The Diagnostic Value of Soluble Urokinase Plasminogen Activator Receptor in Crimean-Congo Hemorrhagic Fever Disease in the Emergency Department

Acil Serviste Kırım Kongo Kanamalı Ateş Hastalığında Soluble Ürokinaz Plazminojen Aktivatör Reseptörünün Tanısal Değeri

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ABSTRACT

Aim: The urokinase-type plasminogen activator (uPA) system consists of a protease, a receptor (urokinase-type plasminogen activator receptor, uPAR), and inhibitors that can be expressed on various cell types. Previous literature shows that the amount of soluble urokinase-type plasminogen activator receptor (suPAR) secreted from affected cells is higher in Crimean-Congo hemorrhagic fever (CCHF) patients than in healthy controls. Thus, we aimed to investigate the diagnostic value of suPAR in the differential diagnosis of CCHF in emergency services.

Material and Methods: Individuals over 16 years old with a preliminary diagnosis of CCHF disease were divided into two groups as real time-polymerase chain reaction (RT-PCR) and/or IgM positive (CCHF group) and RT-PCR and/or IgM negative (control group).

Results: Eighty patients were included in this study. Forty patients with CCHF virus PCR and/or CCHF virus IgM were identified as CCHF group and 40 patients included as negative control group. The median age of the patients was 45 (range, 16-91) years, and 49 patients (61.3%) were male. Leukocyte, platelet, and fibrinogen levels were significantly lower, while creatinine kinase, aPTT, and D-dimer levels were significantly higher in CCHF group. There was no statistically significant difference between the control group and CCHF group for SuPAR (p=0.386). In addition, control group patients not diagnosed with CCHF were examined, brucellosis, influenza, and pneumonia were found to be the most common.

Conclusion: The use of suPAR as a biomarker in the differentiation of patients with similar findings in emergency services was investigated and found to have no diagnostic value.

Keywords: Hemorrhagic fever virus; Crimean-Congo; receptors; urokinase plasminogen activator; diagnosis.

ÖZ

Amaç: Ürokinaz tipi plazminojen aktivatör (uPA) sistemi, çeşitli hücrelerden salınan proteaz, reseptör (ürokinaz tipi plazminojen aktivatör reseptör, uPAR) ve inhibitörlerden oluşur. Literatürde, enfekte olan hücrelerden salgılanan solüble ürokinaz plazminojen aktivatör reseptörü (suPAR) düzeyinin Kırım-Kongo kanamalı ateşi (KKKA) hastalarında sağlıklı kontrollere göre daha yüksek olduğu gösterilmiştir. Bu çalışmada acil serviste KKKA'nın ayırıcı tanısında suPAR'ın tanısal değerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: KKKA hastalığı ön tanısı alan 16 yaşın üstündeki bireyler gerçek zamanlı polimeraz zincir reaksiyonu (real time-polymerase chain reaction, RT-PCR) ve/veya IgM pozitif (KKKA grubu) ve RT-PCR ve/veya IgM negatif (kontrol grubu) olarak iki gruba ayrıldı.

Bulgular: Bu çalışmaya 80 hasta dahil edildi. KKKA virus PCR ve/veya KKKA virus IGM'li 40 hasta KKKA grubu olarak ve 40 hasta negatif kontrol grup olarak belirlendi. Hastaların ortanca yaşı 45 (aralık, 16-91) yıldı ve 49 (%61,3) hasta erkekti. KKKA grubunda lökosit, trombosit ve fibrinojen seviyeleri istatistiksel anlamlı olarak düşüktü, kreatinin kinaz, aPTT ve D-dimer seviyeleri ise istatistiksel anlamlı olarak yüksekti. SuPAR için kontrol grubu ile KKKA grubu arasında istatistiksel olarak anlamlı bir farklılık yoktu (p=0.386). Ayrıca KKKA tanısı almayan kontrol grubu hastaları incelendiğinde, en sık bruselloz, influenza ve pnömoni olduğu bulundu.

Sonuç: Acil serviste benzer bulgulara sahip hastaların ayırt edilmesinde bir biyobelirteç olarak suPAR'ın kullanımı araştırıldı ve tanısal değeri olmadığı bulundu.

Anahtar kelimeler: Hemorajik ateş virüsü; Kırım-Kongo; reseptörler; ürokinaz plazminojen aktivatör; tanı.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a viral infectious disease with fatal outcomes that currently affects a wide geographical region, including Africa, Asia, Europe, and the Middle East (1,2). Within the last 15 years, epidemics have been reported in Turkey at levels second only to those in Iran, Afghanistan, and Russia (3).

CCHF is a viral hemorrhagic fever disease that may present with fever and bleeding that can progress to shock and severe disease with high (10-40%) mortality (4,5). CCHF virus infection first leads to virus proliferation in dendritic cells and other local tissues, followed by virus migration to regional lymph nodes and subsequent spread to a wide variety of tissues and organs, including the liver, spleen, and lymph nodes via lymphocytes and monocytes (1). Biomarkers are urgently needed for the diagnosis and prognosis of this high-mortality disease, and many studies in the literature have addressed this purpose (5-10).

One potential biomarker is the urokinase-type plasminogen activator (uPA) system. The uPA system consists of a protease, a receptor (urokinase-type plasminogen activator receptor, uPAR), and inhibitors that can be expressed on various cell types, including neutrophils, lymphocytes, monocytes/macrophages, and endothelial and tumor cells. The soluble form of the uPAR is defined as the soluble urokinase-type plasminogen activator receptor (suPAR) and involved in immunological functions ranging from cell adhesion, migration, and chemotaxis to proteolysis, immune activation, tissue remodeling, invasion, and signal transduction (11,12). The available literature indicates that suPAR secretion is greater from lymphocytes and monocytes from patients with CCHF than from healthy controls (13).

The aim of the present study was to investigate the diagnostic value of suPAR in differential diagnosis of CCHF at emergency medicine.

MATERIAL AND METHODS

The participants in this study, held from June to September 2018, were over the age of 16 admitted to our hospital's emergency service who had received a preliminary diagnosis of CCHF disease, had been diagnosed in the relevant clinics, and agreed to participate. Patients less than 16 years of age and who did not agree to participate in the study were not included. The study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (05.03.2018, 05-35).

The medical records of the patients were retrospectively reviewed. Clinical findings and laboratory results upon admittance to emergency services were recorded. Real-time polymerase chain reaction (RT-PCR) (QiagenR CCHFV viral RNA KIT, Qiagen, Hilden Germany) and CCHF virus IgM tests with the indirect immunofluorescence test method were studied in the reference laboratory. RT-PCR and/or IgM positivity were used for the definitive diagnosis of the CCHF cases. Patients were classified as serum RT-PCR and/or IgM positive (CCHF group) and RT-PCR and/or IgM negative (control group). The clinical diagnoses made for the patients in the control group were recorded.

The serum and plasma of the blood samples taken for the examination of the patients in the emergency service were used. After the samples were taken into tubes without anticoagulants, they were kept at room temperature for 30 minutes in line with the ELISA kit instructions we used. Then they were centrifuged at 3000 rpm for 20 minutes at +4 °C. Serum remaining on top of tubes was transferred to Eppendorf tubes and lifted to -80 °C by the date of the study. SuPAR was manually studied using the ELISA Kit (cat.no: SL2132Hu) according to the kit procedures. ELISA reader was performed with ChemWell® 2910 Automated EIA and Chemistry Analyzer (Awareness Technology, USA).

Statistical Analysis

Statistical analyses were made with the SPSS v.20.0 package. Normality assumption was evaluated using histograms and the Kolmogorov-Smirnov test. Differences between two groups were analyzed using Student's t-test for the quantitative variables and the Mann-Whitney U test for the variables not distributed normally. Categorical variables were analyzed with Pearson chi-square and Fisher's exact test. Spearman correlation analysis was performed to evaluate the correlation between suPAR and other parameters. Quantitative data were expressed as median, 25%-75% quartiles, minimum-maximum or mean±standard deviation, and categorical variables as frequency (percentage). A two-sided p value of 0.05 was considered as statistically significant.

RESULTS

Two-hundred and nine patients who met the inclusion criteria were identified. While 71 of these 209 patients were diagnosed with CCHF, 138 of them were not. According to the number of kits, 80 patients admitted to the emergency service with a CCHF pre-diagnosis, 40 patients for the CCHF group and 40 for the control group, were selected randomly.

The median age of the patients was 45 (range, 16-91) years, and 49 (61.3%) patients were male. Forty patients with positive PCR and/or IgM results for CCHF virus were identified as the CCHF group, and 40 patients with disease symptoms but without CCHF positivity were designated as the negative control group. Median age was 50.5 (range, 16-91) years in control group, and 27 (67.5%) of the patients were male and 13 (32.5%) were female; while median age was 43.5 (range, 16-91) years in CCHF group, and 22 (55.0%) of the patients were male and 18 (45.0%) were female. There was no statistically significant difference between CCHF and control groups in terms of age (p=0.988) and gender (p=0.251).

The comparison of laboratory values between these two groups is presented in Table 1. Creatinine kinase, D-dimer, aPTT, fibrinogen, leukocyte, and platelet values were found to be significantly different between the CCHF and control groups. Leukocyte, platelet, and fibrinogen levels were significantly lower in the CCHF group (p<0.001, p=0.006, p<0.001; respectively). Creatinine kinase, activated partial thromboplastin time (aPTT), and D-dimer levels were significantly higher in the CCHF group (p=0.001, p=0.005, p=0.013; respectively). No statistically significant difference was detected in the SuPAR levels between the control group and the CCHF group (p=0.386). The suPAR levels of the CCHF patients were positively correlated with alanine aminotransferase (ALT) and aPTT levels (r=0.295, p=0.008, and r=0.309, p=0.006, respectively).

Table 1. Comparison of laboratory parameters in CCHF and control groups

	Control (n=40)			CCHF (n=40)			p
	Median	**Q1 - Q3**	**Min - Max**	**Median**	**Q1 - Q3**	**Min - Max**	
AST (IU/L)	47.5	22.5 - 97.5	15 - 913	53.5	32.0 - 148.75	18 - 914	0.105
ALT (IU/L)	36.5	16.0 - 79.5	7 - 853	36.5	19.0 - 88.5	15 - 604	0.516
LDH (IU/L)	303.0	235.75 - 376.25	125 - 1426	298.0	229.5 - 496	116 - 1995	0.427
CPK (mg/dL)	108.5	66 - 203	20 - 2492	247.5	128.25 - 474.75	38 - 4003	**0.001**
WBC (10^3/μL)	6539	4001 - 9750	2254 - 14440	2736	2268.5 - 3549.5	802 - 13490	**<0.001**
PLT (10^3/μL)	130100	106400 - 148800	33000 - 307200	107950	61500 - 128900	6780 - 263500	**0.006**
CRP (mg/dL)	6.33	1.33 - 11.80	0.32 - 21.00	1.61	0.32 - 3.63	0.30 - 8.08	**<0.001**
aPTT (second)	26.4	24.0 - 28.6	20.3 - 38.3	28.3	26.1 - 33.9	22.0 - 53.5	**0.005**
D-dimer	1.33	0.92 - 3.34	0.19 - 32.7	2.45	1.4 - 5.09	0.19 - 80.0	**0.013**
INR	1.13	1.05 - 1.22	0.89 - 1.90	1.1	1.01 - 1.19	0.92 - 1.82	0.128
Creatinine (mg/dl)	0.89	0.77 - 1.2	0.45 - 3.57	0.79	0.73 - 0.95	0.63 - 2.72	0.067
Fibrinogen (mg/dl)	298	250 - 384	177 - 605	223	204.75 - 265	118 - 900	**<0.001**
suPAR (pg/ml)	4740	3775 - 6905	2615 - 13935	4477.5	3108.75 - 6410	1885 - 12985	0.386

CCHF: Crimean-Congo Hemorrhagic Fever, Q1-Q3: 25th - 75th percentile, Min-Max: Minimum-Maximum, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, WBC: white blood cells, PLT: thrombocyte count, CRP: C-reactive protein, aPTT: activated partial thromboplastin time, INR: international normalized rate, suPAR: soluble urokinase-type plasminogen activator receptor

A weak positive correlation was also found between suPAR and both aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels (r=0.264, p=0.018, and r=0.231, p=0.040, respectively, Table 2).

The most common clinical findings in CCHF patients were fever (n=38, 95.0%), headache (n=37, 92.5%), myalgia (n=37, 92.5%), weakness, nausea and vomiting (n=23, 57.5%). However, no statistically significant difference was found between the control group and CCHF patients in terms of clinical findings (Table 3).

The control group patients had brucellosis (n=7, 17.5%), influenza (n=7, 17.5%), and pneumonia (n=7, 17.5%) as the most common diagnoses (Table 4).

Table 2. Correlation of suPAR value and some biomarkers in CCHF patients

	suPAR	
	r	**p**
AST	**0.264**	**0.018**
ALT	**0.295**	**0.008**
LDH	**0.231**	**0.040**
CPK	0.048	0.670
WBC	0.051	0.656
PLT	-0.034	0.762
CRP	0.053	0.641
aPTT	**0.309**	**0.006**
D-dimer	0.030	0.792
INR	0.013	0.911
Creatinine	0.126	0.267
Fibrinogen	-0.040	0.726
Sedimentation	-0.094	0.407

suPAR: soluble urokinase-type plasminogen activator receptor, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, WBC: white blood cells, PLT: thrombocyte count, CRP: C-reactive protein, aPTT: activated partial thromboplastin time, INR: international normalized rate

Table 3. Comparison of clinical findings in CCHF and control groups, n (%)

Clinical findings	Control (n=40)	CCHF (n=40)	p
Fever	35 (87.5)	38 (95.0)	0.432[*]
Hypotension	6 (15.0)	3 (7.5)	0.481[*]
Tachycardia	3 (7.5)	3 (7.5)	0.999[*]
Blur of Consciousness	2 (5.0)	3 (7.5)	0.999[*]
Ecchymosis	2 (5.0)	2 (5.0)	0.999[*]
Bleeding	4 (10.0)	3 (7.5)	0.999[*]
Headache	36 (90.0)	37 (92.5)	0.999[*]
Myalgia	32 (80.0)	37 (92.5)	0.105[**]
Nausea-vomiting	19 (47.5)	23 (57.5)	0.370[**]
Diarrhea	8 (20.0)	12 (30.0)	0.302[**]
Abdominal pain	13 (32.5)	16 (40.0)	0.485[**]

*: Fisher's exact test, **: Pearson chi-square test

Table 4. Distribution of final diagnoses of the control group

Final diagnose	n (%)
Brucellosis	7 (17.5)
Flu	7 (17.5)
Pneumonia	7 (17.5)
Isolated thrombocytopenia	4 (10.0)
Lower gastrointestinal tract bleeding	3 (7.5)
Acute gastroenteritis	2 (5.0)
Drug intoxication	2 (5.0)
Urinary tract infection	2 (5.0)
Acute hepatitis A	1 (2.5)
Acute pancreatitis	1 (2.5)
Q Fever	1 (2.5)
ITP	1 (2.5)
Acute cholecystitis	1 (2.5)
Skin, soft tissue infection	1 (2.5)

DISCUSSION

CCHF cases may show some clinical symptoms, including leukopenia, leukocytosis, anemia, thrombocytopenia, elevated AST and ALT levels, increased LDH levels, raised creatine phosphokinase (CPK) levels, prolonged prothrombin time (PT), aPTT levels, increased D-dimer levels, and elevated amounts of fibrin breakdown products (5-10). We detected elevations in thrombocytopenia, leukopenia, CK, and D-dimer levels in our CCHF group, as well as reduced levels of fibrinogen. However, these laboratory findings are known to be non-specific for CCHF (14).

There is need for an easy, inexpensive, and perfect single biomarker for the diagnosis, follow-up, and prognosis of diseases like CCHF, and studies have been conducted to search for this type of biomarker (15,16). The aim of our study was to determine the diagnostic value of suPAR in the differential diagnosis of laboratory samples and clinically similar patients in the emergency department.

Activation of lymphocytes, monocytes, and macrophages and the resulting excess secretion of cytokines have been reported to play an important role in the pathogenesis and prognosis of CCHF, as in other viral hemorrhagic diseases. Infected monocytes and lymphocytes have been shown to express high cell surface uPAR levels, and the serum suPAR level may be associated with the number of infected cells in the organism. For this reason, suPAR levels are predicted to be higher in CCHF-virus-infected patients than in healthy controls (17,18).

The expression of suPAR has been shown to increase during endotoxemia (19). Also, although its diagnostic value is lower than that of procalcitonin and C-reactive protein in sepsis (61.2% of which is bacterial), the suPAR level has been reported to increase during sepsis (20). In the cerebrospinal fluids of patients with proven central nervous system infections, suPAR levels were statistically significantly higher than in patients without infection (21). In patients with CCHF infection, compared to healthy controls, suPAR levels were found to be significantly higher, and a high diagnostic value was obtained with a threshold value of 3.06 ng/ml (13).

Biomarkers are also known to be important in predicting morbidity and mortality. In the study conducted by Yılmaz et al. (13), they found that suPAR levels were shown to have a prognostic significance (cut-off, 10.6 ng/mL) for mortality in patients with CCHF. Also, suPAR concentrations may reflect the severity of infection in other diseases. For example, suPAR levels are associated with poor outcomes in communicable and non-communicable diseases and with high mortality in malaria, tuberculosis, human immunodeficiency virus infection, and some forms of cancer (22-25). As seen in our study, no specific clinical findings and biomarkers were identified for CCHF, although suPAR has been indicated in the literature to be a diagnostic and prognostic biomarker that differentiates between patients with CCHF and healthy individuals (13). However, we found no statistically significant difference between our patients with CCHF and the control group in terms of suPAR. This situation is thought to reflect the fact that the control group selected in our study had diseases that could be confused with CCHF, both clinically and in laboratory findings. In our study, the most common diagnoses in the control group were again infectious diseases such as brucellosis, influenza, and pneumonia, and suPAR levels have been reported to increase in infectious diseases like pneumonia, brucellosis, pancreatitis, sepsis, tuberculosis, and malaria (22,26-30). In a previous study that reported a significant difference between CCHF patients and healthy individuals, a positive correlation was found between suPAR and the ALT, aPTT, AST, and LDH values in CCHF patients, as in our study (13). This result suggests that suPAR acts as another non-specific biomarker of infection and may be useful in diagnostic algorithms.

This study had some limitations, including the small number of enrolled patients, its design as a single-center study, and the lack of a healthy control group.

CONCLUSION

This study confirms the importance of isolating patients who come to the emergency service with clinical and laboratory findings resembling CCHF infection in terms of disease control and referring them to the relevant clinic. However, the use of suPAR as a biomarker appears to have no diagnostic value in differentiating patients with similar findings in clinical practice in the emergency department. Nevertheless, suPAR could be useful as a parameter in algorithm development due to its correlation with other non-specific biomarkers.

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