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Can Serum Ferritin Level Predict Disease Severity in Patients with Crimean-Congo Hemorrhagic Fever?

Kırım-Kongo Kanamalı Ateşi Olan Hastalarda Serum Ferritin Düzeyleri ile Hastalık Şiddeti Tahmin Edilebilir mi?

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Abstract

Objective: Crimean-Congo hemorrhagic fever (CCHF) is an acute viral disease. Several factors have already been suggested to explain the pathogenesis as well as predict the disease severity. In our study we aim to investigate the role of serum ferritin level as a possible predicting factor of disease severity in these patients.

Materials and Methods: We evaluated all patients with laboratory confirmed diagnosis of CCHF who were admitted to Boo-Ali Hospital of Zahedan from May 2011 to June 2012. Confirmation of the disease determined using the presence of anti- CCHFV IgM in the serum by enzyme-linked immunosorbent assay (ELISA) or by polymerase chain reaction(PCR). After ethical approval, patients were categorized into two groups of mild and severe disease according to disseminated intravascular coagulation (DIC) severity using the scoring system of International Society on Thrombosis and Hemostasis (ISTH) . Serum ferritin levels were evaluated and compared between these two groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the optimal cutoff value of serum ferritin for predicting the disease severity.

Results: A total of 42 patients (36 men, 6 women, age range: 17-78 years) were included in this study, of whom 38% had Persian and 62% had Baloch ethnicity. According to DIC severity score, 54.7% of the patients had severe disease and 45.3% had mild disease. The area under the ROC curve was 0.896 and 95% CI was 0.801-0.991 ($p<0.0001$). A cut-off point of 1060 ng/dL, had a sensitivity of 78.9%, a specificity of 87%, a positive predictive value of 6% and a negative predictive value of 100%. Positive and negative likelihood ratios for this serum ferritin level were 6.05 and 0.24, respectively.

Conclusion: Increased serum ferritin level has a significant positive correlation with disease severity in patients with CCHF and can evaluate the prognosis of these patients with a high sensitivity and specificity.

Key Words: Crimean-Congo hemorrhagic fever, disease severity, ferritin

Özet

Amaç: Kırım-Kongo Kanamalı Ateşi (KKKA) akut viral bir hastalıktır. Patogenezi açıklamak ve KKKA hastalığı şiddetini tahmin etmek için çeşitli faktörler önerilmiştir. Çalışmamızda, bu hastalarda hastalığın şiddeti için olası bir tahmin faktörü olarak serum ferritin düzeyi rolünün araştırılması amaçlamaktadır.

Gereç ve Yöntem: Çalışmamızda Mayıs 2011-Haziran 2012 döneminde Zahedan Boo-Ali Hastanesine başvururan, tamamı KKKA tanısı doğrulanmış hastalar değerlendirildi. Hastalık tanısı ELISA ile anti-KKKA IgM veya polimeraz zincir reaksiyonu (PZR) pozitifliği ile konuldu. Etik onay alındıktan sonra hastalar Uluslararası Tromboz ve Hemostaz Derneği nin (ISTH) tanımladığı Dissemine İntravasküler Koagülasyon (DİK) skorlama sistemine göre orta ve ağır olarak iki gruba ayrıldı. Bu iki grubun serum ferritin seviyeleri karşılaştırıldı. Bu iki grup Alıcı işletim karakteristiği (ROC) eğrisi analizi ile hastalık şiddetini tahmin etmek için en uygun serum ferritin kesim değeri belirlendi.

Bulgular: Toplam 42 hasta (36 erkek, 6 kadın, yaş aralığı: 17-78 yıl olmak üzere) bu çalışmaya dahil edilmiştir, hastaların %38 Pers ve %62 Baloch etnik grubuna dahildir. DIC şiddet skoruna göre, hastaların %54.7 ciddi ve %45.3 'ü hafif olarak sınıflandırılmıştır. ROC eğrisi altında kalan alan 0.896 ve %95 CI 0.801-0.991 (p değeri <0.05) bulunmuştur. 1.060 ng/dL bir kesim noktası %78.9 bir duyarlılık, %87 özgüllük, %6 bir pozitif prediktif değer ve %100 bir negatif prediktif değer tespit edilmiştir. Bu serum ferritin düzeyi için pozitif ve negatif olabilirlik oranları sırasıyla 6.05 ve 0.24 olarak bulunmuştur.

Sonuç: Artmış serum ferritin düzeyi KKKA hastalarında hastalık şiddeti ile anlamlı pozitif korelasyona sahiptir ve bu hastalarda prognozu yüksek bir duyarlılık ve özgüllük ile gösterebilir.

Anahtar Kelimeler: Ferritin, hastalık şiddeti, Kırım-Kongo kanamalı ateşi

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute febrile hemorrhagic disease caused by a tick-borne virus belonging to the *Nairovirus* genus of the Bunyaviridae family. Primary modes of disease transmission to humans include tick bites (Hyloma marginatum) or direct contact with blood or body discharges of the infected human or viremic livestock [1].

The disease is mostly reported from Sub-Saharan Africa, Eastern Europe, Middle East, Iraq, India, Afghanistan, Pakistan, Iran and West China [2, 3]. Since 1999 Iranian Ministry of Health reported the disease mostly from Sistan-Balouchestan, Isfahan and Golestan provinces in Iran [4].

Incubation period is from 3 to 13 days, after which prodromal symptoms develop including sudden fever, headache, myalgia, nausea and vomiting and epigastric pain. Leukopenia and thrombocytopenia in this phase of the disease might be severe and life threatening. Prodromal period averagely lasts for 1-7 days and is followed by the hemorrhagic phase which usually begins between the third to fifth days of the disease and continues for 4 days. Reticular system is affected by the virus which commonly results in extensive involvement of the liver cells manifesting by hepatitis and icterus. Diagnosis is made by laboratory tests including viral culture methods, serology using ELISA and RT-PCR [5].

CCHF causes severe lethal disease with 30 to 80% mortality rate [2, 3]. Although, in Turkey epidemia mortality rate has been reported low nearly 10% [6].Early treatment within the first three days can significantly decrease the mortality rate [7]. Mortality is typically due to hypovolemic shock resulted from severe bleeding, disseminated infection or disseminated intravascular coagulation (DIC). According to clinical pathology of the disease, severity of the DIC developed during the disease is considered as an important parameter of the disease severity [8].

Several studies have investigated effective factors on the severity of CCHF disease. One study reported higher mortality rate to be associated with: platelet count lower than 20,000/mm^3, PTT longer than 60 seconds [9]. Coagulopathy parameters (thrombocytopenia, prolonged PT, PTT, INR and d-dimer level)and their correlation with disease severity in CCHF have been suggested in another study [9]. Another study designed to evaluate criteria predicting the disease severity reported the lab parameters indicating disease severity: platelet count<20000/mm^3, and decrease of levels of hematocrit and fibrinogen, elevation of creatine phosphokinase titer and lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, prothrombin time (PT) and partial thromboplastin time (PTT) , developing melena and loss of consciousness [10]. Other studies have shown that the presence of risk factors including plt<90,000/mm^3, increased levels of AST, ALT and PTT, are associated with significantly disease severity in these patients [11] and also high viremia predicted higher mortality rate [13, 14]. Patients with severe lethal CCHF disease have been reported to have significantly higher serum levels of IL-6 and TNF-α and lower levels of IL-10 [8].

Ferritin is an acute phase protein which is increased during inflammatory diseases. Recently, increased serum levels of ferritin has been proposed as an independent single predicting factor for severity of various diseases such multiple sclerosis (MS) and also acute interstitial lung disease (ILD) caused by dermatomyositis, histiocytic malignancies, adult still disease and hemophagocytic lymphohistiocytosis [15-19]. Hemophagocytic lymphohistiocytosis phenomenon has recently been suggested in pathogenesis of CCHF [20].

Only two study from Turkey have addressed the relation between increased serum level of ferritin with disease severity in CCHF patients [21, 22]. Moreover, introducing a safe and simple method to evaluate the disease severity in CCHF patients is of great importance in order to start early treatment and intensive care in this group. In the present study we aim to evaluate the performance of serum level of ferritin in predicting disease severity in patients with CCHF.

Materials and Methods

In this analytical cross-sectional, target population included all the patients admitted to Boo-Ali Hospital who were considered as probable cases of CCHF according to clinical and laboratory criteria of Iranian National guideline(having; 1-acute onset of fever, myalgia, and headache, 2- an epidemiologic factor, and 3- platelet count <100,000/mm^3) for CCHF from May 2011 to June 2012. Written informed consents were taken from all patients before enrollment in the study. Serum samples from the patients were sent to Iran Pasteur Institute for serology evaluation or PCR diagnosis of CCHF. Patients with a positive result were included in this study. Blood samples were also taken for performing laboratory tests including platelet count, FDP, fibrinogen, PT, PTT and serum ferritin.

Patients with other known hematologic or rheumatologic diseases, coagulopathies or malignancies, all patients who had a history of receiving any type of antiviral, blood or blood products between the beginning of their symptoms until admission to our hospital were excluded from this study.

The severity of DIC was determined using the scoring system of International Society on Thrombosis and Hemostasis (ISTH). According to this scoring system, DIC severity is evaluated as following: platelet count >100,000/mm^3, 50,000-100,000 and <50,000/mm^3 (0, 1 and 2 scores, respectively); FDP<10mg/L, 10-25 mg/L and >25mg/L (0, 2 and 3 scores, respectively); fibrinogen>1g/L, and <1g/L (0 and 1 score respectively); PT <3 seconds, 3-6 seconds and >6 seconds

Table 1. Demographic characteristics of study subject according to the severity of DIC

Variable		DIC Severity Class				p-value*
		Mild		Severe		
		n	%	n	%	
Sex	Male	20	87.0	16	84.2	0.801
	Female	3	13.0	3	15.8	
Age group	≤25 years	7	30.4	7	36.8	0.909
	26 to 40 years	8	34.8	6	31.6	
	>40 years	8	34.8	6	31.6	
Ethnicity	Balouch	15	65.2	11	57.9	0.627
	Persian	8	34.8	8	42.1	

*p-value for the Pearson's chi-square test

(0, 1 and 2 scores, respectively). A total score ≥5 shows severe DIC and scores <5 are considered as mild DIC [21]. Accordingly, the patients were divided into two groups with mild and severe DIC and serum ferritin level was evaluated and compared in these two groups.

A questionnaire was designed for collecting data. The questionnaire included questions on demographic information such as age, sex, and ethnic character.

Data analysis

All continuous variables were tested for normality of distribution using Kolmogorov-Smirnov goodness of fit tests. Categorical variables were presented as counts and percentages. The Chi square test was used to compare the distribution of categorical variable between different groups. None of continuous variables had a normal distribution. Hence, non-Parametric Mann-Whitney test was used to compare means of quantitative variables between groups.

Receiver operating characteristic (ROC) curve analysis was performed to assess the optimal cutoff value of serum ferritin for predicting the disease severity, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio (23).

A p value <0.05 was considered significant for all analyses. Data analysis was performed using SPSS version 20 statistical software package (Chicago, IL, USA).

Results

A total of 42 patients with laboratory-confirmed CCHF diagnosis were investigated during the one year study period which included 36 men (85%) and 6 women (15%). Age range was from 17 to 78 years (mean age, 36.6 years). Of the studied patients 26 (62%) were from Balouch ethnicity and 16 (38%) were Persians. Regarding the disease severity according to DIC score, 23 (54.7%) patients were categorized in mild group and 19 (45.3%) were found to have severe disease. No significant differences were found in the distribution of demographic variables such as sex, age group and ethnicity between DIC severity groups (Table1).

According to the Kolmogorov-Smirnov test, none of the continuous studied variables including platelet count, PT, PTT, FDP, fibrinogen, ferritin and hospital admission time showed a normal distribution. Therefore, non-parametric tests such as Mann-Whitney were used to fro comparing means between groups.

The mean of the time of hospital admission from the beginning of the symptoms was 3.26 days in the mild DIC group as compared with 3.58 in the severe group and the difference was not statistically significant (Table2).

A total of 34 patients (81%) had a full recovery and 8 patients (19%) died. The mean of platelet count was lower in patients in the severe DIC group as compared with patients with mild DIC (i.e. 41.2×10^3 mg/dL versus 54.3×10^3 mg/dL). Moreover, in comparison with mild DIC group the mean of prothrombine time and partial throboplastin time was longer in severe DIC group. Although none of these differences were statistically significant. On the other hand, the mean of serum concentration of fibrin degradation products was in patients with severe DIC was much higher than the mild DIC group (31.4 mg/L versus 8.4 mg/L) and the difference was statistically significant (p<0.0001). Conversely, the mean of serum concentration of fibrinogen was much lower in severe DIC group (i.e. 0.6 g/L) in comparison with the mean serum fibrinogen concentration of 1.4 in the mild group and the difference was statistically significant (p=0.020). The mean of serum ferritin in patients classified as having severe DIC was approximately five times the mean serum ferritin concentration in patients with mild DIC (i.e. 6251 ng/mL versus 1259 ng/mL) and the difference was statistically significant (p<0.0001) (Table 3).

Table 2. Comparing mean time of hospital admission from the beginning of the symptoms (days) between DIC severity groups

Variable	DIC severity class				p-value
	Mild (n=23) (mean) days	(SD)	Severe (n=19) (mean) days	(SD)	
Hospital admission from the beginning of the symptoms	3.58	2.36	3.26	2.11	0.828

Table3. Comparing mean of serum ferritin, Platelet, PT, PTT, FDP, Fibrinogen and Ferritin between DIC severity groups

Variable	DIC Severity Class				p-value*
	Mild (n=23) Mean	SD	Severe (n=19) Mean	SD	
Platelet count ($\times 10^3$)	54.3	39.8	41.2	0.3	0.330
PT (sec)	13.5	1.8	15.3	3.5	0.052
PTT (sec)	53.2	21.3	63.4	21.5	0.053
FDP (mg/L)	8.4	7.5	31.4	11.7	0.000
Fibrinogen (g/L)	1.4	1.0	0.6	0.6	0.020
Ferritin (ng/mL)	1259.3	2056.4	6251.1	3646.0	0.000

PT: Prothrombine time; PTT: Partial thromboplastin time; FDP: Fibrin degradation products
*p value for Mann-Whitney U test

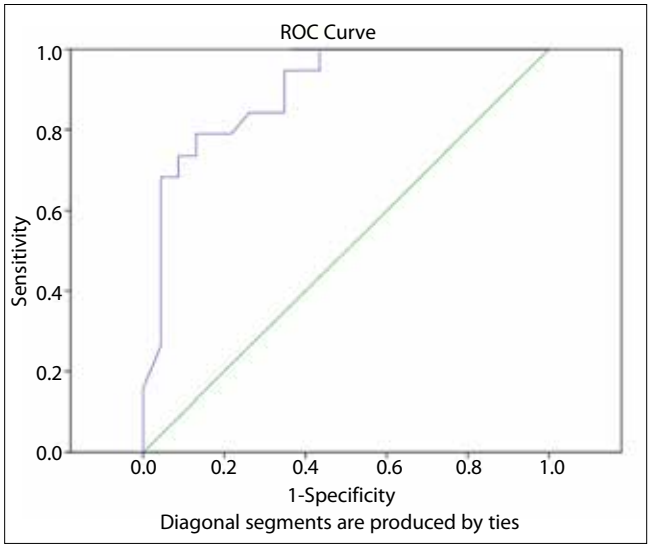

Figure 1. *ROC curve.*

Receiver operating characteristic (ROC) curve analysis was used to investigate the performance of serum ferritin level in distinguishing severe DIC cases from those with mild DIC. In our study, the area under the curve was 0.896 (95% CI: 0.801-0.991) which was statistically significant (p<0.0001) (Figure 1).

ROC curve analysis was also used to calculate, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio for different levels of serum ferritin. Youden's J and minimum d statistics [22] were used to identify the optimal cut-off value for serum ferritin level to distinguish mild from severe CCHF disease.In our analysis serum ferritin concentrations of 1060 ng/mL and above showed the an optimal performance with a sensitivity of 78.9% and specificity of 87%. Positive predictive value (PPV) and negative predictive value (NPV) in our study were 6% and 100%, respectively. The positive and negative likelihood ratios at this level of serum ferritin were 6.05 and 0.24, respectively (Table 4) .

Discussion

Findings from the present study showed that increased serum ferritin level in patients with CCHF could reasonably distinguish patients with severe DIC from those with mild DIC.

Physiopathology of this disease has been already studied in several studies [12, 13, 20]. To this date, many parameters have been suggested to evaluate the severity of the disease including decreased thrombocytopenia, prolonged PT and PTT, liver transaminases, muscular enzymes, cytokines such as IL-6 and IL-10 [8, 24, 25]

Table 4. Sensitivity, specificity, Positive predictive value, negative predictive value, positive Liklihood ratio and negative Liklihood ratio and estimated Youden's J statistics and minimum d for different levels of serum ferritin

Ferritin	Sensitivity	1-Specificity	Specificity	Youden Index	Minimum D	Positive predictive value	Negative predictive value	Likelihood ratio positive	Likelihood ratio negative
187.0	1.000	1.000	0.000	0.000	1.000	.001		1.000	
193.0	1.000	0.957	0.043	0.043	0.957	0.001	1.000	1.045	0.000
222.5	1.000	0.913	0.087	0.087	0.913	0.001	1.000	1.095	0.000
300.5	1.000	0.870	0.130	0.130	0.870	0.001	1.000	1.150	0.000
399.0	1.000	0.826	0.174	0.174	0.826	0.001	1.000	1.211	0.000
455.5	1.000	0.783	0.217	0.217	0.783	0.001	1.000	1.278	0.000
468.5	1.000	0.739	0.261	0.261	0.739	0.001	1.000	1.353	0.000
480.0	1.000	0.696	0.304	0.304	0.696	0.001	1.000	1.438	0.000
529.5	1.000	0.652	0.348	0.348	0.652	0.002	1.000	1.533	0.000
583.5	1.000	0.609	0.391	0.391	0.609	0.002	1.000	1.643	0.000
610.0	1.000	0.565	0.435	0.435	0.565	0.002	1.000	1.769	0.000
670.5	1.000	0.522	0.478	0.478	0.522	0.002	1.000	1.917	0.000
856.5	1.000	0.478	0.522	0.522	0.478	0.002	1.000	2.091	0.000
1002.5	1.000	0.435	0.565	0.565	0.435	0.002	1.000	2.300	0.000
1013.0	0.947	0.435	0.565	0.513	0.438	0.002	1.000	2.179	0.093
1017.5	0.947	0.391	0.609	0.556	0.395	0.002	1.000	2.421	0.086
1023.5	0.947	0.348	0.652	0.600	0.352	0.003	1.000	2.724	0.081
1027.5	0.895	0.348	0.652	0.547	0.363	0.003	1.000	2.572	0.161
1028.5	0.842	0.348	0.652	0.494	0.382	0.002	1.000	2.421	0.242
1031.5	0.842	0.304	0.696	0.538	0.343	0.003	1.000	2.767	0.227
1034.5	0.842	0.261	0.739	0.581	0.305	0.003	1.000	3.228	0.214
1037.5	0.789	0.217	0.783	0.572	0.303	0.004	1.000	3.632	0.269
1045.0	0.789	0.174	0.826	0.616	0.273	0.005	1.000	4.539	0.255
1060.0	0.789	0.130	0.870	0.659	0.248	0.006	1.000	6.053	0.242
1185.0	0.737	0.130	0.870	0.606	0.294	0.006	1.000	5.649	0.303
2550.0	0.737	0.087	0.913	0.650	0.277	0.008	1.000	8.474	0.288
3940.0	0.684	0.087	0.913	0.597	0.328	0.008	1.000	7.868	0.346
5240.0	0.684	0.043	0.957	0.641	0.319	0.016	1.000	15.737	0.330
6650.0	0.632	0.043	0.957	0.588	0.371	0.014	1.000	14.526	0.385
7000.0	0.579	0.043	0.957	0.535	0.423	0.013	1.000	13.316	0.440
7150.0	0.526	0.043	0.957	0.483	0.476	0.012	1.000	12.105	0.495
7250.0	0.474	0.043	0.957	0.430	0.528	0.011	0.999	10.895	0.550
7450.0	0.368	0.043	0.957	0.325	0.633	0.008	0.999	8.474	0.660
7700.0	0.316	0.043	0.957	0.272	0.686	0.007	0.999	7.263	0.715
8900.0	0.263	0.043	0.957	0.220	0.738	0.006	0.999	6.053	0.770
10250.0	0.158	0.000	1.000	0.158	0.842	1.000	0.999		0.842
10850.0	0.053	0.000	1.000	0.053	0.947	1.000	0.999		0.947
11201.0	0.000	0.000	1.000	0.000	1.000		0.999		1.000

The severity of DIC developed during the disease course has been accepted by most authors as a predicting factor for disease severity [8, 26, 27] and thus, we used it in our study to categorize our cases in two groups of mild and severe disease. Our study indicated that increased serum ferritin level in patients with CCHF is predicted disease severity with 78.9% sensitivity and 87% specificity. Serum ferritin level to distinguish mild from severe CCHF disease is determined to be 1060 ng/mL with 0.801 to 0.991 confidence interval and probability ratio is 6.053.

One previous study in Turkey was the only study to investigate the correlation between serum ferritin level and disease severity in CCHF patients. This study was carried out on 66 CCHF patients during a two year period in which the patients were grouped as mild or severe according to their platelet count (higher or lower than 20,000/mm^3) and serum ferritin level was found to be significantly higher in the group with severe disease. They reported that serum ferritin level higher than 1862 ng/mL indicates severe disease with 87.5% sensitivity and 83.8% severity [22].

Hemophagocytic lymphohistiocytosis phenomenon has recently been suggested in pathogenesis of CCHF [21]. Increased serum levels of ferritin is considered as an important parameter of this phenomen [28]. In a study, 50% of Patients with CCHF disease have been reported to have reactive hemophagocytosis [29].

We chose the severity of DIC determined using ISTH scoring system to categorize our patients as severe or mild and the results from our study also suggests that increased serum ferritin level is significantly associated with disease severity. Given the fact that measurement of serum ferritin level is a fast and cost benefit lab test, it is suggested to be performed for all CCHF patients in endemic areas at their admission, so that the disease severity can be evaluated for early preparation of the required therapeutic and supportive measures.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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