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Examination of the specific clinical symptoms and laboratory findings of Crimean-Congo hemorrhagic fever

Cetin Kilinc[1], Ridvan Gückan[1], Mustafa Capraz[2], Kenan Varol[3], Erman Zengin[4], Zafer Mengeloglu[5] & Elif Menekse[6]

[1]*Department of Microbiology;* [2]*Department of Internal Medicine;* [3]*Department of Radiology, Sabuncuoglu Serafeddin Training and Research Hospital, Amasya University, Amasya;* [4]*Amasya Institute of Public Health, Amasya;* [5]*Department of Medical Microbiology, Faculty of Medicine, Abant Izzet Baysal University, Bolu;* [6]*Laboratory of Biochemistry Department, Sabuncuoglu Serafeddin Training and Research Hospital, Amasya University, Amasya, Turkey*

ABSTRACT

Background & objectives: Crimean-Congo hemorrhagic fever (CCHF) is a fatal disease, caused by a tick-borne virus (Nairovirus), having a high mortality rate. The study was aimed to evaluate the risk factors, the presenting symptoms and findings of the patients with prediagnosis of CCHF disease, and to compare these variables between the CCHF-positive and CCHF-negative patients. It was also aimed to develop a scoring formula for the diagnosis of CCHF.

Methods: In total, 281 patients who were admitted to the Sabuncuoglu Serafeddin Training and Research Hospital, Amasya, Turkey between 2011 and 2015 and were prediagnosed with CCHF based on the clinical symptoms, laboratory findings and risk factors were included in the study. The definitive laboratory diagnosis of patients with prediagnosis of CCHF was ensured via molecular and serological methods. In addition, a mathematical diagnostic scoring formula was developed for enhancing the laboratory results of CCHF.

Results: The ratio of certain clinical symptoms such as fever ($p<0.001$), headache ($p<0.001$), widespread body pain ($p<0.001$), fatigue ($p = 0.001$), nausea and vomiting ($p = 0.013$) in CCHF-positive patients were found to be significantly higher compared to the ratio in CCHF-negative patients. In terms of laboratory findings such as presence of leucopenia ($p<0.001$), creatine kinase (CK) elevation ($p<0.001$), thrombocytopenia ($p<0.001$), aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation ($p<0.001$), lactate dehydrogenase (LDH) levels ($p = 0.002$), absence of abnormal findings on chest radiograph ($p = 0.042$), and the absence of anaemia ($p = 0.007$), the CCHF-positive patients had higher rates in comparison to CCHF-negative ones.

Interpretation & conclusion: It was inferred that certain clinical symptoms and laboratory findings such as fever, headache, widespread body pain, fatigue, leucopenia, nausea, vomiting, high CK levels, thrombocytopenia, AST/ALT elevation and elevated LDH levels are highly specific and are required to be considered in the definitive diagnosis of CCHF, particularly in regions where this infection is observed as endemic.

Key words CCHF; hemorrhagic fever; Turkey

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a fatal disease with 10–40% mortality[1]. The disease was first characterized in the Crimea in 1944, and later recognized in 1956 as the cause of illness in the Congo. The disease is caused by a tick-borne CCHF virus in the genus of Nairovirus of the *Bunyaviridae* family[2]. The medically important tick-borne viruses are the ones that are most commonly observed in nature. CCHF has been reported in >30 countries in Africa, Asia, Southeast Europe and the Middle East[3]. The disease virus is primarily transmitted to individuals/people through infected tick bite however, it can also be transmitted with the blood or body fluids of infected individuals or animals via contact[4–5].

In Turkey, CCHF is considered as endemic in middle Anatolian region and middle Black Sea region as pathogen viruses of CCHF have been reported to be transmitted by ticks since 2002[6]. The CCHF disease can manifest itself through various clinical symptoms like fever, fatigue, generalized muscle pain, headache, chest pain, arthralgia, and diarrhoea as well as by laboratory findings such as elevated liver enzymes, increased duration of bleeding and thrombocytopenia. It is very crucial to identify the disease particularly in regions where it occurs frequently in order to take necessary precautions and initiate the treatment without delay[7].

The study was aimed to evaluate the associated risk factors, the presenting symptoms and findings of the patients with prediagnosis of CCHF disease, and to com-

pare these variables between the CCHF-positive and CCHF-negative patients. It was also aimed to develop a diagnostic scoring formula for more accurate diagnosis of CCHF.

MATERIAL & METHODS

The present study involved evaluating all the patient records retrospectively. A total of 281 patients were included, who were admitted to the Sabuncuoglu Serafeddin University Training and Research Hospital, Amasya, Turkey and pre-diagnosed with CCHF on the basis of their clinical symptoms, laboratory findings and risk factors between 2011 and 2015. The study also included the data of patients obtained from different health institutions in Amasya, where the patients were further tested. Blood and body fluid samples of these prediagnosed patients were analysed in order to make a definitive laboratory diagnosis of CCHF. The viral nucleic acid was quantified by using real time reverse transcriptase polymerase chain reaction (RT-PCR). Further, the anti-CCHF virus IgM positivity or IgG seroconversion was determined by using ELISA in the laboratory of public health institutions of the Ministry of Health, Turkey.

The risk factors, clinical symptoms and laboratory findings of CCHF-positive (102) and CCHF-negative (179) patients were examined and the results were statistically analyzed and compared to each other in order to identify more specific laboratory findings and clinical symptoms of CCHF. Statistical analyses were performed by using the statistical package for the social sciences version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Independent group *t*-tests were used in order to determine the mean comparisons of continuous variables. Chi-square tests were conducted for proportion comparisons for categorical variables, whereas Fisher's exact test was used in case the data were sparse. The '*p*' values lower than 0.05 ($p<0.05$) were considered as statistically significant.

In addition, a mathematical formula/score was developed for the diagnosis of CCHF according to the symptoms and clinical findings which were found to be significantly different in the CCHF-positive patient group from the CCHF-negative ones. The percentage of the CCHF-positive group for each significant symptom or finding was divided by the percentage of the CCHF-negative group, and a coefficient was determined. The coefficients for all the significantly different findings were rolled up for one decimal, and were added to get/obtain the total coefficient. Finally, the diagnostic score was calculated by adding all the coefficients of the symptoms or findings of the patient which are concordant with the significantly different ones, and dividing the sum of all the coefficients to the obtained total coefficient.

Step-1: Coefficient for each significant symptom/finding (C)= (Percentage of the CCHF-positive group)/(Percentage of the CCHF-negative group); *Step-2:* Total coefficient (TC) = Sum of all the coefficients; and *Step-3:* Calculation of a patient's diagnosis score (DS) = 100× (Sum of all coefficients of only the positive symptoms/findings of the patient)/(TC of the study).

RESULTS

Out of 281 patients, 102 (36.3%) were detected as CCHF-positive and 179 (63.7%) were detected as CCHF-negative by using serological test and PCR. No increpencies were observed between the two methods. The mean age of the CCHF-positive patients was 46.48 ± 25.12 yr, among which 54% (55) of them were males and 46% (47) of them were females. The four of positive patients (3.9%) expired. Most frequently observed symptoms in CCHF-positive patients were fatigue (86.2%), widespread body pain (74.5%), fever (71.5%), headache (68.6%), nausea, and vomiting (46%); while, most frequently encountered laboratory findings were leucopenia (84.3%), thrombocytopenia (83.3%), prolongation of the aPTT duration (76.4%), and elevated LDH levels (63.7%). Risk factors observed in the life of CCHF-positive patients were rural life (97%), contact with animals (80.4%), dealing with agriculture-livestock (59.8%) (Table 1).

The two groups of patients were statistically compared according to their clinical symptoms and laboratory findings. Certain clinical symptoms such as fever ($p<0.001$), headache ($p<0.001$), widespread body pain ($p<0.001$), fatigue ($p = 0.001$), nausea and vomiting ($p = 0.013$) were found significantly higher in case of CCHF-positive patients compared to the CCHF-negative patients (Table 2). However, there was no statistically significant difference between these two patients groups in case of some other clinical findings, *viz.* the presence

Table 1. Risk factors in Crimean-Congo hemorrhagic fever positive patients

Risk factors	No. of patients	%
Rural life	99	97
Contact with animals	82	80.4
Tick bite	64	62.7
Dealing with farming-husbandry	61	59.8
Animal tissue contact	31	30.4
Contact with CCHF patients	1	1

of bleeding, abdominal pain, diarrhoea, rashes, splenomegaly, tachycardia, impairment of consciousness and hypotension (Table 2). According to the results of laboratory and radiographic findings like presence of leucopenia ($p<0.001$), CK elevation ($p<0.001$), thrombocytopenia ($p<0.001$), AST/ALT elevation ($p<0.001$), elevated LDH levels ($p = 0.002$), absence of abnormal findings on chest radiograph ($p = 0.042$) and the absence of anaemia ($p = 0.007$), the rates of CCHF-positive patients were significantly higher compared to CCHF-negative patients (Table 3). On the other hand, there was no statistically significant difference between two groups regarding the

Table 2. Comparison of the clinical symptoms according to CCHF test results of the patients

Variables	Results	CCHF-positive		CCHF-negative		Total number of patients	*p*-value
		No. of patients	%	No. of patients	%		
Fever	Present	73	45.1	89	54.9	162	<0.001
	Absent	29	24.4	90	75.6	119	
Headache	Present	70	47.9	76	52.1	146	<0.001
	Absent	32	23.7	103	76.3	135	
Widespread body pain	Present	76	48.4	81	51.6	157	<0.001
	Absent	26	21	98	79	124	
Fatigue	Present	88	41.9	122	58.1	210	0.001
	Absent	14	19.7	57	80.3	71	
Nausea and vomiting	Present	47	45.6	56	54.4	103	0.013
	Absent	55	30.9	123	69.1	178	
Diarrhea	Present	25	43.9	32	56.1	57	0.170
	Absent	76	34.1	147	65.9	223	
Stomachache	Present	23	32.4	48	67.6	71	0.455
	Absent	78	37.3	131	62.7	209	
Bruises in the body	Present	3	30	7	70	10	0.695
	Absent	97	36.1	172	63.9	269	
Skin eruption	Present	8	40	12	60	20	0.810
	Absent	94	36	167	64	261	
Bloody diarrhea	Present	1	12.5	7	87.5	8	0.156
	Absent	101	37	172	63	273	
Impairment of consciousness	Absent	3	42.9	4	57.1	7	0.707
	Present	99	36.1	175	63.9	274	
Gum bleeding	Absent	1	16.7	5	83.3	6	0.424
	Present	100	36.5	174	63.5	274	
Hypotension	Absent	5	31.3	11	68.8	16	0.665
	Present	97	36.6	168	63.4	265	
Tachycardia	Absent	14	53.8	12	46.2	26	0.051
	Present	88	34.5	167	65.5	255	
Epistaxis	Absent	1	16.7	5	83.3	6	0.422
	Present	101	36.7	174	63.3	275	
Petechiae	Absent	3	37.5	5	62.5	8	0.943
	Present	99	36.3	174	63.7	273	
Splenomegaly	Absent	1	20	4	80	5	0.656
	Present	101	36.6	175	63.4	276	
Ecchymosis	Absent	2	50	2	50	4	0.623
	Present	100	36.1	177	63.9	277	
Hematuria	Absent	2	25	6	75	8	0.500
	Present	100	36.6	173	63.4	273	
Gastrointestinal bleeding	Absent	3	27.3	8	72.7	11	0.525
	Present	99	36.7	171	63.3	270	

CCHF: Crimean-Congo hemorrhagic fever.

Table 3. Comparison of the laboratory and radiographic findings according to CCHF test results of the patients

Variables	Results	CCHF-positive		CCHF-negative		Total number of patients	*p*-value
		No. of patients	%	No. of patients	%		
Anaemia	Present	8	18.2	36	81.8	44	0.007
	Absent	94	39.7	143	60.3	237	
Aspartate transferase/ alanine transferase) AST/ALT increment	Present	67	51.5	63	48.5	130	<0.001
	Absent	35	23.5	114	76.5	149	
Findings on chest radiograph	Present	1	8.3	11	91.7	12	0.042
	Absent	95	37.1	161	62.9	256	
Leukopenia	Present	86	53.8	74	46.3	160	<0.001
	Absent	16	13.2	105	86.8	121	
Creatine kinase (CK) increment	Present	49	54.4	41	45.6	90	<0.001
	Absent	51	27.6	134	72.4	185	
Thrombocytopenia	Present	85	44.3	107	55.7	192	<0.001
	Absent	17	19.1	72	80.9	89	
Lactate dehydrogenase (LDH) increment	Present	65	45.1	79	54.9	144	0.002
	Absent	35	26.9	95	73.1	130	
International normalized ratio (INR)	<0.9	18	54.5	15	45.5	33	0.07
	0.9–1.2	52	34.4	99	65.6	151	
	>1.2	32	33.3	64	66.7	96	
Activated partial thromboplastin time (aPTT)	<11	24	35.8	43	64.2	67	0.906
	>11	78	36.6	135	63.4	213	

aPTT duration and international normalized ratio (INR) values (Table 3).

The coefficients calculated to develop a scoring formula are listed in Table 4. According to it, the total coefficient obtained was 29.2. So, a patient's diagnostic coefficient can be calculated by adding up all the coefficients of the positive findings, and dividing the total number by 29.2. For instance, if a patient has fever (the coefficient is 1.9), headache (2.0), body pain (2.4), and fatigue (2.1); the total coefficient is 1.9+2.0+2.4+2.1= 8.4; and the diagnostic score is $100 \times 8.4/29.2 = 28.8\%$.

DISCUSSION

CCHF is a deadly disease with 10–40% mortality caused by a type of Nairovirus (Bunyaviridae family) infection[1]. Majority of CCHF cases have been reported from former Soviet Union countries such as Crimea, Tajikistan, Uzbekistan, Bulgaria and an African country; Congo before 1970s[4]. Later, the cases were also reported from Eastern Europe, Central Asia, Africa and many other countries primarily Saudi Arabia, Pakistan, India, Iran, *etc*[8–11]. CCHF was noticed for the first time in Turkey during 2002 and it is now observed as endemic and sporadic in various cities in Turkey[12].

Tick bites can be observed in any region of Turkey, particularly in places where livestock is common and where there are forest, bush and bushy pastures. At the same time, tick bites can be seen in individuals who live in rural areas, deal with livestock, veterinaries, health professionals, soldiers and individuals who go to camps and picnics[11–13]. In this study, CCHF-positive patients had some common risk factors such as rural life (97%), contact with animals (80.4%), and dealing with agriculture-livestock (59.8%). Almost all of the CCHF-positive patients [99 of 102 (97%)] were living in rural area, and it was observed that two of the rest three CCHF-positive patients, who were not living in rural region, visited a rural area shortly before they developed the disease. Similar to this study, Taskesen *et al*[14] and Sumer *et al*[15] have shown that tick bites are observed mostly in farmers and individuals who are engaged in animal husbandry or live in rural areas. This shows that we should be extremely careful while examining the patients coming from rural areas.

Clinical symptoms and laboratory findings can vary

during the course of the disease. However, primary symptoms of CCHF disease are sudden onset of fever, malaise, myalgia, rash and headache. Nausea, vomiting, abdominal pain, conjunctivitis, pharyngitis, hypotension and bradycardia can be observed in the early hemorrhagic term of CCHF. During the advanced late stages of the disease, various bleedings problems/symptoms such as epistaxis, hematemesis, melena, hematuria and hemoptysis and can be observed. In some of the cases, hepatomegaly and splenomegaly can also be seen. Central nervous system dysfunction, delirium, convulsions and coma can develop. Common laboratory findings are anaemia, leucopenia, thrombocytopenia, increase in the level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK) and lactic dehydrogenase (LDH) enzymes, and prolongation of the duration of active partial thromboplastin time (aPTT) and prothrombin time (PT). In order to make a definite diagnosis of CCHF disease, the presence of the virus in blood and body fluid samples should be confirmed by using serological or molecular techniques[16–18].

In this study, the CCHF-positive and negative patients were compared in terms of their clinical symptoms and laboratory findings in order to detect more specific signs of the disease. Clinical symptoms such as fever ($p<0.001$), headache ($p<0.001$), widespread body pain ($p<0.001$), fatigue ($p = 0.001$), nausea and vomiting ($p = 0.013$) was observed in significantly higher rates in CCHF-positive patients than the negative ones. However, there was no significant difference between the two groups as reflected in some of the clinical findings like the presence of bleeding, abdominal pain, diarrhoea, rash, splenomegaly, tachycardia, impairment of consciousness and hypotension.

In terms of the results of laboratory and radiographic findings such as presence of leucopenia ($p<0.001$), CK elevation ($p<0.001$), thrombocytopenia ($p<0.001$), AST/ALT elevation ($p<0.001$), increased LDH levels ($p = 0.002$), absence of abnormal findings on chest radiograph ($p = 0.042$) and the absence of anaemia ($p = 0.007$), the rates of CCHF-positive patients were significantly higher compared to CCHF-negative patients. Even though there was elongation in the aPTT durations and increase in INR values of CCHF-positive patients with respect to negative ones, the difference detected was statistically insignificant. In different studies, certain laboratory findings such as leukopenia and thrombocytopenia have attracted the attention. The increase in the levels of alkaline phosphatase, gamma glutamyl transferase and lactate dehydrogenase follows the increase in the AST, ALT, CK and bilirubin values. Also, there is a prominent distortion in prothrombin time (PTT), aPTT and other coagulation tests[19–20].

In the present study, a diagnostic score was developed according to the significantly different symptoms and findings that would help the clinician to predict the accurate diagnosis probability of CCHF in a patient. However, this score can be improved with larger studies. It will contribute to the diagnostic approach in CCHF prediagnosed cases.

CONCLUSION

In places where this endemic infection is observed, certain clinical symptoms and laboratory findings (such as fever, headache, widespread body pain, fatigue, leukopenia, nausea, vomiting, high CK levels, thrombocytopenia, AST/ALT elevation, elevated LDH levels, absence of abnormal finding in chest X-ray and absence of anemia) along with risk factors (such as tick bite, contact with animals, living in the countryside, dealing with farming and animal husbandry) are highly specific findings which should be checked in the definitive CCHF diagnosis. Hence, it is very important to ensure the early diagnosis of this disease that can also lead to nosocomial infections, in order to take necessary precautions and checking further delay in the treatments. Besides, for the definitive diagnosis of CCHF, it is also very crucial to assess suspected patients in terms of their clinical symptoms, risk factors and laboratory findings as explained in the present study.

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Correspondence to: Dr Cetin Kilinc, Department of Microbiology, Amasya University, Sabuncuoglu Serafeddin Training and Research Hospital, Amasya, Turkey.
E-mail: elifzehra2008@hotmail.com

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