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A Newly Established Severity Scoring System in Predicting the Prognosis of Patients with Severe Fever with Thrombocytopenia Syndrome

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Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by novel Bunyavirus. Due to the peculiarity of SFTS, accurate assessment is difficult to achieve with the current score systems. This study aimed to establish a new severity scoring system in predicting the prognosis of patients with SFTS. We included 123 patients with SFTS: 92 patients (45 males and 47 females), aged 59 ± 12 years, in survive group and 31 patients (17 males and 14 females), aged 61 ± 10 years, in death group. The lactate dehydrogenase (LDH), the activated partial thromboplastin time (APTT), the saturation of pulse oximeter oxygen (SpO_2) and Glasgow Coma Scale (GCS) were measured. SFTS severity scoring system was set up based on the above four factors and compared with the Rapid Emergency Medicine Scores (REMS) and Acute Physiology and Chronic Health Evaluation (APACHE II) Scores. Four parameters in the death group were all significantly higher than survival group. The areas under the curves (AUC) of REMS, APACHE II scores and SFTS severity scores were 0.734, 0.746 and 0.780 respectively. The Youden index of the SFTS severity score was the highest among all the three scores ($P < 0.01$). If 15 was used as the cutoff value, the sensitivity and specificity of SFTS severity score in predicting the death risk for the patients were 74.2% and 76.1% respectively. The newly established SFTS severity scoring system is more efficient to predict the prognosis of patients with SFTS, compared with REMS and APACHE II.

Keywords: Acute Physiology; Chronic Health Evaluation scores; Rapid Emergency Medicine Scores; severe fever with thrombocytopenia syndrome; severity score
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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by novel Bunyavirus (SFTSV) with acute onset of fever, low counts of peripheral white blood cells and platelets, and multiple organ failure as major clinical manifestation (Yu et al. 2011). It was firstly identified in 2010. By the end of 2012, 11 provinces in China have reported SFTS cases (Liu et al. 2014). From 2011 to 2012, 2,047 cases were reported, among which 129 died with an average case-fatality ratio of 7.3% (Deng et al. 2013). The condition of patients with critical SFTS may proceed quickly and end in multi-organ failure and death. Therefore, early assessment and positive intervention for SFTS patients are critically important.

Currently, the major score systems for SFTS in clinic include rapid emergency medicine score (REMS) (Ghanem-Zoubi et al. 2011) and acute physiology and chronic health evaluation (APACHE II) (Malone et al. 2001). By quantizing the assessment of the development and prognosis of some severe illnesses from different aspects, these score systems have played significant roles in clinical treatments. However, due to the peculiarity of SFTS in pathophysiology and clinical treatment process, accurate assessment is difficult to achieve with the current score systems. In order to address the problem, in this study we have designed this SFTS severity score based on the clinical characteristics of SFTS, and proved that this score system could ensure a more accurate prediction on the development and prognosis of SFTS patients' condition in a more convenient way.

Materials and Methods

Patients

123 SFTS patients hospitalized in Jinan Hospital of Infectious

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Diseases affiliated to Shandong University from June 2011 to October 2014 were enrolled in the study. This study was approved by Ethics Review Committee of the Jinan Hospital of Infectious Diseases, and conducted in compliance with the principles of the Declaration of Helsinki. Informed consents have been obtained from all participants involved in this study.

The diagnosis of SFTS was based on clinical manifestations and laboratory test as described previously (Sun et al. 2012b). Suspected cases were defined as meeting all of the following criteria: the epidemiological history (working in mountain area or forest region in epidemic season, or tick-bites within two weeks before onset) and clinical manifestations such as fever, and reduced numbers of peripheral platelet and leukocyte. Laboratory tests confirmed cases were defined when suspected cases met one or more of the following criteria: positivity of SFTSV RNA, positive seroconversion of IgG antibodies against SFTSV, more than 4-fold increase of the titer of antibodies in recovery phase than acute phase, or the isolation of new SFTSV from the patient's specimen.

Quantitative real-time PCR

Quantitative real-time PCR for SFTSV viral RNA was performed using SFTS rRT-PCR Kit (Daan Gene, China) according to manufacturer's instructions. Amplification was performed in triplicates on ABI7500 with a total volume of 25 μl. PCR mixtures were incubated at 50˚C for 15 min and then 95˚C for 15 min, followed by 45 cycles of 95˚C for 15 s and 55˚C for 45 s. Positive results were identified when the Ct value was less than 35 with "S" shaped amplification curve.

Establishment of SFTS severity score system

Based on a review of the references, statistical indicators including age, gender, temperature (maximum) (°C), mean arterial pressure (MAP) (mmHg), peripheral white blood cells (PWBC) ($\times 10^9$/L), platelet (PLT) ($\times 10^9$/L), creatinine (Cr) (mmol/L), serum potassium (mmol/L), activated partial thromboplastin (APTT) (sec), lactate dehydrogenase (LDH) (IU/L), creatine kinase (CK) (U/L), Glasgow Coma Scale (GCS), albumin (Alb) (g/L), serum sodium (mmol/L) and the saturation of pulse oximeter oxygen (SpO_2) (%), were selected for the unconditional univariate logistic regression analysis, from which death-related indicators were worked out. And based on this rating scale, SFTS severity score system was set up and its predictive ability on prognosis was compared with REMS and APACHE II score systems(Gai et al. 2012; Deng et al. 2013; Liu et al. 2013).

REMS and APACHE II score

Based on the methods mentioned in the references, we included parameters such as pulse (bpm), breathing rate (bpm), systolic pressure (mmHg), Glasgow Coma Scale (GCS), age and blood oxygen saturation (%) (Ghanem-Zoubi et al. 2011) in REMS. The acute physiology and chronic health evaluation scoring system (APACHE II) (Malone et al. 2001) was consisted of acute physiology score, age score, chronic health evaluation score and the score with three scores in total. The theoretical maximum score was 71, and higher score indicated worse condition. Besides, the acute physiology score was given based on 12 physiological parameters.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Kolmogorov-Smirnova test was implemented first, after which homogeneity of variance was assessed by Levene's test. If the continuity data fell into the normal distribution and the variance was homogeneous, they would be described as Mean ± SD and the differences between groups would be analyzed with two-tailed unpaired student t-test. However, if the continuity data did not comply with normal distribution, mean rank would be adopted and the differences between the groups would be obtained by Mann-Whitney test. Unconditional univariate logistic regression analysis was conducted to study death-related factors. The areas under receiver operating characteristic curves (ROC) were used to compare the abilities of the three scoring methods in predicting death risk. Based on ROC curve, optimal threshold, as well as its sensitivity and specificity, was determined and Youden index was obtained accordingly. $P < 0.05$ was considered to be statistically significant.

Results

Patients' characteristics

The outcome of these 123 SFTS patients involved in the study was 92 patients (45 males and 47 females) aged 59 ± 12 years were survived and 31 patients (17 males and 14 females) aged 61 ± 10 years were dead (Table 1). No significant differences were observed between this two group regarding gender and age. Information on other death-related factors is also listed in Table 1.

Logistic regression analysis

Univarate logistic regression analysis was conducted with all the risk factors as the independent variables and the occurrence of death as the dependent variable. The results indicated that scores of GCS [OR = 0.815, 95%CI (0.689, 0.964), P = 0.017], LDH [OR = 1.028, 95% CI (1.001, 1.055), P = 0.044], APTT [OR = 1.031, 95% CI (1, 1.062), P = 0.049] and SPO_2 [OR = 0.018, 95% CI (0.66, 0.962), P = 0.018] were relevant to death with statistically significant difference ($P < 0.05$), while gender, age, temperature (maximum), mean arterial pressure (MAP), peripheral white blood cells (PWBC) and platelet (PLT), creatinine (Cr), serum potassium, creatine kinase (CK), albumin (Alb) and serum sodium were not associated with death ($P > 0.05$) (Table 2).

Set-up of SFTS severity scoring methods

Based on the results of univariate analysis mentioned above, the scoring system was set up by taking death-related factors into the scoring gauge. The score system was consisted of four parameters including conscious state scale, LDH, APTT and SpO_2. The scores of each parameter were ranked into six grades and marked with 0, 2, 4, 6, 8, 10 according to the severity. And the maximum total score was 40. Besides, the conscious state score was calculated by subtracting GCS score from 15 (Table 3).

Comparison between survival group and death group

The data of state of consciousness and LDH fell into normal distribution and their variances were homogeneous,

Table 1. Patients' characteristics and levels of death-related factors in survival and death group.

	Survival (n = 92)	**Death (n = 31)**	**P**
Sex	45M/47F	17M/14F	> 0.05
Age	59 ± 12	61 ± 10	> 0.05
Temperature	38.14 ± 1.36	38.46 ± 1.27	0.126
MAP	85.05 ± 10.71	84.83 ± 11.94	0.462
WBC	3.54 ± 3.11	2.84 ± 1.77	0.119
PLT	50.64 ± 24.49	44.74 ± 22.02	0.12
Cr	83.4 ± 78.38	84.09 ± 42.54	0.481
K	3.69 ± 0.55	3.9 ± 0.7	0.015
LDH	873.76 ± 847.98	1400.16 ± 915.27	0.002
APTT	55.8 ± 29.1	72.3 ± 41.52	0.008
SpO_2	96.8 ± 4.38	94 ± 5.11	0.005
GCS SCORE	12.72 ± 2.73	9.67 ± 3.37	0
CK	873.12 ± 817.66	1474.092 ± 1369.88	0.025
Alb	33.07 ± 4.76	31.92 ± 3.93	0.12
Na	132.24 ± 5.7	127.98 ± 24.29	0.06

Table 2. Unconditional regression analysis of death-related factors of STFS patients.

Factors	**Partial regression coefficient**	**Wald χ^2**	**P Value**	**OR Value**	**95% Confidence Interval of OR Value**	
Sex	0.039	0.714	0.398	0.968	0.897	1.044
Age	0.042	0.659	0.417	1.043	0.943	1.153
Temperature (maximum)	0.128	1.484	0.223	0.856	0.666	1.1
MAP	0.039	0.714	0.398	0.968	0.897	1.044
WBC	0.051	0.659	0.217	1.043	0.943	1.153
PLT	0.028	0.485	0.286	1.019	0.966	1.076
Cr	0.04	0.423	0.616	1.026	0.949	1.109
K	0.631	0.336	0.562	0.694	0.202	2.388
LDH	0.027	4.065	0.044	1.028	1.001	1.055
APTT	0.03	3.887	0.049	1.031	1.000	1.062
SpO_2	−0.228	5.589	0.018	0.797	0.66	0.962
GCS Score	−0.204	5.674	0.017	0.815	0.689	0.964
CK	0.019	0.485	0.486	1.019	0.966	1.076
Alb	−0.156	1.484	0.223	0.856	0.666	1.1
Na	−0.033	0.714	0.398	0.968	0.897	1.044

Table 3. Comparison of severity scores between survival group and death group.

Group	N	Conscious State Scores （15-GCS） ($\bar{x} \pm s$)	LDH ($\bar{x} \pm s$)	APTT (mean rank)	Blood Oxygen Saturation (mean rank)
Survival	92	2.02 ± 1.99	7.33 ± 3.88	57.40	77.03
Death	31	4.39 ± 2.45	9.23 ± 2.40	73.13	55.78
Statistics		28.89 (t)	6.559 (t)	−2.226 (Z)	−3.019 (Z)
P		0.000	0.012	0.026	0.003

Table 4. SFTS critical scoring method.

Parameters	Scores					
	0	2	4	6	8	10
Conscious State Scores	0	1-3	4-6	7-9	10-12	12-15
LDH	< ULN (245 U/L)	≥ 1 and < 3 ULN	≥ 3 and < 6 ULN	≥ 6 and < 9 ULN	≥ 9 and < 12 ULN	≥ 12 ULN
APTT	< ULN （44s）	≥ 1 and < 1.5 ULN	≥ 1.5 and < 2 ULN	≥ 2 and < 2.5 ULN	≥ 2.5 and < 3ULN	≥ 3 ULN
SpO_2	> 95	90-94	85-89	80-85	75-80	< 75

Table 5. Comparison of scores in three scoring systems between survival group and death group.

Group	N	REMS	APACHEII Score	SFTS Severity Score
Survival	92	8.55 ± 4.50	17.63 ± 5.20	11.69 ± 6.65
Death	31	12.45 ± 4.63	23.97 ± 7.60	18.13 ± 6.39
t		17.14	26.851	22.131
P		0.000	0.000	0.000

so student t-test was used to evaluate the differences between groups. However, data of APTT and SpO_2 didn't fall into normal distribution, and Mann-Whitney test was adopted. After analysis, the scores of each parameter in the severity score system in death group were found to be all higher than those in survival group ($P < 0.05$), as shown in Table 4.

Comparison of scores in three scoring systems between survival and death

In the three scoring systems of REMS, APACHE II and critical SFTS severity score, scores of the death group were all higher than those in the survival group ($P < 0.01$) (Table 5).

Comparison of the ability to predict death among SFTS severity score, REMS, and APACHE II score

The AUCs of SFTS severity score, REMS, and APACHE II score were 0.734, 0.746 and 0.788 respectively (all > 0.7). Youden indexes ranking from high to low were SFTS severity score, APACHE II score and REMS (Fig. 1). When 15 was used as the cutoff value, the sensitivity and specificity of SFTS severity score in predicting the death risk of patients were 74.2% and 76.1% respectively (Table 6).

Discussion

The pathogenesis of SFTS is very complicated, involving several factors. It is found that levels of inflammatory cytokines, including IL-6, IL-8, IL-10, IFN-γ, MCP and MIP-1b, were increased in SFTS patients (Yu et al. 2011; Deng et al. 2012; Sun et al. 2012a), and that the viral loads

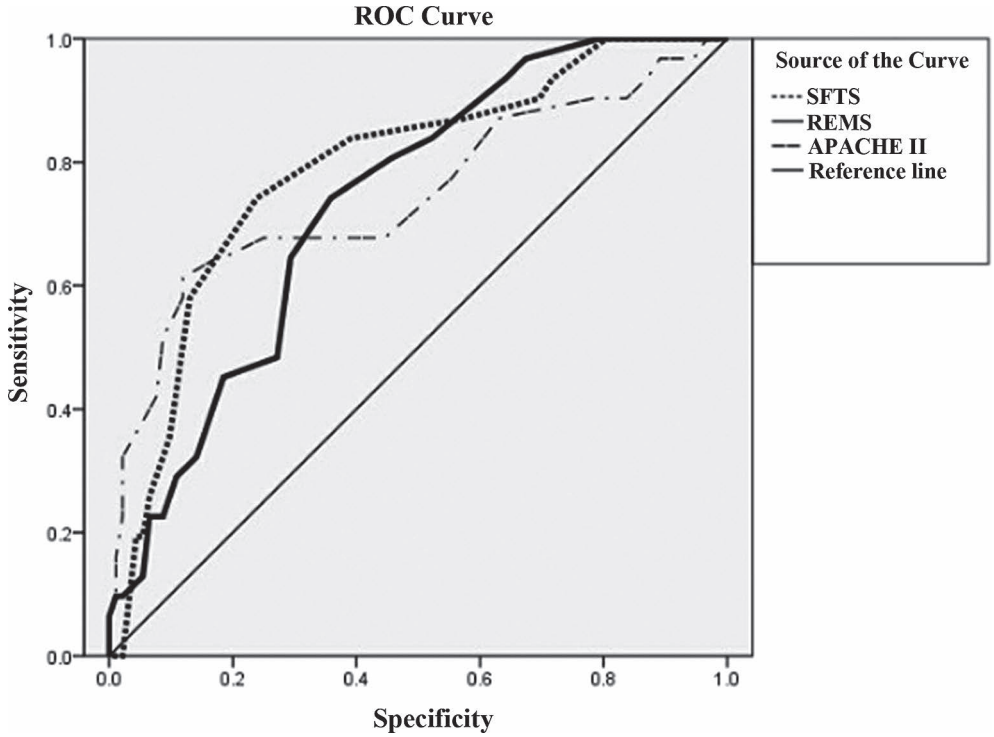

Fig. 1. The receiver operating characteristic curves (ROCs) of SFTS severity score, REMS, and APACHE II score.

Table 6. Comparison of the abilities to predict the prognosis for SFTS patients within the three scoring systems.

Scoring Method	AUC	95%CI	*P*	Thres hold Value	SN (%)	SP (%)	Youden Index
REMS Score	0.734	0.641-0.827	0.000	9.5	74.2	64.1	0.383
APACHE II Score	0.746	0.632-0.859	0.000	23.5	61.3	88.0	0.493
SFTS Severity score	0.788	0.695-0.880	0.000	15	74.2	76.1	0.503

of the death are higher than those of the survivors (Yu et al. 2011). Therefore, it can be inferred that both the action of virus and immunologic injury have participated in the induction of SFTS. Typical disease course undergoes three stages: fever, multi-organ failure, and recovery (Liu et al. 2015). Some patients may die in the period of multi-organ failure. Early prognosis and relevant treatment are of great importance in curing SFTS. Therefore, to establish a sound predictive scoring system is necessary in the clinical treatment of SFTS.

With the development of emergency medicine, prediction and evaluation of patients' condition and outcome by quantitative scoring system has become common methods in clinical treatment (Dellinger et al. 2008). The current severity scoring systems of various kinds have been applied to clinical practice for more than 30 years. APACHE II is an upgraded version of APACHE I with the guiding principles that the prognosis of a patient with acute disease depends on the nature of the disease itself and the patient's immunity. And the immunity, or disease resistance capacity, is related to the patient's age and health condition, as well as the degree of physiological disorder. APACHE II is currently the authoritative scoring system for evaluating the severity of patients with acute illnesses, and numerous clinical studies have proved APACHE II to be accurate and scientific (Meng 2001). However, we found in our clinical practice that APACHE II is hard and inconvenient for clinical use due to high demand for parameters and complicated scoring methods. For example, for APS alone, 12 physiological parameters are required. REMS with only 6 parameters, was updated by Olsson in 2003 by adding two parameters (age and SpO_2) to previous RAPS (Rapid Acute Physiology Score) (Olsson and Lind 2003). REMS could also be used to evaluate the condition and prognosis of patients with critical internal illnesses but the heart rate and breathing rate within the system are highly prone to be affected, which may lead to false judgment.

There are many studies on evaluating the clinical risk factors of death in SFTS patients. According to Liu's research, advanced age, disturbance of consciousness, high

lactate dehydrogenase and creatine kinase are all significant risk factors of death caused by SFTS (Liu et al. 2013). The research conducted by Gai et al. (2012) showed that central nervous symptoms (apathy, hypersomnia, coma, muscle twitching and hyperspasmia), bleeding tendency (including skin petechia, goodpasture syndrome, tarry stools and disseminated inravascular coagulation), high virus load ($> 10^5$ copies/ml), and increased creatine (GOT > 400 U/L, LDH > 800 U/L, CK > 1,000 U/L, CKMB > 50 U/L) are high risk factors of death in SFTS patients. By conducting multi-factor analysis in SFTS patients, Deng et al. (2013) found albumin < 30 g/L, APTT ≥ 66 seconds, serum sodium ≤ 130 mmol/L and neurologic symptoms to be independent predictive factors. In addition, they also found that acute lung injury, acute respiratory distress syndrome and disseminated intravascular coagulation are independent predictive factors of death among patients with critical SFTS. Due to the complexity of SFTS and its varied manifestations, we deem that the analysis and evaluation of any single factor may not reflect the actual severity and prognosis of the disease in a comprehensive and objective way. Therefore, the prognostic evaluation of SFTS should be based on its pathophysiological and clinical characteristics together with multi-factor analysis.

Based on the major pathophysiological characteristics of SFTS and the results of previous studies conducted by others, we performed a retrospective analysis of the clinical data of 123 cases with SFTS. Through logistic regression analysis, some easily-obtained death-related predictive parameters were selected and used in the set up of a new severity scoring system, among which were conscious state score, LDH, APTT, and SpO_2. To prove the value and importance of this severity scoring system in the prognostic judgment for SFTS, this scoring system was compared with APACHE II and REMS scoring system. The results of the study revealed that scores of the four single parameters in death group were all higher than those in survival group ($P < 0.05$), indicating that these parameters are related with adverse consequences of SFTS and the selection of these parameters is reasonable. On the other hand, the scores of APACHE II, REMS and SFTS severity scoring systems in death group were all higher than those in survival group ($P < 0.01$). The AUC of REMS, APACHE II and SFTS severity scores were 0.734, 0.746, and 0.788, respectively (all larger than 0.7) suggesting these three scoring systems can all well predict the SFTS prognosis. The Youden index of SFTS severity scoring system was the highest, followed by those of APACHE II, and REMS, demonstrating that the screening test of SFTS scoring system has the best effect. This study shows that SFTS severity scoring system has the largest AUC and Youden index, and therefore has the best predictive ability. If 15 was used as the cutoff value, the sensitivity and the specificity of SFTS severity score in predicting the death risk for the inpatients were 74.2% and 76.1%, respectively.

In conclusion, SFTS severity scoring system can be applied in clinical prognostic judgment of SFTS. And compared with REMS and APACHE II scoring systems, it is well-targeted and easily-operated. It can facilitate the judgment of severity and prognosis of SFTS, and is more practical in clinical treatment.

Conflict of Interest

The authors declare no conflict of interest.

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