European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 3, Winter 2022

ORIGINAL RESEARCH

Evaluation of Clinical Features and Risk Factors of Thrombocytopenia Syndrome in Association with Severe Fever: An Institutional Based Study

Ashok Parmar

Assistant Professor, Department of Medicine, Shantabaa Medical College & General Hospital, Amreli, Gujarat, India

Correspondence:
Ashok Parmar
Assistant Professor, Department of Medicine, Shantabaa Medical College & General Hospital, Amreli, Gujarat, India
Email: anparmar@yahoo.com

ABSTRACT

Introduction: Severe fever with thrombocytopenia syndrome is found to be gradually increasing every year and it is reported to be caused by group of viruses which belong to the group of Phlebovirus genus in Bunyaviridae family. The prime goal of this study is to determine the risk factors in patients with SFTS and to reduce the severity of SFTS through early intervention.

Materials and Methods: A total of 65 laboratory-confirmed cases and the complete medical records were thoroughly checked and clinical and laboratory features were compared. All significance tests were two-tailed and P values < 0.05 were considered statistically significant.

Results: The major clinical manifestations of SFTS were fever (100%), fatigue (76.5%), diarrhoea (49.02%), myalgia (47.1%), nausea (43.14%) and vomiting (31.4%). The symptoms of central nervous system characterized by conscious disturbance were found in 37 cases (56.9%). Bone marrow examinations were performed in 29 patients and heteromorphic lymphocyte and haemophagocytosis could be observed in SFTS patients.

Conclusion: The identified clinical and laboratory parameters might predict severe outcome and various novel treatment strategies such as effective vaccine or anti-inflammatory therapy are in much of necessity in people living in a SFTS prone areas.

Keywords: SFTS, Haemophagocytosis, Risk Factors, Severe Fever.

INTRODUCTION

One of the most notable emerging infectious conditions is reported to be severe fever with thrombocytopenia syndrome whose incidence is observably increasing each year. It is caused by group of viruses namely SFTS virus (STFSV) which belongs to the group of Phlebovirus genus in the Bunyaviridae family.[1,2] The SFTS have a wide range of clinical manifestations include fever, fatigue, chill, headache, lymphadenopathy, anorexia, nausea, myalgia, diarrhoea, vomiting, abdominal pain, gingival haemorrhage, conjunctival congestion etc. Almost around 12% of the positive cases were identified to have ended with fatal outcomes.[3,4] SFTS was first reported in the rural areas of Hubei and Henan provinces in Central China in 2009.[1] As of 2016, SFTS like or confirmed SFTS patients have been reported in South Korea, Japan, United Arab Emirates, and United Stated outside China.[5-8]
SFTSV is thought to be transmitted through the tick bites, direct contact with SFTS patients' blood or secretion and possible aerosol transmission.[9-11]Identifying the risk factors is of vital importance for the control and prevention of SFTSV infection. In the year 2011, research on

risk factors for SFTSV infection was performed in Henan Province, Hubei Provinceand Shandong Province. They observed that farmers were more commonly affected among cases and tick bites, cat or cattle ownership and presence of weeds and shrubs in the working ambience were at risk factors.[12] The severity and mortality rates of SFTS differ considerably for each country. Specifically, the mortality rate in Japan has been shown to be approximately 30%, indicating a poor prognosis.[13,14] In contrast, various other countries like China and South Korea have observed to show lower mortality rates, despite the lack of significant differences in the quality of medical care provided. Moreover, the prevalence rate ranges from low to high among few researches published in East Asia which suggests that there is a wide degree of variability in the data.[13]

Thus, estimating the related risk factors for death and intervening early are important for reducing mortality in such patients. This study retrospectively analysed the clinical data of patients with SFTS confirmed by laboratory tests at our hospital. The prime goal of this studyis to determine the risk factors for mortality in patients with SFTS and to reduce the mortality rate of SFTS through early intervention.

MATERIALS AND METHODS

A total of 65 laboratory-confirmed cases and the complete medical records were thoroughly checked and obtained and reviewed to analyse all the clinical characteristics and laboratory parameters. The requirement to fetch the written informed consent from each patient included in the study was waived since this was an observational retrospective study. The patients' information was found to be anonymous and non-identifiable.

Data were probably written as medians and ranges. Continuous variables were performed using Mann–Whitney U-tests and categorical variables were compared using Chi-square test or Fisher's exact test (theoretical frequency <5). All significance tests were two-tailed and P values < 0.05 were considered statistically significant. Binary logistic regression analysis was performed to note the risk factors for mortality of SFTS, variables with p – value < 0.05 were entered into the multivariate model by method of enter. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

All 65 SFTS patients aged between 30 and 80 years were farmers or those residing in the wooded and hilly areas as tabulated in table 1. All the patients were diagnosed to be found through a tick from one patient, most cases did not realize that they had been bitten by tick.

As revealed in Table 1, the major clinical manifestations of SFTS were fever (100%), fatigue (76.5%), diarrhoea (49.02%), myalgia (47.1%), nausea (43.14%) and vomiting (31.4%). The symptoms of central nervous system characterized by conscious disturbance were found in 37 cases (56.9%). Lymph node enlargement and haemorrhage were common.

As per the details given in table-2, significantly increased ageand increased levels of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), prothrombin time (PT) and activated partial thromboplastin time (APTT), also have renal function depravation. Platelet count (PLT) was significantly decreased in patients with severe disease.

Bone marrow examinations were performed in 29 patients. Heteromorphic lymphocyte and haemophagocytosis could be observed in SFTS patients. And the proportion of heteromorphic lymphocyte and haemophagocytosis was seen as shown in table-3

Table1: Information and Clinical Characteristics of SFTS

Characteristics	SFTS, n=65(%)
Gender (male/female)	34,31
Age (years)	62 (31 - 80)
Tick bite/contact/unclear	11/5/49

Fever	65 (100)
Fatigue	50 (76.5)
Nausea	28 (43.2)
Vomiting	20 (31.4)
Diarrhoea	32 (49.02)
Myalgia	31 (47.1)
Disturbance in consciousness	37 (56.9)
Superficial lymph node	31 (47.1)
Haemorrhage	34 (53)

Table2: Laboratory Data of moderate and severe with SFTS Patients

Variables	Moderate (n=43)	Severe (n=22)	P – value
Age	54 (31 - 80)	68.2 (49 - 79)	
WBC	1.74 (0.84 – 5.63)	1.92 (0.82 – 3.25)	0.458
Neutrophils	1.04 (0.44 – 4.31)	1.05 (0.42 – 2.44)	0.589
Lymphocyte	0.53 (0.22 – 1.62)	0.51 (0.22 – 1.34)	0.969
Haemoglobin	109 (47 – 153)	119 (47 - 165)	0.337
Platelets	32 (9 - 77)	18 (7 - 59)	0.009
Alanine transaminase	164 (25 - 371)	194 (47 – 2599)	0.295
Aspartate aminotransferase	299 (72 - 1493)	1073 (132 - 7502)	<0.001
Creatine kinase	1054 (52 - 6331)	1697 (227 - 6121)	0.075
Lactate dehydrogenase	1407 (232 - 4361)	2045 (506 - 9368)	0.011
Blood urea nitrogen	6.3 (1.92 - 61)	12.44 (4.23 - 39)	<0.001
Creatinine	79 (39 - 377)	171 (47 - 699)	0.001
Prothrombin	11.2 (10.6 – 19.7)	14.5 (11.9 – 34.8)	0.001
APTT	47.2 (31.5 – 97.3)	81.6 (42.3 – 147.1)	<0.001
Fibrinogen	2.19 (1.07 – 6.58)	1.79 (1.33 – 2.57)	0.109
D – dimer	3393 (847 - 50002)	10967 (231 - 40003)	0.175
Serum ferritin	7951 (299 – 22639)	12,709 (647 - 37339)	24.2 – 336.8

Table3: Heteromorphic Lymphocyte and Ha

Variables	Moderate(n=19) cases	Severe (n=10) cases	P-value
Heteromorphic lymphocyte <5%	11 (57.14)	9 (88.89)	0.179
Haemophagocytosis	3 (14.3)	7 (66.67)	0.025

DISCUSSION

SFTS has been proven to be the most commonly emerging infectious condition. Generally, tick bite is shown to be a risk factor which is associated with SFTSV infection. Therefore, many cases are unclear and still confusing whether they had previous history of tick bite because of being unfamiliar with ticks or few painless bites.[15]Since most of the cases has occur through tick bites, group of SFTS in family member or healthcare personnel also have been documented. Person-to-personTransmission of SFTSV occurs rarely through contact with infected blood, bloody respiratory secretions, cadaveric blood[16] and probable aerosol transmission,[17] which highlighted the uniqueness of adding universal precaution which include airborne precaution and full personal protective equipment.

Various other studies,[18] except for abnormal haematological routine, our data figures also demonstratedthat alanine aminotransferase (ALT), AST, LDH, creatine phosphokinase (CK), D-Dimer, APTT and serum ferritin are highly elevated. Since they have provedvaluable

laboratory markers though they lack specificity. SFTS could easily misdiagnosed as haemorrhagic fever with renal syndrome since they share similar clinical manifestations which are characterized by fever, diarrhoea, myalgia, thrombocytopenia and abnormal coagulation.[19]Therefore, SFTS has its own characteristics. In our obtained values and about a half of the patients in this group had consciousness disturbance. Significantly, SFTS rarely induced severe kidney injury where most of them belongto the non-survivor group.Also, owing to leukopenia, thrombocytopenia and abnormal coagulation function, some SFTS patients can be easily suspected of leukaemia which particularly hypo-proliferative acute promyelocytic leukaemia. Therefore, acute leukaemic patients usually does not have extremely elevated ALT, AST and CK which are basically the markers to indicate liver and muscle injury. And based on the results of bone marrow aspirate, these two diseases could be considered.

Ding et al documented the incidence rate of SFTS was reported to be significantly higher in patients over 4 decades old and fatal cases had only occurred in patients over 50-years-old.[20] This is in corroboration with our result. Additionally, APTT, as another independent major risk factors in determining the fatal outcomes which indicated the coagulation disorder caused by SFTS virus might be directly associated to the disease severity. SFTSV can possibly inhibit the host immune response whichcould lead to rapid virus replicationaffecting the multiple organs, causing conscious disturbance, liver dysfunction, coagulation dysfunction and rhabdomyolysis. The mechanism remains unclear where the potential reason might include direct organ invasion by virus and immune mediated inflammatory process.[21] SFTSV can usually target microvascular endothelium which resulted in a hyperpermeability due to the disruption of intercellular junction, enhancing the cytokine storm. SFTSV-infected endothelium also can control the circulating platelets which adhere to white blood cells and allow them to transmigrate into the interstitial spaces and hence contributing to leukopenia and thrombocytopenia.[22]

There are few studies whichinstigated that the cytokine storm might be related with the disease severity.[2,3]Spontaneously, many cytokines are significantly higher in SFTS patients than in healthy controls.[11] SFTSV infection-induced cytokine storm indirectly initiated consciousness disturbance.[14] More than half of patients usually affected with consciousness disturbance in our data. In clinical structure, steroid pulse therapy and plasma exchange are being widely used to subtle the excessive cytokine production thus showing few visible effects.[14,15]Meanwhile, cytokine storm can majorly attribute to haemophagocytic lympho-histiocytosis (HLH).[4], *Takahashi* et al documented that five SFTS patients who had undergone bone marrow aspirate in which all exhibited haemophagocytosis which was also seen in lymph nodes and spleen.[8] In our research, bone marrow aspirate was conducted in 29 patients. Heteromorphic lymphocyte can be found to be observed in more than half of surviving patients. More haemophagocytosis occurs in non-survivors' group. Hence, HLH might be a critical pathogenesis in determining the fatality of SFTS.[14] Recent study displayed that SFTSV could directly adhere to platelets and facilitate the phagocytosis of platelet by mouse primary macrophages.[14]Additionally, SFTSV RNA could be detected in cytoplasm of phagocytosing macrophages in bone marrow, liver and spleen during the autopsy procedure thus indicating that SFTSV infected macrophages might induce haemophagocytosis and result in a cytokine storm, which leads to viral haemorrhagic fever, even resulted in death of the individuals.[28]Hence, bone marrow examination should be carried out in patients to identify hemophagocytosis.

CONCLUSION

SFTS is mostly characterized by the disturbance of consciousness, myalgia, abnormal coagulation function and rarity severe renal injury. The age and APTT are found to be major

markers for diagnosing theseverity. The identified clinical and laboratory parameters might predict severity and various novel treatment strategies such as effective vaccine or anti-inflammatory therapy are in much of necessity in people living in a SFTS prone areas.

REFERENCES

1. Yu, X. J. et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med. 364, 1523–1532 (2011).
2. Xu, B. et al. Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (FTLS) in Henan Province, China: discovery of a new bunyavirus. PLoS Pathog. 7, e1002369 (2011).
3. Liu, K. et al. A national assessment of the epidemiology of severe fever with thrombocytopenia syndrome, China. Sci Rep. 5, 9679 (2015).
4. Liu, Q. et al. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. Lancet Infect Dis. 14, 763–772 (2014).
5. Denic, S. et al. Acute thrombocytopenia, leucopenia, and multiorgan dysfunction: the first case of SFTS bunyavirus outside China? Case Rep Infect Dis. 204056 (2011).
6. McMullan, L. K. et al. A new phlebovirus associated with severe febrile illness in Missouri. N Engl J Med. 367, 834–841 (2012).
7. Shin, J., Kwon, D., Youn, S. K. & Park, J. H. Characteristics and factors associated with death among patients hospitalized for severe fever with thrombocytopenia syndrome, South Korea, 2013. Emerg Infect Dis. 21, 1704–1710 (2015).
8. Takahashi, T. et al. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. J Infect Dis. 209, 816–827 (2014).
9. Luo, L. M. et al. Haemaphysalis longicornis Ticks as reservoir and vector of severe fever with thrombocytopenia syndrome virus in China. Emerg Infect Dis. 21, 1770–1776 (2015).
10. Bao, C. J. et al. A family cluster of infections by a newly recognized Bunyavirus in eastern China, 2007: further evidence of personto-person transmission. Clin Infect Dis. 53, 1208–1214 (2011).
11. Gai, Z. T. et al. Person to person transmission of severe fever with thrombocytopenia syndrome Bunyavirus through blood contact. Clin Infect Dis. 54, 249–252 (2012).
12. Ding, F. et al. Risk factors for Bunyavirus-associated severe fever with thrombocytopenia syndrome, China. PLoS Negl Trop Dis. 8, e3267 (2014).
13. Kim, K.H.; Yi, J.; Kim, G.; Choi, S.J.; Jun, K.I.; Kim, N.H.; Choe, P.G.; Kim, N.J.; Lee, J.K.; Oh, M.D. Severe fever with thrombocytopenia syndrome, South Korea, 2012. Emerg. Infect. Dis. 2013, 19, 1892–1894.
14. Kato, H.; Yamagishi, T.; Shimada, T.; Matsui, T.; Shimojima, M.; Saijo, M.; Oishi, K.; SFTS Epidemiological Research Group-Japan. Epidemiological and clinical features of severe fever with thrombocytopenia syndrome in Japan, 2013–2014. PLoS ONE 2016, 11, e0165207.
15. Sun J, Gong Z, Ling F, et al. Factors associated with Severe Fever with Thrombocytopenia Syndrome infection and fatal outcome. Sci Rep. 2016;6:33175. doi:10.1038/srep33175.
16. Jung IY, Choi W, Kim J, et al. Nosocomial person-to-person transmission of severe fever with thrombocytopenia syndrome. Clin Microbiology Infection. 2019;25(5):633.e1–633.e4.
17. Chen H, Hu K, Zou J, Xiao J. A cluster of cases of human-to-human transmission caused by severe fever with thrombocytopenia syndrome bunyavirus. Int j Infect Dis. 2013;17(3):e206.

18. Kim UJ, Oh TH, Kim B, et al. Hyperferritinemia as a Diagnostic Marker for Severe Fever with Thrombocytopenia Syndrome. Dis Markers. 2017:6727184. doi:10.1155/2017/6727184.
19. Qi R, Qin XR, Wang L, et al. Severe fever with thrombocytopenia syndrome can masquerade as hemorrhagic fever with renal syndrome. PLoS Negl Trop Dis. 2019;13(3):e0007308. doi:10.1371/ journal.pntd.0007308.
20. Ding S, Niu G, Xu X, et al. Age is a critical risk factor for severe fever with thrombocytopenia syndrome. PLoS One. 2014;9(11): e111736.
21. Kim MG, Jung J, Hong SB, et al. Severe Fever with Thrombocytopenia Syndrome Presenting with Rhabdomyolysis. Infect Chem. 2017;49(1):68–71. doi:10.3947/ic.2017.49.1.68.
22. Li XK, Zhang SF, Xu W, et al. Vascular endothelial injury in severe fever with thrombocytopenia syndrome caused by the novel bunyavirus. Virology. 2018;520:11–20. doi:10.1016/j.virol.2018.05.00.