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Use of Routine Laboratory Tests in Diagnosis of Crimean-Congo Hemorrhagic Fever in the Emergency Department

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is a disease effecting multiple organ systems by microvascular damage and deterioration of hemostasis. Even though the main diagnosis relies on reverse transcriptase-polymerase chain reaction (rt-PCR), it is also known that thrombocytopenia, and/or leukopenia, elevated levels of alanine aminotranferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase and creatine kinase may be determined. In this study, our aim was to analyse the patients who were hospitalized with suspected CCHF and consequently undergone PCR testing. PCR (+) and PCR (-) patients were compared according to their laboratory results obtained in the emergency department (ED). In a 2-year period, a total of 150 (female/male: 47/103) patients of any age hospitalized with the suspicion of CCHF were involved into the study. The patients were divided into 2 groups according to their rt-PCR results as PCR (+) (and PCR (-) patients. Two groups were compared according to the laboratory results obtained in the ED. The most common complaint on admission was weakness (n=111, 74%) followed by fever (n=95, 63.3%) and headache (n=16, 10.7%). Ribavirin therapy was administered to 62 patients (41.3%). In 62 patients, PCR test was positive (41.3%). When PCR (+) and PCR (-) groups were compared according to the laboratory results obtained in the ED, number of patients with high AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels were significantly higher in PCR (+) group. The diagnosis of CCHF is a challenging issue which requires high suspicion, particularly in the endemic regions. High AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels determined in the ED should raise the suspect for the possibility of PCR positivity.

Key words: *Crimean-Congo hemorrhagic fever, Diagnosis, Emergency department.*

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a serious disease caused by the CCHF virus of the Bunyaviridae family (1). Transmission of the virus to humans occurs through tick bites, squashing an infected tick without gloves, exposure to blood and tissues of infected animals or contact with the blood of an infected person during the acute phase of the disease (2,3). Commonly known reservoires of the virus are cattle, sheep, goats, hedgehogs and hares. Numerous species of ticks can carry the virus; however, very few of them have been implicated as vectors. Hyalomma spp. is the most important tick vector since the virus is commonly isolated from it and its geographic distribution coincides with that of the disease (2).

The exact diagnosis of the disease is based on molecular biology tests. CCHF may be documented by PCR detection of the virus genome during the first daysafter the onset of illness, and then by serological testing for IgM antibodies as from the 2nd week afterinfection (3).

Similar to other viral hemorrhagic fevers, the disease may be divided into 3 clinical phases. The pre-hemorrhagic phase is characterised by non-spesific symptoms. In this phase, high fever of 39-41° C which lasts for 4-5 days can be determined. Also, myalgia, headache, retro-orbital pain and sometimes a stiff neck can be present. It can also be associated with gastrointestinal symptoms then occur withnausea and/or vomiting and more rarely diarrhea. The pre-hemorrhagic phase may last up to one week. Mucous tissue bleeding emerges in the hemorrhagic pahse. Besides epistaxis,hematemesis, more rarely melena, hemoptysis and hematuria, skin manifestations such as ecchymosis/purpura may be observed. Third phase is the convalescence phase. It starts 10–20 days after the onset of the first clinical symptoms and lasts for 10 days. Fatigue, tachycardia with labile blood pressure, temporary alopecia and memory impairment may be observed (3).

Infection with the CCHF virus results in endothelial dysfunction and capillary leaking of red blood cells and plasma into tissue. Endothelial damage leads to activation of the coagulation cascadeand thrombocytopenia, which increases bleeding (4). Thus, patients with CCHF disease have leukopenia, thrombocytopenia, and elevated AST, ALT, LDH and CPK levels. Additionally, higher AST and ALT levels are associated with severe cases (5).

In treatment, a nucleosid analog Ribavirin is used since it has been shown to inhibit CCHF virus replication. If administered in the early phase, Ribavirin descreases the mortality (1). It is essential to detect the disease in the early phase and initiate the treatment with ribavirin and supportive measures (6).

It was previously reported that the predictors of CCHF in the Emergency Department (ED) were epistaxis and elevated K+, WBC and AST levels (2). In this study, we aimed to determine the patients who will experience the severe disease by analysing findings in the ED.

Materials and Methods

After obtaining ethical approval from the Local Ethics Comitee, (Decision no: 373, date 23/12/2020), we retrospectively collected the medical data of the patients hospitalized in Hitit University Hospital with suspected CCHF. A total of 150 (female/male: 47/103) patients of any age

hospitalized with the suspicion of CCHF between January 1st 2019 and December 31st 2020 were involved into the study. Blood samples of the patients were sent to an advanced center for RT-PCR test. CCHF virus RNA in the blood samples through rt-PCR evaluation were considered confirmed CCHF cases.

Patients were divided into two groups as PCR (+) (group 1) and PCR (-) (group 2) according to the test results. Demographical features, complaints on admission, vital signs (temperature, blood pressure, pulse rate) and physical examination findings (according to the systems) of the patients were investigated. Besides, laboratory findings of the patients such as complete blood count (CBC), blood biochemistry test, and coagulation panel were investigated and compared according to the groups.

Statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation (SD). The ShapiroWilk test was used to analyze normal distribution assumption of the quantitative outcomes. To compare two groups, Student t test was used for normally distributed data and Mann-Whitney U test was used for non-normal data. $p<0.05$ was accepted as statistically significant in comparisons.

Results

Into the study, a total of 150 patients were included. Of these patients, 103 (68.7%) were male. Mean age of male patients was 47.88 ± 17.37 (min-max: 18-89 years). Number of female patients was 47 and mean age of female patients was 45.43±8.8 (min-max: 18-75 years). Ninety-six patients lived in rural areas (64%) and 54 patients lived in the city center (36%). When complaints on admission to the ED were investigated, 111 had weakness (74%), 95 had fever (63.3%), 16 had headache (10.7%), 12 had diarrhea (8%), 4 had abdominal pain (2.7%), and 3 had syncope (2%). General characteristics of the patients are listed in Table 1.

Table 1: General characteristics of the groups.

	n (%)	**n PCR (+)**	**n PCR (-)**	***p***
Symptoms				
Weakness	111 (73.5%)	52	59	0.021
Fever	95 (62.9%)	35	60	0.142
Headache	16 (10.6%)	10	6	0.069
Diarrhea	12 (7.9%)	6	6	0.525
Abdominal pain	4 (2.6%)	1	3	0.501
Syncope	3 (% 2)	3	0	0.037
Method of Treatment				
Ribavirin Therapy	62 (41.1%)	40	22	0.0
Outcome				
Discharge	149 (98.7%)	62	87	0.4

In 62 patients, PCR test was positive (41.3%). Ribavirin treatment was performed to 62 patients (41.3%). Mean length of stay in the hospital was 5.13±3.15 days (min-max: 1- 21 days). When two groups (PCR (+) and PCR (-) were compared, number of patients with high AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels were significantly higher in PCR (+) when compared to the number of PCR (-) patients. Comparison of PCR (+) and (-)

groups in terms of laboratory results are summarized in Table 2.

Table 2: Comparison of laboratory findings of the groups.

Laboratory Finding	n (%)	PCR (+)	PCR (-)	*p*
AST elevation	84 (55.6%)	50	34	0.015*
ALT elevation	63 (41.7%)	40	23	0.019*
CK elevation	48 (31.8%)	25	23	0.067
CRP elevation	107 (70.9%)	42	65	0.589
Fibrinogen decrease	6 (4%)	4	2	0.008*
INR elevation	2 (1.3%)	0	2	0.232
aPTT elevation	132 (87.4%)	59	73	0.023*
PLT decrease	122 (80.8%)	56	66	0.018*
WBC decrease	90 (59.6%)	52	38	0.0

Discussion

Our results revealed that high AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels are more common in PCR (+) group when compared to the PCR (-) patients group.

In our study, majority of the patients were male adults. In a study with 21,680 patients who presented to the ED due to tick bite, it was reported that 60.2% of the patients were male (5). In another study by Tekin et al., it was reported that number of male patients were higher than females in both CCHF survivors and non-survivors (7). This finding may not be surprising since nearly 90% of the cases occur in farmers, slaughterhouse workers or butchers (8). These jobs, which are risky in terms of the disease are usually performed by men. Additionally, when the endemic regions are considered (Africa, Eastern Europe, the Middle East, and Asia), men tend to pariticipate into the social life and expose to ticks and their hosts more often than females.

Another finding in our study was that majority of the patients were middle-aged individuals living in rural areas. It well-known that the disease is common in the rural areas of the region and in the actively working age group (9). However, it must be kept in mind that individuals living in the city center who often visit rural areas are also under the risk of tick exposure (5). Although age and gender do not have any significance on survival, as mentioned above, male individuals in the active-working age are under greater risk of the disease (7).

Signs and symptoms of CCHF are well-documented in the literature. However, none of these signs and symptoms are specific to the disease, hence the disease may be misdiagnosed easily, particularly in the prehemorrhagic stage. Symptoms may include fevers, chills, myalgias, dizziness, headache, mood swings, soreness, photophobia, sore throat, neck pain and stiffness, lymphadenopathy, and gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea Patients may also present with bleeding from various sites of the body as an initial complaint (such as epistaxis, petechiae, ecchymosis, melena, gingival bleeding, hematemesis, hematuria, and hematoma) (9,10). In our study, compatible with the literature, fever was the most common symptom followed by weakness, diarrhea, headache, abdominal pain and syncope. Clinicians, particularly those who work in endemic regions, must be aware of non-specific signs and symptoms of CCHF to prevent delays in treatment initiation.

In our study ribavirin therapy was given to 62 patients. Ribavirin is a synthetic guanosine analogue, which directly inhibits replication of the viral genome (11). The usefullness of ribavirin is enhanced when initiated in the early (pre-haemorrhagic) phase. At this stage, the number of the virus increases rapidly in the abdominal cavity. At the other hand, the virus has not yet systemically spread to other organs. So, ribavirin is most effecctive in this phase thanks to its high gastrointestinal tract absorbability property (12). One reason for low ribavirin therapy percentage in our study may be the delays in the diagnosis of the disease. The patients may totally recover with supportive thearpy before the results of PCR test is obtained.

Another possible reason may be the controversies on efficacy of ribavirin therapy. Studies with a higher level of evidence are rare and suggest a lack of efficacy for ribavirin. Superiority of ribavirin therapy over supportive care in terms of mortality, length of hospital stay, need for transfusion and platelet countrecovery time has not been clearly proved (3).

As mentioned above, diagnosis of the disease with laboratory tests in the early phase is crucial for patients (12). In many facilities, the definite diagnosis of CCHF relies on Reverse-transcription PCR (RT-PCR) testing. The viral load detected in RT-PCR also correlates with the disease severity. The percentage of correct results may be increased by usin Real-time PCR test. However, there is still a need for a rapid diagnostic tool which could be performed with low technical requirements as a point-of-care test to facilitate early therapeutic intervention and appropriate infection control precautions to minimize the potential for nosocomial spread (10).

Crimean-Congo hemorrhagic fever causes thrombocytopenia in almost all cases. Other prominent laboratory findings are decreased prothrombin time (PT), increased activated partial thromboplastin time (aPTT) and hypofibrinogenemia. Cytopenia due to macrophage activation syndrome, elevated LDH and CK levels may also be observed (3). It was also reported that higher AST and ALT levels might help predicting the severe cases (13). In a study, clinical features and laboratory findings of PCR (+) and PCR (-) patients were compared and elevated AST and K levels along with lower PLT and WBC levels were obtained in PCR (+) group (2). In our study, predictors of CCHF Disease in terms of laboratory findings in the ED were high AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels. Studies on a rapid and simple test for CCHF diagnosis such as prognostic capacity of the mean platelet volume-to-platelet count ratio (MPVPCR) and the red cell distribution width-to-platelet count ratio (RDWPCR) for the systemic inflammatory response in patients with CCHF still continues [7]. Despite promising results, CCHF continues to be a challenging issue for Emergency Medicine and Infectious Diseases specialists.

Conclusion

Crimean-Congo hemorrhagic fever disease has been reported in 30 countries in Africa, Asia, Eastern Europe, and the Middle East (14). Although numerous species of ticks can carry the virus the most important tick vector is the Hyalomma spp. (15). The disease should be suspected in patients with unexplained bleeding (epistaxis, petechiae, ecchymosis, melena, gingival bleeding, hematemesis, hematuria, hematoma…) and compatible laboratory

findings (thrombocytopenia, leukopenia, and increased levels of aminotransferases) in endimic regions. Ribavirin and supportive therapy are the mainstays of treatment and early initiation of therapy is related with good outcome in CCHF. The main diagnosis of the disease relies on rt-PCR testing, however, according to our results, high AST/ALT, thrombocytopenia, low fibrinogen and aPTT levels may help predicting ill patients on admission to the ED. Thus, treatment may be initiated in the early stage of the disease and morbidity/mortality may be reduced.

Conflict of interest

The authors declare no conflict of interest.

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