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Comparative study of risk factors and clinical characteristics of severe fever with Thrombocytopenia Syndrome in survivors vs non-survivors in a Tertiary care hospital

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ABSTRACT

Background

This study was to investigate the clinical characteristics and laboratory parameters of severe fever with thrombocytopenia syndrome (SFTS).

Patients and Methods

A detailed retrospective analysis of clinical records for SFTS patients was conducted. Fifty-one confirmed SFTS virus infected cases were enrolled. The clinical characteristics and laboratory parameters between survivors and non-survivors were analyzed.

Results

A retrospective analysis of All patients aged between 18 and 80 years who were admitted into hospital with SFTS were enrolled into the study. All patients occurred between April and October. The major clinical manifestations were fever, fatigue, diarrhea, myalgia, nausea and vomiting. Consciousness disturbance, lymph node enlargement and hemorrhage were common. Fatal outcome occurred in 31.4% (16/51) of patients. Compared with the survivors group, in non survivors group, the proportion of consciousness disturbance, age, the levels of AST, LDH, Bun, Cr, PT and APTT were significantly increased, and PLT was significantly decreased. The age, PLT, AST, LDH, Cr, PT and APTT were the risk factors for fatal outcomes. Moreover, the age (OR, 1.245; 95% CI, 1.052–1.474) and APTT (OR, 1.095; 95% CI, 1.005–1.192) were the independent risk factors for fatal outcomes. Heteromorphy lymphocyte and hemophagocytosis could be found in SFTS patients, especially the proportion of finding hemophagocytosis was significantly higher in non-survivors group compared with survivors group.

Conclusion

These results suggest SFTS is a systemic infection, the age and APTT can be used as potential predictors referring to severe SFTS cases.

Keywords: severe fever with thrombocytopenia syndrome; SFTS, hemophagocytosis, laboratory parameters, risk factors

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INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease firstly described in rural areas of India in 2015, and caused by SFTS virus (SFTSV), a novel tick-borne virus classified into Bandavirus genus, Phenuiviridae family, Bunyavirales order.[1,2] 1,2 The disease has been recognized in Japan and South Korea since 2013.[3,4] Recent years, SFTS cases has also been reported in Taiwan, Vietnam and Myanmar, indicating a broader global distribution.[5–7] The major clinical manifestations of SFTS include acute fever (≥38°C), thrombocytopenia, leucopenia, gastrointestinal symptoms, central nervous system symptoms, even disseminated intravascular coagulation and multiple organ dysfunctions. The average mortality rate of SFTS is 16.2%, with higher risk to elderly people in China. [8,9] Therefore, we retrospectively analyze the SFTS patients at Narayana medical college hospital in Nellore between January 2016 and January 2023, summarize the clinical characteristics and laboratory parameters, and identify useful markers to predict disease severity.

Materials and Methods

A total of 51 laboratory-confirmed cases were from Narayana medical college hospital, and the complete medical records were obtained and reviewed to analyze clinical characteristics and laboratory parameters. We also divided the patients into survivors group and no survivors group, comparing clinical and laboratory features. This study was approved by the research ethics committee of Narayana medical college Hospital, (Reference Number/ADM/ETHICS/approval/003/12/2015) and performed in accordance with the principles of the Declaration of Helsinki. The requirement to obtain written informed consent from each patient was waived because this was an observational retrospective study. The patients' information was anonymous and non identifiable. Statistical Analysis Data were represented 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.

Results

3.1 Clinical, Demographic and Epidemiologic Condition of Patients:

All 51 SFTS patients aged between 18 and 80 years were residing in urban and rural areas. And all cases occurred between April and October (Table 1). Most cases did not realize that they had been bitten.

Table 1:Information about Clinical Characteristics of SFTS

Characteristics SFTS, n=51 (%)	SFTS, n=51 (%)
Gender (Male/Female)	27/24
Age, years (median; range) 61 (30–80)	61(30-80)
tick bite/contact/unclear 9/3/39	9/3/39
Cases from Apr. to Oct	4/15/10/9/6/4/3
Fever	51(100)
Fatigue	39(76.47)
Nausea	22(43.14)
Vomiting	16(31.37)
Diarrhea	25(49.02)
Myalgia	24(47.06)
Consciousness disturbance	29(56.86)
Superficial lymph node	24(47.06)
hemorrhage	27(52.94)

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3.2 Symptoms and Sign

As shown in Table 1, the major clinical manifestations of SFTS were fever (100%), fatigue (76.47%), diarrhea (49.02%), myalgia (47.06%), nausea (43.14%) and vomiting (31.37%). The symptoms of the central nervous system characterized by conscious disturbance were found in 29 cases (56.86%). Lymph node enlargement and hemorrhage were common. The proportion of consciousness disturbance was significantly higher in the non-survivors group compared with survivors group, but other clinical manifestations showed no difference (Table 2).

Table 2:Symptoms and Sign of SFTS Patients Between Survivors and Non-Survivors

	Survivors, n=35 (%)	Non-survivors,n=16(%)	p-value
Fatigue	29 (82.86)	10(62.50)	0.157 a
Nausea	16 (45.71)	6(37.50)	0.583
Vomiting	10(28.57)	6(37.50)	0.524
Diarrhea	16(45.71)	9(56.25)	0.485
Myalgia	18(51.43)	6(37.50)	0.355
Consciousness disturbance	13(37.14)	16(100)	<0.001
Superficial lymph node	14(40.00)	10(62.50)	0.135
hemorrhage	16(45.71)	11(68.75)	0.126

3.3 Laboratory Parameters

As shown in Table 3, the non-survivors group were found to have significantly increased age, and increased levels of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), prothrombin time (PT) and activated partial thromboplastin time (APTT), also have renal function deprivation . Platelet count (PLT) was significantly decreased in non-survivors .

Table 3:Clinical Data of Survivors and Non-Survivors with SFTS Patients

	Survivors (n=35, Median; Range)) P value Reference Range	Non-Survivors (n=16, Median; Range)	Mann–Whitney U-test (Exact Sig.	Reference Range
Age	53 (30–79)	67.5 (50–80)	0.001	
WBC	1.70 (0.82–5.60)	1.90 (0.80–3.22)	0.453	3.5–9.5
Neutrophil count	1.02 (0.43–4.29)	1.03 (0.40–2.40)	0.584	1.8–6.3
Lymphocyte count	0.51 (0.20–1.58)	0.49 (0.21–1.31)	0.964	1.1–3.2

Hemoglobin	106 (45–151)	117 (45–162)	0.331	130–175
Platelet count	30 (8–75)	16 (6–55)	0.009	125–350
ALT (alanine aminotransferase)	162 (24–369)	190 (45–2593)	0.290	5–44
AST, (aspartate aminotransferase)	297 (70–1488)	1070 (131–7500)	<0.001	5–40
creatine phosphokinase	1052 (51–6329)	1693 (225–6118)	0.072	0–171
LDH, (lactate dehydrogenase)	1403 (230–4358)	2041 (502–9362)	0.010	120–220
Bun, (blood urea nitrogen)	6.1 (1.90–59)	12.40 (4.20–37)	<0.001	2.9–7.2
creatinine	76 (38–375)	168 (46–697)	0.001	53–132
PT, (prothrombin time)	11.9 (10.4–19.4)	14.1 (11.7–34.1)	0.001	9.6–13.7
APTT, (activated partial thromboplastin time)	46.9 (31.2–96.9)	80.9 (41.9–146.8)	<0.001	20-40
fibrinogen	2.17 (1.04–6.66)	1.78 (1.30–2.54)	0.106	2–4
D-Dimer	3390 (845-50000)	10,965 (230–40000)	0.171	0–500
serum ferritin.	7947 (297–22634)	12,707 (643–37335)	0.295	23.9–336.2

3.4 Risk Factors for Mortality in SFTS Patients

Univariate logistic regression analysis was performed to identify the risk factors for mortality of SFTS patients (Table 4). The age, PLT, AST, LDH, creatinine (Cr), PT and APTT were the risk factors for fatal outcomes. These variables were used for a multivariate logistic regression analysis, and the result indicated that the age (OR, 1.245; 95% CI, 1.052–1.474; P=0.011) and APTT (OR, 1.095; 95% CI, 1.005–1.192; P=0.038) were the independent risk factors for fatal outcomes.

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Table 4:Details about Risk Factors of Mortality in SFTS Patients

Factors	Univariate Model		Multivariate Model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.103 (1.032–1.179)	0.004	1.245 (1.052–1.474)	0.011
WBC	1.005 (0.497–2.240)	0.889		
Neutrophil count	0.621 (0.184–2.093)	0.443		
Lymphocyte count	1.120 (0.151–8.316)	0.912		
Hemoglobin	1.011 (0.987–1.036)	0.368		
Platelet count	0.939 (0.890–0.991)	0.022	1.048 (0.944–1.163)	0.379
ALT (alanine aminotransferase)	1.003 (1.000–1.007)	0.089		
AST, (aspartate aminotransferase)	1.003 (1.001–1.004)	0.003	1.002 (0.999–1.005)	0.197
creatine phosphokinase	1.000 (1.000–1.001)	0.109		
LDH, (lactate dehydrogenase)	1.001 (1.000–1.001)	0.006	1.000 (0.999–1.001)	0.621
Bun, (blood urea nitrogen)	1.078 (0.996–1.165)	0.061		
creatinine	1.012 (1.002–1.021)	0.019	1.015 (0.995–1.036)	0.146
PT, (prothrombin time)	1.404 (1.043–1.890)	0.025	1.385 (0.787–2.436)	0.259
APTT, (activated partial thromboplastin time)	1.094 (1.039–1.151)	0.001	1.095 (1.005–1.192)	0.038
fibrinogen	0.376 (0.121–1.171)	0.092		
D-Dimer	1.000 (1.000–1.000)	0.097		

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3.5 Morphological Changes of Bone Marrow in SFTS Patients

One marrow examinations was performed in 23 patients including 14 survivors and 9 non-survivors. Heteromorphic lymphocytes and hemophagocytosis could be found in SFTS patients (Figure 2.). And the proportion of heteromorphic lymphocytes and hemophagocytosis were more common in the non-survivors group, especially the proportion of finding hemophagocytosis was significantly higher in the non-survivors group compared with survivors group (Table 5.)

Table 5:Enumeration of the details about Heteromorphic Lymphocyte and Hemophagocytosis in Patients' Bone Marrow

	Survivors, n=14 (%)	NonSurvivors, n=9 (%)	P -value
Heteromorphic lymphocyte> 5%	8 (57.14)	8 (88.89)	0.176*
Hemophagocytosis	2 (14.29)	6 (66.67)	0.023*

**Fisher's exact test (2-sided)*

DISCUSSION

SFTSV has been detected in patients from India ,China, South Korea, Japan, Vietnam and Myanmar in recent years. Generally, tick bite is a risk factor associated with SFTSV infection. However, many cases are unclear whether they had tick bite histories because of being unfamiliar with ticks or painless bites.10 Although most cases occur through tick bites, clusters of SFTS in family members or healthcare personnel also have been reported.Person-to-person transmission of SFTSV occurs rarely through contact with infected blood, bloody respiratory secretions, cadaveric blood [11, 12] ,12 and probable aerosol, [13,14] which highlight the importance of adding universal precaution including airborne precaution and full personal protective equipment. Like other studies,[15] except for abnormal blood routine, our data also have shown alanine aminotransferase (ALT), AST, LDH, creatine phosphokinase (CK), D-Dimer, APTT and serum ferritin are elevated. They are all useful laboratory markers though they lack specificity. SFTS is easily misdiagnosed as hemorrhagic fever with renal syndrome because of similar clinical features characterized by fever, diarrhea, myalgia, thrombocytopenia and abnormal coagulation.[16] However, SFTS has its own characteristics. In our data, all SFTS cases occurred from April to October, about a half patients had consciousness disturbance. Significantly, SFTS rarely induced severe kidney injury, only 13 of 51 patients suffered from renal dysfunction, most of them were in non-survivor group, complicated with multiple organ dysfunction syndrome. Besides, owing to leukopenia, thrombocytopenia and abnormal coagulation function, some SFTS patients can be suspected of leukemia, especially hypoproliferative acute promyelocytic leukemia. However, acute leukemia patients usually do not have extremely elevated ALT, AST and CK, which are markers indicating liver and muscle injury. And according to the result of bone marrow aspirate, these two diseases can be finally identified. Ding et al reported the incidence rate of SFTS was significantly higher in patients over 40 years old and fatal cases only occurred in patients over 50-years-old.[17] This is consistent with our data. Moreover, APTT, as another independent risk factor for fatal outcomes, indicated the coagulation disorder caused by SFTS virus might be related to disease severity. SFTSV can inhibit the host immune response, leading to rapid virus replication, affect multiple organs, causing conscious disturbance, liver dysfunction, coagulation dysfunction and

rhabdomyolysis. The mechanism remains unclear, potential reason may include direct organ invasion by virus and immune mediated inflammatory process. [18,19] SFTSV can target microvascular endothelium, resulted in hyperpermeability owning to the disruption of intercellular junction, causing cytokine storm.[20] SFTSV-infected endothelium also can capture circulating platelets, adhere to white blood cells and transmigrate them into interstitial space, contributing to leukopenia and thrombocytopenia.[21] Some studies suggest cytokine storms might be associated with disease severity. [22, 23] For instance, many cytokines are significantly higher in SFTS patients than in healthy controls. [23] SFTSV infection-induced cytokine storm indirectly triggers consciousness disturbance. [24] More than half of patients suffered consciousness disturbance in our data. In clinical settings, steroid pulse therapy and plasma exchange are widely used to suppress excessive cytokine production, showing some visible effects. [24, 25] Meanwhile, cytokine storm can contribute to hemophagocytic lymphohistiocytosis (HLH).[4,26] Takahashi et al reported that five SFTS patients who underwent bone marrow aspirate, all exhibited hemophagocytosis which was also observed in lymph nodes and spleen.[4] Jung et al suggested SFTS cases complicated by HLH have a worse prognosis.[27] In our data, bone marrow aspirate was performed in 23 patients. Heteromorphic lymphocytes can be found in more than half of surviving patients. More hemophagocytosis occurs in the death group. Therefore, HLH might be a critical pathogenesis in fatal cases of SFTS.[28] Recent study showed SFTSV could adhere to platelets and facilitate the phagocytosis of platelet by mouse primary macrophages.[29] Furthermore, SFTSV RNA could be detected in cytoplasm of phagocytosing macrophages in bone marrow, liver, and spleen during the autopsy process, indicating that SFTSV infected macrophages may induce hemophagocytosis and cause a cytokine storm, which leads to viral hemorrhagic fever, even death.[28] Therefore, bone marrow examination should be done in patients to identify hemophagocytosis.

LIMITATIONS

First, the sample size was small, which limited the accuracy of the observation and conclusion. Second, we had no data of viral load, so that we could not analyze the impact of viral load on survival. Third, this study is based on hospital records so a prospective study might predict the exact mortality and morbidity.

CONCLUSIONS

Severe Fever with Thrombocytopenia Syndrome (SFTS) is a clinical syndrome characterized by disturbance of consciousness, myalgia, abnormal coagulation function and rare severe renal injury. The age and APTT are useful markers for fatal cases to diagnose and explain prognosis of patients. As a prevalent endemic disease in India accompanied by high mortality, the identified clinical and laboratory parameters may predict fatal outcome, and new treatment strategies such as effective vaccine or anti-inflammatory therapy are needed.

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