ORIGINAL ARTICLE

FACTORS DETERMINING THE SEVERITY AND POOR OUTCOME OF CRIMEAN CONGO HEAMRHAGGIC FEVER: EXPERIENCE IN TERTIARY CARE HOSPITALS, KHYBER PAKHTOONKHWA

Ziauddin[1], Inayat Ullah[1], Iqbal Haider[2], Rehmanuddin[3], Shah Zeb[3], Muhammad Kashif[1]

[1]Department of Medicine, Lady Reading Hospital (MTI), Peshawar - Pakistan

[2]Department of Medicine, Khyber Teaching Hospital (MTI), Peshawar - Pakistan

[3]Department of Medicine, Mardan Medical Complex (MTI), Mardan - Pakistan

ABSTRACT

Objective: To identify markers of poor prognosis in patients with Crimean Congo hemorrhagic fever (CCHF).

Materials and Methods: One hundred and twelve (112) cases of fever and thrombocytopenia that had been referred to tertiary care hospitals of Khyber Pakhtunkhwa during July 2017 to July 2018 were studied. Demographic features, vital signs, clinical and laboratory findings were collected on a pre-designed performa and analyzed by SPSS 21. A significant P value was set at <0.05.

Results: Fifteen cases of Crimean Congo hemorrhagic fever confirmed by positive Reverse Transcriptase –PCR were included in this study. Mortality rate was 33.3%. Late presentation to tertiary care hospital, disseminated intravascular coagulation, luecocytosis and abnormal coagulation profile were associated with high mortality.

Conclusion: Correlation between clinical and biochemical findings with outcomes in Crimean Congo Hemorrhagic fever can be used as guidance for risk evaluation and treatment advice.

Keywords: Crimean Congo Hemorrhagic Fever, Factors, Prognosis.

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INTRODUCTION

Crimean Congo Hemorrhagic Fever (CCHF) is a deadly enzootic viral infection caused by Crimean Congo Hemorrhagic Fever Virus (CCHFV). It is a sphere shaped RNA virus with a diameter of 80-100nm belonging to Bunyaviridae family[1-4]. The virus primarily affects animals (both domestic and wild). Though the virus can be acquired through direct contact with infected secretions and tissues, ticks remain the key in transmission of the virus from animals to humans via its bite[5,6].

Though the disease was first identified in Crimea (1944) and Congo (1969), now the disease is world widely distributed. Worth mentioning are the Asian, Middle east, Central Asian and African countries[7,8]. With a case fatality rate of 39% in Pakistan, CCHF stands an important public health concern in our country as well. Here the disease is endemic with periodic upsurges. Almost every province has been affected but Balochistan has been affected the most. Health care workers and butchers are at risk of acquiring this disease[9-11].

In animals, usually the disease passes uneventfully. In humans, mostly the disease is self-limiting but it may progress to fatal hemorrhages, shock, multi-organ failure and death. Exact mechanism of pathogenesis is still unclear but injury to vascular endothelium with its sequelae is considered as the possible mechanism[12-15]. The overall case fatality rate of CCHF is about 40%[9]. No single factor best describe the disease severity and prognosis. Several factors determine this[13,14]. Limited data and research is available about this disease in this part of the world. In this study, we aim to identify the

Dr. Inayatullah (Corresponding Author)
Assistant Professor
Department of Medicine, Lady Reading Hospital (MTI).
Peshawar - Pakistan
E-mail: doctorziauddin2011@gmail.com
Contact: +92 - 313-9857982
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factors that best describe the prognosis and severity of CCHF in our setup.

MATERIAL AND METHODS

This descriptive retrospective study was conducted at Medical units of Lady Reading Hospital Peshawar and Mardan Medical Complex Mardan. A total of 112 suspected cases of CCHF were enrolled from July 2017 to July 2018. Based on the outcomes of the patients, patients were divided in two groups:

(1) survivors (2) expired, and their different clinical and laboratory features were studied and were associated with the outcomes. Clinical features included were presenting complaints, presentation to hospital after the onset of symptoms and blood pressure. Laboratory features were full blood counts (FBC) including platelets count, liver function tests (LFTs), renal function tests (RFTs), Serum electrolytes, Coagulation profile and rising titer of anti-CCHFV antibodies(for confirmation of CCHF). Based on presentation to hospital, patients were divided into 03 groups, (A) those who presented within 05 days after onset of symptoms were defined as early presentation, (B) between 5 to 10 days were defined delayed and (C) after 10 days were defined as late. Thrombocytopenia was defined in 03 groups based on platelet count: mild thrombocytopenia (platelet count more than 50,000), moderate thrombocytopenia (platelet count between 20,000 and 50,000) and severe thrombocytopenia (platelet count less than 20,000). Total 15 patients were strongly suspected for CCHF whose blood sample were sent to NIH (National Institute of Health, Islamabad) for RT-PCR. Data was analyzed by SPSS version 21. Statistically significant p-value was set at < 0.05.

RESULTS

Out of 112 suspected patients, RT-PCR for CCHFV RNA was positive in 15 patients. Amongst them, 13 (86.7%) were males and 2 (17.3%) females. Male to female ratio was 6.5:1. Age of these patients ranged from 17 to 70 years with mean age of 37 ± 13 years. Most common presenting complaint was fever (90%) followed by Petechial hemorrhages and bruises (73.3%). Five patients (33.3%) presented in shock with blood pressure (BP) less than 100/60 mmHg on arrival. Rest (10 patients, 66.6%) had BP in the normal range. Two patients presented early to the hospital. Nine patients were delayed and 04 presented late. Thrombocytopenia was the most common laboratory finding present in all patients (100%). Six patients (40%) had mild thrombocytopenia, 04 (26.6%) had moderate and 05 (33.3%) had severe thrombocytopenia. Minimum platelet count recorded was 6000 and maximum was 95000 with mean platelet count of 40,900. Five (33.3%) out of 15 patients expired and 10 patients (66.6%) survived. Among the patients who expired, 04 were those who presented late to the hospital and 01 patient presented early. Among survivors, 09 presented early and 01 was delayed. P-value for outcomes with presentation to hospital was 0.002. Two out of 05 expired had mild thrombocytopenia, 01 had moderate and 02 had severe thrombocytopenia. Among the survivors, 04 had mild thrombocytopenia, 03 had moderate and 03 had severe thrombocytopenia (Table 1). Four expired patients had leukocytosis (Table 2). Out of 5 expired patients, 03 had raised INR (cut off 1.2; Table 3). Serum ALT was raised by more than 5 times the upper normal in 4 expired patients. Among the survivors, only 02 patients had deranged liver function tests, rest had within normal limits. Creatinine level was more than 1.2mg/dl in 03 patients out of 05 who expired. All the survivors had normal renal function tests.

Table 1: Thrombocytopenia Outcome

Platelet Count		Outcome	
Mild Thrombocytopenia	**Patient Recovered n(%)**	**Patient Expired n(%)**	**Total**
	04(66.6%)	02(33.3%)	06
Moderate Thrombocytopenia	03(75.0%)	01(25.0%)	04
Severe Thrombocytopenia	03(60.0%)	02(40.0%)	05
Total	10	05	15

Table 2: Leucocyte Count Outcome

Total Leucocytes Count		Outcome	
Normal Leucocytes count	**Patient Recovered n(%)**	**Patient Expired n(%)**	**Total**
	09(90.0%)	01(10.0%)	10
Leucocytosis	00(00.0%)	04(100.0%)	04
Leucopenia	01(100.0%)	00(00.0%)	01
Total	10	05	15

Table 3: Coagulation Profile Outcome

INR* Group		Outcome	
Normal INR	**Patient Recovered n(%)**	**Patient Expired n(%)**	**Total**
	07(77.7%)	02(22.2%)	09
Raised INR(>1.4)	03(50.0%)	03(50.0%)	06
Total	10	05	15

*International Normalized ratio

DISCUSSION

CCHF is an acute viral illness caused by an RNA virus belonging to the family Bunyaviridae[1]. Clinical picture may vary from mild symptoms of viremia to fatal hemorrhages[13,14]. Treatment is mainly supportive. Overall mortality is 40%[9]. Various clinical and biochemical factors determine the severity of the disease. Here we present the key factors that locate and define poor outcome in CCHF. Four of our patients who expired presented to hospital after five days of onset of symptoms. This is because of lack of awareness among the people about the disease and lack of diagnostic facilities. Late arrival to hospital was one of the factors determining poor outcomes in CCHF. Cevik MA et al stratified the patients in critical group in which duration of symptoms upon arrival to hospital was more than 5 days[15,16]. In our study, severe bleeding manifestations like hematemesis and malena were associated with poor outcomes compared to minor bleed like petechial hemorrhages. Hematemesis was reported by Cevik MA et al in all patients who died of CCHF in his study[16]. Ergonul O reported hematemesis as poor prognostic factor. Severe blood loss leading to shock worsens the scenario. Pathogenesis of bleeding is not clearly understood in CCHF but it may be because of immune mediated endothelium injury[17]. Majority of our patients had leukopenia (TLC<4000 cells/mm^3. Four out of five expired patients had leukocytosis (TLC>11000cells/mm^3) with more than 90% neutrophils. Leukocytosis was associated with more severe outcomes compared to leukopenia (p-value 0.043). The results are comparable to those shown by Bastug A et al in their study[18].

Thrombocytopenia was the most common laboratory finding present in all patients. This is comparable to the results given by other studies. In our patients who expired, 03 had platelet count more than 50,000 and 02 had platelet count of less than 20,000. This is in contrast to other studies by Swanepoel R and Ergonul O where fatal outcome was related to platelet count less than 20,000[19,17]. In our study, we found that in the absence of other factors that determine the severity of the disease, the degree of thrombocytopenia does not determine worst outcomes. One of our patients had platelet count of 5000 with mild bleeding manifestations and normal liver function and renal function tests survived. The exact mechanism of low platelet count in CCHF is not fully understood. Immune mediated injury may be a reason[17, 20].

Our study also documented poor outcomes in patients who had deranged Alanine Aminotransferse (ALT) (cut off >55IU/L). ALT was also raised in some patients who survived. We observed that in patients who expired, ALT was raised more than 5 times the upper normal value compared to those who survived where ALT was raised by 2 or 3 times the upper normal limit. Raised ALT of more than 5 times the normal value was associated with more severe prognosis (p value 0.001). These findings are comparable to those given by Cevik MA et al in their study[16]. Similarly poor prognosis was also observed in patients whose PT and aPTT was prolonged by more than 10 seconds from the upper normal limit and INR more than 1.5 (normal <1.2).

Serum creatinine more than 1.2 IU/L was associated with poor outcomes. Three patients who expired had serum creatinine more than 1.2 IU/L compared to those who survived where majority of the patients had serum creatinine in the normal range (0.8-1.2IU/L). Association of raised serum creatinine with poor outcomes was also reported by Bastug A et al[18]. Limited number of patients, retrospective trial and two centre based study are the main limitations of this study. A large prospective trial involving multicentre hospitals across the country with particular emphasis on high prevalence rate of CCHF are the need of time for better comprehension and effective management of these patients.

CONCLUSION

Late arrival to hospital and more severe bleeding manifestations in the form of hematemesis, hematuria and malena were associated with poor prognosis. Prognosis was poor in patients who had leukocytosis compared to those who had leucopenia. The degree of thrombocytopenia without other severity determining factors do not determine worst prognosis. Prognosis was also poor in patients who had raised serum ALT, creatinine and prolonged PT and aPTT values.

RECOMMENDATIONS

Enhance diagnostic facilities and timely referral to tertiary care hospitals can improve survival in CCHF.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ziauddin:	Contributed to the conception, study design, acquisition of data and drafting the manuscript.
Inayatullah:	Helped in analysis and interpretation of data collection.
Haider I:	Bibliography and critical review of the manuscript
Rehmanundin:	Data Collection and analysis.
Zeb S:	Data collection and analysis.
Kashif M:	Data analysis, interpretation and manuscript writing.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.