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Original Article

Procalcitonin levels in severe fever with thrombocytopenia syndrome patients: a retrospective investigation in Anhui, China

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Abstract

Introduction: This work aim to evaluate the association of procalcitonin (PCT) levels with disease severity and prognosis in severe fever with thrombocytopenia syndrome (SFTS) patients.

Methodology: The medical records of 158 confirmed SFTS patients at two hospitals were reviewed. The patients were divided into survival group and nonsurvival group according to outcomes. Additionally, to assess mortality rates at different PCT levels, patients were divided into two groups, PCT < 0.25 ng/mL and PCT ≥ 0.25 ng/mL.

Results: Among the 158 confirmed SFTS patients, 26 died; the case fatality rate was 16.46%. PCT data were available for 132 of these patients; 66 were in the PCT < 0.25 ng/mL group, and 66 were in the PCT ≥ 0.25 ng/mL group. The SFTS patients had abnormal results on routine blood tests, indicating varying degrees of thrombocytopenia and leukopenia, and most patients presented with multiple organ dysfunction. The PCT level of the nonsurvival group was significantly higher than that of the survival group ($p < 0.01$). Additionally, the mortality of the PCT ≥ 0.25 ng/mL group was significantly higher than that of the PCT < 0.25 ng/mL group ($p < 0.01$); mortality increased sharply (≥ 25%) when the PCT level exceeded 0.1 ng/mL.

Conclusions: PCT levels in SFTS patients are closely related to the severity and prognosis of their illness. The serum PCT level is a promising predictor of mortality and severity in SFTS patients when considered in combination with clinical data and other laboratory tests.

Key words: severe fever; thrombocytopenia syndrome; procalcitonin; tick-borne disease.

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease caused by the SFTS virus (SFTSV) in the family Phenuiviridae, order Bunyavirales [1] and is transmitted via *Hemaphysalis longicornis* tick bites [2]. The disease was first reported in China and has been identified in Japan and Korea [3,4]. Fever, a decline in platelets, and leukopenia are prominent clinical symptoms. Other clinical symptoms such as weariness, gastrointestinal issues, discomfort in the muscles, lymphadenectasis, and hemorrhagic signs are also common in infected patients [5,6]. According to the China Information System for Disease Control and Prevention, China has the highest number of SFTS cases, with more than 23 provinces affected; Anhui Province is one such SFTS-endemic area. To date, there is no effective clinical treatment for SFTS, which leads to a high mortality rate in critically ill patients. The case fatality rate in SFTS patients in China, South Korea, and Japan ranges from approximately 6% to over 40% [1,7-9].

Procalcitonin (PCT), the 116-amino-acid precursor of the hormone calcitonin, is normally synthesized and released by thyroid parafollicular cells. Different tissues and cell types can produce PCT and release it into the blood when there is inflammation, particularly when sepsis or bacterial infection is present [10,11]. Studies have demonstrated that serum PCT levels in healthy individuals who have not been exposed to infectious pathogens are less than 0.05 ng/mL [12,13]. In viral illnesses, PCT does not increase or just marginally increases [14,15]. However, Jereb *et al*. [16] found that in some life-threatening viral infections with organ failure, PCT levels are elevated. Compared to other conventional inflammatory biomarkers, such as

C-reactive protein (CRP), PCT levels rise within 2–4 hours after systemic inflammation, peak at 8–24 hours, and have a half-life of 24 hours. This allows for faster diagnosis and better disease progression tracking [17]. A low PCT level of 0.25 g/L (ng/mL) successfully rules out bacterial infection in patients with moderate disease and diagnostic ambiguity, according to research by Schuetz *et al*. [18], and these individuals do not benefit from antibiotic treatment. However, there is not much information currently available on PCT levels in SFTS patients.

Since it is convenient to test PCT in the hospital ward and repetitive test data regarding PCT are reliable, this study evaluated the association of PCT levels with the outcomes of SFTS patients, and examined the predictive value of PCT levels in predicting the disease severity and prognosis of these patients.

Methodology

Study design and participants

This study enrolled 158 patients from two sentinel hospitals in two SFTSV-endemic areas of Anhui Province (90 patients from The First Affiliated Hospital of Wannan Medical College and 68 patients from Chaohu Hospital of Anhui Medical University) from April 2015 to November 2021. SFTS was diagnosed according to the clinical guidelines released by the Ministry of Health of China in 2010. The basis for a confirmed diagnosis of SFTS was the simultaneous presence of two of the following conditions: fever (temperature > 37.5 °C for over 24 hours), history of exposure (previous field activities in SFTS-endemic areas or tick bites within 2 weeks before the onset of fever), decreased platelet count ($< 100 \times 10^9$/L) or white blood cell count, and laboratory-confirmed presence of SFTSV according to reverse transcription–polymerase chain reaction (RT–PCR) using total RNA extracted from a peripheral blood sample [19]. The tests were performed at the Centers for Disease Control and Prevention of Wuhu and Hefei cities in Anhui Province. Patients with a diagnosis of any known hematological disorder and confirmed primary bacterial infections such as sepsis were excluded. In this study, the patients were divided into survival and nonsurvival groups according to their final outcomes. Additionally, to assess the mortality rates at different PCT levels, the participants were divided into a PCT < 0.25 ng/mL group and a PCT ≥ 0.25 ng/mL group.

Ethics statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Wannan Medical College and Chaohu Hospital of Anhui Medical University. The need for written informed consent was waived due to the retrospective nature of the study. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Data collection

A medical review method was used to collect data retrospectively. This method collected data from three broad categories: demographic features, clinical symptoms related to the disease, and laboratory parameters obtained during the clinical course (routine blood tests, biochemical tests, coagulation function, CRP, and PCT levels). In addition, all patients underwent blood culture tests and chest imaging examinations after admission. Sputum culture was performed when the patient exhibited cough or expectoration, and urine culture was performed when the patient had a urinary tract infection. Two investigators who checked all the information against the medical records conducted the medical review. After collection, patient blood samples were processed, and the tests were carried out as quickly as possible after sample extraction.

PCT detection

PCT levels within 24 hours of hospital admission were measured by immunofluorescence chromatography according to the manufacturer's instructions (Jinhuai Biomedical, Shenzhen, China). The standard reference range was a PCT level < 0.5 ng/mL.

Data analysis and statistics

Descriptive statistics are reported as frequencies and percentages for categorical variables and as the means ± standard deviations or medians (ranges) for continuous variables. Categorical variables were evaluated using the χ^2 test. Normally distributed data were analyzed using Student's *t*-test. For non-normally distributed data, differences between groups were analyzed using the Mann–Whitney U test. A two-tailed p value < 0.05 was considered to indicate a significant difference. Data processing was carried out using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA).

Results

From April 2015 to November 2021, 158 patients were diagnosed with SFTS. A total of 26 patients died, a case fatality rate of 16.46%. Of the total patients, 68 (43.04%) were men; the mean age was 64.40 ± 1.15 years. One hundred thirty-two patients with available

PCT data were identified (26 patients did not have available PCT data). Of the patients with available PCT data, 66 were in the PCT < 0.25 ng/mL group, and 66 were in the PCT ≥ 0.25 ng/mL group. The flow chart of the participant selection and grouping is shown in Figure 1.

Demographic features

The demographic features of the 158 patients are shown in Table 1. For all SFTS patients, 111 patients were over 60 years old, and exactly half of the patients had underlying diseases (79/158; 50.0%). The two groups (survival group and nonsurvival group) showed significant differences in age distribution, hospital length of stay, and underlying disease ($p < 0.05$). In the 132 patients with available PCT data, 94 patients were over 60 years old and more than half of the patients had underlying diseases (71/132; 53.79%). Between the PCT < 0.25 ng/mL group and PCT ≥ 0.25 ng/mL group, there were significant differences in the age distribution, length of hospital stay, and underlying disease (cerebrovascular disease and chronic kidney disease) ($p < 0.05$). Notably, there were four deaths in the PCT < 0.25 ng/mL group and 22 deaths in the PCT ≥ 0.25 ng/mL group, and this difference was statistically significant ($p < 0.01$).

Clinical characteristics

The clinical characteristics of the 158 patients are shown in Table 2. All patients exhibited fever during the disease; most patients had a maximum temperature > 39 °C. The major nonspecific systemic symptoms included fatigue and muscle soreness; the less common symptoms were cough and expectoration, abdominal pain, diarrhea, vomiting, skin petechiae or ecchymosis, headache, and disturbance of consciousness. There were significant differences in the rates of muscle soreness, cough and expectoration, abdominal pain, vomiting, skin petechiae or ecchymosis, and disturbance of consciousness between the survival group and the nonsurvival group ($p < 0.05$). In contrast, these groups did not significantly differ in the other symptoms. In the patients with available PCT data, common symptoms, such as fatigue, muscle soreness, cough and expectoration, abdominal pain, diarrhea,

Figure 1. Flowchart of the study.

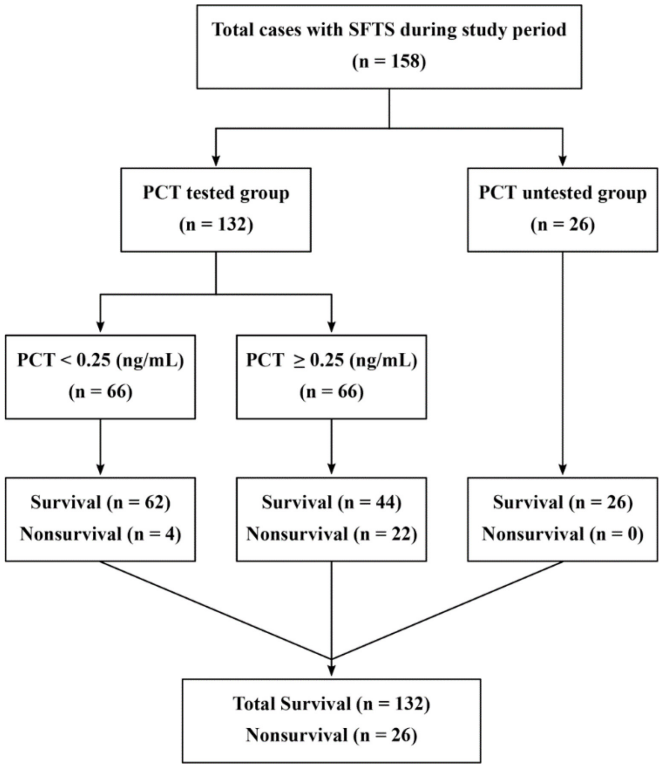

Table 1. Basic characteristics of patients with SFTS.

Basic data	PCT level				Prognosis			
	Total (N = 132)	PCT<0.25 (ng/mL) group (N = 66)	PCT ≥ 0.25 (ng/mL) group (N = 66)	*p* value	Total (N = 158)	Survival group (N = 132)	Nonsurvival group (N = 26)	*p* value
Sex, n (male/female)	57/75	28/38	29/37	0.861	68/90	58/74	10/16	0.606
Age (years)	64.40 ± 1.15	61.71 ± 1.61	67.09 ± 1.60	**0.008**	64.40 ± 1.15	63.12 ± 1.14	69.65 ± 1.00	**0.020**
≥ 60 years (n)	94	42	52	0.071	111	88	23	**0.026**
Onset of illness to admission (days)	5.55 ± 0.31	5.09 ± 0.51	6.21 ± 0.49	0.098	5.71 ± 0.29	5.59 ± 0.34	6.21 ± 0.34	0.136
Length of hospital stay (days)	7.74 ± 0.82	9.37 ± 0.90	4.93 ± 1.33	**0.002**	7.05 ± 0.64	7.73 ± 0.73	4.00 ± 0.95	**0.028**
Underlying disease (n)								
Diabetes	15	5	10	0.170	18	12	6	**0.040**
Hypertension	31	13	18	0.305	33	21	12	**0.001**
Cardiovascular disease	7	5	2	0.244	9	5	4	**0.020**
Cerebrovascular disease	9	1	8	**0.016**	10	5	5	**0.003**
Chronic kidney disease	9	1	8	**0.016**	9	5	4	**0.020**
Cases of death (n) (case fatality rate)	26	4 (6.06%)	22 (33.33%)	**< 0.005**	26	0	26	1.000

Statistically significant correlations ($p < 0.05$) are in bold.

Table 2. Clinical characteristics of patients with SFTS.

Signs and symptoms	PCT level				Prognosis			
	Total (N = 132)	PCT<0.25 (ng/mL) group (N = 66)	PCT ≥ 0.25 (ng/mL) group (N = 66)	*p* value	Total (N = 158)	Survival group (N = 132)	Nonsurvival group (N = 26)	*p* value
Fever	132	66	66	1.000	158	132	26	1.000
Highest temperature ≥ 39°C	82	39	43	0.473	98	79	19	0.204
fatigue	118	59	59	1.000	124	105	19	0.463
Muscle soreness	51	28	23	0.371	57	33	24	**< 0.005**
Cough and expectoration	31	16	15	0.837	33	22	11	**0.003**
Abdominal pain	31	12	19	0.151	32	23	9	**0.046**
Diarrhea	51	22	29	0.211	52	40	12	0.116
Vomit	19	7	12	0.215	22	13	9	**0.001**
Skin petechiae or ecchymosis	26	16	10	0.189	27	15	12	**< 0.005**
Headache	27	11	16	0.281	28	20	8	0.057
Disturbance of consciousness	46	12	34	**< 0.005**	47	27	20	**< 0.005**

Statistically significant correlations ($p < 0.05$) are in bold.

vomiting, skin petechiae or ecchymosis, headache, and disturbance of consciousness, were observed in 89.39%, 38.64%, 23.48%, 23.48%, 38.64%, 14.39%, 19.70%, 20.45% and 34.85% of patients, respectively. There were significant differences in disturbance of consciousness between the PCT < 0.25 ng/mL group and the PCT ≥ 0.25 ng/mL group ($p < 0.01$). In contrast, these groups did not significantly differ in the other symptoms.

Laboratory indices

The changes in the laboratory indices in the patients with available PCT data and all the SFTS patients are shown in Tables 3 and 4, respectively. For the hematological parameters, the SFTS patients had abnormal results on routine blood tests, indicating varying degrees of thrombocytopenia and leukopenia. In addition, most patients presented with multiple organ dysfunction, which usually manifested as liver involvement, pancreatic injury, abnormal kidney function, myocardial involvement, and abnormal

Table 3. Laboratory parameters of the PCT tested patients with SFTS.

Variable	Normal range	PCT< 0.25 (ng/mL) group (N = 66)	PCT ≥ 0.25 (ng/mL) group (N = 66)	*p* value
WBC (10^9/L)	4-10	2.21 ± 0.15	2.67 ± 0.28	0.436
NEU (%)	50-75	1.46 ± 0.20	2.48 ± 0.50	0.289
LYM (%)	20-40	0.86 ± 0.13	0.74 ± 0.08	0.851
RBC (10^{12}/L)	4.0-5.5	3.85 ± 0.12	4.21 ± 0.12	**0.031**
Hb (g/L)	120-160	117.14 ± 3.68	126.70 ± 3.81	0.070
PLT (10^9/L)	100-300	45.5 ± 3.1	32.7 ± 2.1	**0.001**
ALB (g/L)	40.0-55.0	32.20 ± 1.035	29.72 ± 1.00	0.078
PA (g/L)	21.0-41.0	13.17 ± 1.15	9.83 ± 0.85	**0.031**
ALT (U/L)	9-50	90.97 ± 11.01	120.27 ± 15.47	0.098
AST (U/L)	15-40	225.76 ± 30.42	404.41 ± 51.00	**0.002**
BUN (mmol/l)	2.3-7.1	5.37 ± 0.51	10.56 ± 1.52	**0.011**
Cr (μmol/l)	40-130	64.50 ± 4.41	133.44 ± 21.29	**0.002**
CK (U/L)	26-140	981.38 ± 255.15	2083.64 ± 347.76	**< 0.001**
CKMB (U/L)	0-25	28.48 ± 2.70	57.51 ± 7.10	**0.001**
LDH (U/L)	135-225	935.33 ± 135.81	1516.32 ± 176.31	**< 0.001**
HBDH (U/L)	76-195	673.26 ± 222.06	1214.48 ± 209.83	**0.004**
AMY (U/L)	0-95	187.13 ± 15.84	281.12 ± 25.52	**0.005**
LIP (U/L)	0-60	478.95 ± 62.73	773.77 ± 97.66	**0.008**
cTnI (ng/mL)	0-0.03	0.83 ± 0.50	0.84 ± 0.19	0.118
CO_2CP (mmol/L)	22.0-31.0	21.84 ± 0.80	19.49 ± 0.89	0.099
CRP (mg/l)	0-5	12.16 ± 2.51	19.98 ± 2.55	**< 0.001**
PCT (ng/mL)	0-0.5	0.11 ± 0.01	4.39 ± 1.78	**< 0.001**
PT (s)	9-14	12.31 ± 0.21	13.44 ± 0.37	**0.026**
APTT (s)	25-45	47.02 ± 2.92	62.66 ± 3.34	**0.017**
D-dimer (μg/mL)	0-0.5	3.55 ± 0.50	8.17 ± 1.04	**< 0.001**

Statistically significant correlations ($p < 0.05$) are in bold. Normal range means normal physiological levels for clinical diagnosis. WBC: white blood cell count; NEU: neutrophil count; LYM: lymphocyte count; RBC: red blood cell count; Hb: hemoglobin; PLT: platelet; ALB: albumin; PA: prealbumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; CK: creatine kinase; CKMB: creatine kinase-MB; LDH: lactate dehydrogenase; HBDH: hydroxybutyrate dehydrogenase; AMY: amylase; LIP: lipase; cTnI: cardiac troponin I; CO_2CP: carbon-dioxide-combining power; CRP: C-reactive protein; PCT: procalcitonin; PT: prothrombin time; APTT: activated partial thromboplastin time.

Table 4. Laboratory parameters of patients with SFTS.

Variable	Normal range	Survival group (N=132)	Nonsurvival group (N = 26)	*p* value
WBC (10^9/L)	4-10	2.30 ± 0.14	3.20 ± 0.58	0.503
NEU (%)	50-75	1.63 ± 0.19	2.24 ± 0.89	0.246
LYM (%)	20-40	0.84 ± 0.09	0.67 ± 0.09	0.338
RBC (10^{12}/L)	4.0-5.5	3.82 ± 0.10	4.50 ± 0.15	**0.001**
Hb (g/L)	120-160	116.63 ± 3.13	133.93 ± 4.95	**0.007**
PLT (10^9/L)	100-300	41.75 ± 2.23	287.35 ± 3.00	**0.005**
ALB (g/L)	40.0-55.0	25.28 ± 0.79	27.76 ± 1.10	**0.035**
PA (g/L)	21.0-41.0	9.74 ± 0.74	8.32 ± 1.16	0.658
ALT (U/L)	9-50	93.45 ± 8.51	158.12 ± 31.38	**0.011**
AST (U/L)	15-40	228.55 ± 22.04	663.06 ± 99.68	**< 0.001**
BUN (mmol/l)	2.3-7.1	6.04 ± 0.71	14.43 ± 2.35	**0.002**
Cr (μmol/l)	40-130	69.97 ± 4.78	164.21 ± 36.54	**0.002**
CK (U/L)	26-140	1138.73 ± 190.94	864.40 ± 676.14	**< 0.001**
CKMB (U/L)	0-25	28.95 ± 2.05	94.60 ± 12.93	**< 0.001**
LDH (U/L)	135-225	875.11 ± 61.23	2569.00 ± 427.48	**< 0.001**
HBDH (U/L)	76-195	523.78 ± 50.83	2151.36 ± 394.38	**< 0.001**
AMY (U/L)	0-95	213.02 ± 14.50	338.32 ± 48.04	**0.007**
LIP (U/L)	0-60	553.26 ± 60.25	954.30 ± 153.10	**0.001**
cTnI (ng/mL)	0-0.03	0.40 ± 0.23	1.43 ± 0.29	**< 0.001**
CO_2CP (mmol/L)	22.0-31.0	21.36 ± 0.68	18.66 ± 1.23	0.099
CRP (mg/l)	0-5	13.98 ± 1.92	22.32 ± 4.28	**0.026**
PCT (ng/mL)	0-0.5	0.61 ± 0.23	7.30 ± 4.10	**< 0.001**
PT (seconds)	9-14	12.20 ± 0.18	15.0 ± 1.50	**0.012**
APTT (seconds)	25-45	46.68 ± 2.27	79.64 ± 9.17	**< 0.001**
D-dimer (μg/mL)	0-0.5	5.37 ± 0.68	8.32 ± 1.45	**0.001**

Statistically significant correlations ($p < 0.05$) are in bold. Normal range means normal physiological levels for clinical diagnosis. WBC: white blood cell count; NEU: neutrophil count; LYM: lymphocyte count; RBC: red blood cell count; Hb: hemoglobin; PLT: platelet; ALB: albumin; PA: prealbumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; CK: creatine kinase; CKMB: creatine kinase-MB; LDH: lactate dehydrogenase; HBDH: hydroxybutyrate dehydrogenase; AMY: amylase; LIP: lipase; cTnI: cardiac troponin I; CO_2CP: carbon-dioxide-combining power; CRP: C-reactive protein; PCT: procalcitonin; PT: prothrombin time; APTT: activated partial thromboplastin time.

coagulation (Tables 3 and 4). Compared with the PCT < 0.25 ng/mL group, the PCT ≥ 0.25 ng/mL group had significantly higher rates of severe anemia and multiple organ dysfunction ($p < 0.05$). Likewise, the differences in the rates of anemia and multiple organ dysfunction between the survival and nonsurvival groups were statistically significant ($p < 0.05$). Notably, the PCT levels were 0.61 ± 0.23 ng/mL in the survival group and 7.30 ± 4.10 ng/mL in the nonsurvival group. The PCT level in the nonsurvival group was significantly higher than that in the survival group ($p < 0.001$).

Deaths and case fatality rates at different levels of PCT

The death and case fatality rates at different levels of PCT are shown in Table 5 and Figure 2, respectively. The results revealed that the case fatality rate increased sharply (≥ 25%) when the PCT level exceeded 0.1 ng/mL and that the case fatality rate was greater than 30% when the PCT level exceeded 0.2 ng/mL.

Figure 2. The case fatality rate at different levels of PCT.

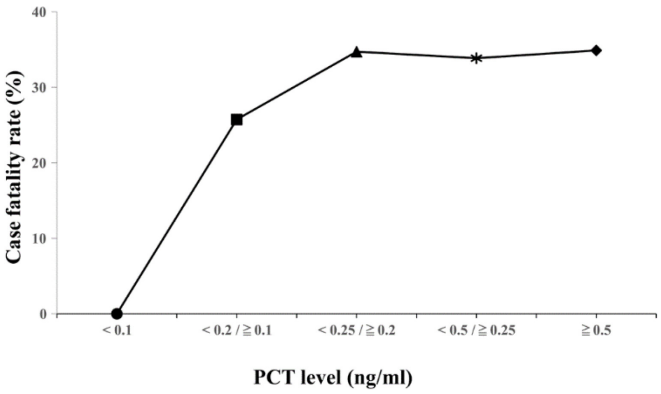

Table 5. Cases of death at different levels of PCT.

PCT level (ng/mL)	Total (N = 158)	Survival group (N = 132)	Nonsurvival group (N = 26)
Untested	26	26	0
< 0.1	31	31	0
≥ 0.1	101	75	26
≥ 0.2	72	47	25
≥ 0.25	65	43	22
≥ 0.5	43	28	15

Discussion

As stated in the Guidelines and Recommendations for Preventing and Controlling SFTSV Infection provided by the Centers for Disease Control and Prevention of China in 2010 [20], early detection, identification, and treatment of SFTS are important measures to prevent severe disease. Therefore, early identification of risk factors associated with the severity of this disease would be advantageous. Here, we report on 158 patients with laboratory-confirmed SFTSV infection who were treated at two sentinel hospitals. Of the 158 patients, 26 died during hospitalization, yielding a mortality rate of 16.46%. The results show that the PCT level of the nonsurvival group was significantly higher than that of the survival group. Additionally, the mortality of the patients in the PCT ≥ 0.25 ng/mL group was significantly higher than that of patients in the PCT < 0.25 ng/mL group, and the case fatality rate increased sharply (≥ 25%) when the PCT level exceeded 0.1 ng/mL. These results provide further insights into the association of PCT levels with SFTS prognosis and facilitate the immediate identification of potentially severe or fatal cases.

SFTSV infections are mainly identified in older individuals, and death is most common in older patients. Age was a significant risk factor for and a driver of morbidity and death in SFTS patients, as well as an important component linked with the condition [21]. Our research found that the nonsurvival group's mean age was noticeably older than the survival group's ($p < 0.05$). Studies have demonstrated that the etiology of SFTS is significantly influenced by the impairment of adaptive immune function and an aberrant rise in inflammatory cytokines [22]. A propensity for bleeding, conditions affecting the central nervous system, higher serum enzyme levels, and a high viral load are risk factors for severe disease [23]. Additionally, SFTS is pantropic and can harm different organ systems by destroying a variety of tissues and cells in the human body [24]. In addition to damaging the hematologic system, SFTS can damage many other tissues and organs, such as the myocardium, coagulation system, liver, and kidneys. The results of our study fully align with its pantropic effects (Tables 2, 3 and 4).

Since its discovery in 1993, PCT has been widely utilized as a prognostic biomarker in severely ill patients with several infectious etiologies [25]. High levels of PCT indicate a very severe systemic inflammatory response and a high risk of death [26]. A steady rise in PCT levels over time suggests that the infection is getting worse or that the treatment is failing, whereas a decline in PCT levels suggests that the infection is getting better or that the treatment is working [27,28]. In COVID-19 patients with moderate disease severity, Hu *et al.* [29] discovered that PCT levels appeared to depend on the severity of the disease and may have been linked to bacterial co-infection, since the rate of coinfection paralleled the rate of elevated PCT levels. There are some randomized controlled experiments that show PCT levels of < 0.25 μg/L can guide the decision to withhold antibiotics or stop therapy early [30,31]. However, caution should be exercised when using PCT levels to exclude a diagnosis. Thus, in patients with mild disease who are highly suspected to have a bacterial infection based on clinical, radiological and microbiological assessments, a PCT level of < 0.25 μg/L argues against bacterial infection; nonetheless, antibiotics may be started based on the clinician's judgment [32,33]. Furthermore, despite low PCT levels, individuals at very high risk should still receive empirical care [18]. Data on PCT levels in SFTS patients, however, are scant. Our research showed that the mortality rate in the PCT ≥ 0.25 ng/mL group was significantly higher than that in the PCT < 0.25 ng/mL group. The mortality increased sharply (≥ 25%) when PCT levels exceeded 0.1 ng/mL, and the case fatality rate was greater than 30% when PCT levels exceeded 0.2 ng/mL. These results show that PCT may predict mortality and may assist the determination of disease severity in SFTS patients. However, whether PCT concentrations reflect the severity of SFTS needs to be confirmed.

According to a few studies, PCT has generated significant attention in mortality prediction and may be useful in determining the severity of the illness [26]. Of the 158 patients in this retrospective study, 26 died, yielding a total case fatality rate of 16.46%. Our research shows that PCT levels were significantly increased in the nonsurvival group compared to the survival group. With increases in PCT levels, mortality gradually increased. The possible reasons why PCT levels increased continuously in patients with severe SFTSV infection are as follows. First, under normal conditions, parafollicular cells in the human thyroid secrete minimal levels of PCT. However, during severe infections, stress, and trauma, all tissues and organs secrete PCT [34,35]. This secretion results in a significant increase in serum PCT levels. Second, patients with severe SFTSV infection are more prone to co-infection with bacteria, resulting in high PCT values. In patients with mild disease and a low probability of bacterial infection, a low PCT level may indicate against the use of antibiotics. For patients with

moderate or severe cases, empirical tests may still be used along with PCT measurements to re-evaluate the need for antibiotic therapy. Clinical decision-making for patients with a suspected bacterial infection may be aided by the incorporation of PCT into the overall assessment, which may supplement conventional clinical criteria and the findings of diagnostic and microbiological testing [36]. All 158 participants in this trial had chest imaging, and chest radiographs showed varying degrees of pulmonary inflammatory infiltration (detailed data are not provided in this study). Considering the high mortality rate of the disease, we used antibiotics empirically on the basis of the culture results and the severity of the patient's condition. However, in clinical practice, it is difficult to completely rule out whether secondary bacterial infections have occurred in SFTSV-infected individuals with negative culture. Thus, for patients with severe SFTSV infection, attention should be given to bacterial culture of different specimens for early detection, and there is a need to combine the level of PCT with other inflammatory response markers to determine whether the severe SFTSV patient has secondary bacterial infection. This information would allow the clinician to initiate early rational antibiotic therapy that may prevent further deterioration of health.

This study was a retrospective analysis and thus did not incur additional costs for or induce additional pain in the patients. However, this investigation still has limitations. First, this was a retrospective study, which makes it difficult to exclude confounding factors. Second, we did not standardize the diagnostic approach to bacterial co-infection but relied on the clinical diagnosis. Thus, we may have overestimated the proportion of SFTS patients with bacterial co-infection. We did not extract the latency to the initiation of antibiotic treatment or the appropriateness of antibiotic administration, which also likely played a key role in the clinical outcomes. Third, this study was only carried out in two SFTS epidemic areas within the same province; thus, the patient sample might not be representative of the general Chinese population. Additionally, we do not used the kit for viral RNA quantification to detect the viral load of SFTSV. Given these limitations, future studies with an adequate sample size are needed to corroborate the findings of this study on a large scale.

Conclusions

In conclusion, the most obvious finding to emerge from this study is that the PCT levels of SFTS patients are closely related to the severity and prognosis of their illness. The serum PCT level is a promising predictor of severity and mortality in SFTS patients when considered in combination with clinical details and other laboratory tests.

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Authors' Contributions

Conceptualization: Jianghua Yang; data curation: Yang Yang, Manman Liang; investigation: Aiping Zhang, Zhaoru Zhang; methodology: Yang Yang, Manman Liang; supervision: Jianghua Yang; writing-original draft: Wenjie Wang; writing-review and editing: Wenjie Wang, Jianghua Yang.

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