-positive rate of CCHF diagnosis especially, and prevents unnecessary medical therapy in individuals without CCHF.

When we just used the laboratory section of the Hitit Index without noting conjunctival hyperemia, 5 (3.4%) of the 149 CCHF-positive patients were negative, while 11 (9.2%) of the 119 CCHF-negative patients were positive. We think that the majority of these patients would be correctly diagnosed if the conjunctival hyperemia results of these five false-negative and eleven false-positive patients were registered in our hospital automation system. This is because the addition of conjunctival hyperemia to the Hitit Index increased the diagnostic accuracy of the index for inpatients given medical therapy in 2018.

The strength of the present study is the selection of a control group. In the study design, by using inpatients with suspected CCHF without CCHFV RNA positivity as a control group instead of healthy individuals, we got more reliable and powerful statistical results. The first limitation of this study is the absence of conjunctival hyperemia records for inpatients administered medical therapy between March 2014 and November 2017. The second limitation is the single center used for the study design. The third limitation is the CCHFV strain circulating in Corum/Turkey may be different than CCHFV strains found elsewhere. Therefore, we do not know the region- and race-derived interference in relation to the Hitit Index.

5. Conclusion

Early diagnosis of CCHF is important for general public health and hospital management to stop or reduce the risk of hospital transmission, and is essential to take necessary precautions, and start medical therapies as soon as possible. Therefore, an accurate, quick, easy, cheap and safe index containing both clinical and laboratory features is mandatory. The Hitit Index can be a useful diagnostic tool to distinguish the patients with CCHF from others by using a cut-off point of zero. Patients with CCHF suspected and Hitit Index values less than zero can be monitored daily as outpatients, while those with Hitit Index values above zero must be hospitalized in the health institution. However, medical history and physical examination features should be noted in making this decision.

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Potential conflicts of interest

All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Corresponding author contact information is mdkayadibi@yahoo.com

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