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RESEARCH ARTICLE

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Pulmonary infection in patients with severe fever with thrombocytopenia syndrome: A multicentre observational study

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Abstract

Co-infection in patients with severe fever with thrombocytopenia syndrome (SFTS) has been reported, posing a serious threat to survival and treatment. We aimed to systematically investigate the SFTS associated pulmonary infection, particularly invasive pulmonary fungal infection (IPFI). During April 2019 to October 2021, we conducted a multicentre observational study on adult hospitalized patients confirmed with SFTS from three tertiary hospital in central China. Demographic, clinical and laboratory data of patients were collected and re-assessed. A total of 443 patients (51.7% were male sex) were included for analysis with median age of 65-year-old. Among them, 190 (42.9%) patients met the criteria for pulmonary infection. Pulmonary infection was associated with shorter survival time ($p < 0.0001$ by log-rank test), and adjusted hazard ratio was 1.729 [95% confidence interval, 1.076–2.780] ($p = 0.024$). Age (odds ratio (OR) 1.040 [1.019–1.062], $p < 0.001$), time from onset to admission (OR 1.163 [1.070–1.264], $p < 0.001$), having severe status (OR 3.166 [2.020–4.962], $p < 0.001$) and symptoms of skin change (OR 2.361 [1.049–5.316], $p < 0.001$) at admission and receiving intravenous immunoglobin (OR 2.185 [1.337–3.569], $p = 0.002$) were independent risk factors for the occurrence of pulmonary infection. A total of 70 (15.8%) patients were defined as IPFI. Multivariate analysis showed that time from onset to admission (OR 1.117 [1.016–1.229], $p = 0.022$), severe status (OR 5.737 [3.054–10.779], $p < 0.001$), having smoking history (OR 3.178 [1.251–8.070], $p = 0.015$) and autoimmunity disease (OR 7.855 [1.632–37.796], $p = 0.010$), receiving intravenous immunoglobin (OR 3.270 [1.424–7.508], $p = 0.005$) were independent risk factors for the occurrence of IPFI. In SFTS patients with pulmonary infection, white blood count $<2.09 \times 10^9$ per L (OR 11.064 [3.708–33.012], $p < 0.001$) and $CD3^+CD4^+$ T cell count <104.0 per μL (OR 10.429 [3.395–32.038], $p < 0.001$) could independently predict IPFI. This study showed the high prevalence and poor outcomes of pulmonary infection and IPFI in

Yan Zuo, Heming Wang, and Jiaxiang Huang contributed equally to this study and share first authorship.

patients with SFTS. These findings highlighted the need for active surveillance of fungal pathogens and early antifungal treatment in patients with SFTS.

KEYWORDS
aspergillosis, invasive pulmonary fungal infection, pulmonary infection, risk factors, SFTS

1 | INTRODUCTION

In last decade, severe fever with thrombocytopenia syndrome (SFTS) has been reported in several provinces in central China, as well as in Japan and Korean.[1,2] It was clinically characterized by the abrupt onset of fever, thrombocytopenia and leukopenia, gastrointestinal symptoms and multiple-organ failure.[3] This disease was caused by a novel bunyavirus which was named as SFTS virus (SFTSV).[4] To date, the overall mortality of this disease in China was reported to be 10.5%, and there are no specific antiviral drugs available.[5]

Recent studies have reported the significantly high incidence of co-infections in SFTS, and these studies suggested consistently that respiratory infections were predominant and should be of sufficient concern.[6,7] SFTSV can cause cytokine storm and immunosuppression in severe cases. It has been demonstrated that fatal patients were more biased towards negative immune modulation, including significantly increased Th17 and decreased $CD4^+$ T lymphocytes.[8] Such complexity of immune environment and the characteristics with thrombocytopenia and leukopenia in this disease may help explain the high incidence of secondary infection. However, util now, little knowledge of pulmonary infection in SFTS patients and its risk factors unknow reduce the efficient early surveillance and treatment of such secondary infection.

Under the complex immune characteristics reported in SFTS, it is important to determine whether SFTS patients may be at particular risk of developing invasive pulmonary fungal infection (IPFI) such as mold infections and pneumocystosis. Until now, a small series of investigations reported the significant higher prevalence of SFTS-associated invasive aspergillosis (SAPA), compared to the prevalence of IPA reported in other virus infection, such as SARS-CoV-2 and influenza.[9–13] Xu et al.[13] reported that 31.9% of SFTS patients in their series developed SAPA with wheezing as predictive on multivariate analysis for the development of SAPA. IPA was associated with decreased survival in SFTS patients.[9,13] Hu et al.[11] identified 30/76 as SAPA and found several immune predictors for IPA in severe SFTS patients. However, several factors (i.e., the stringent definition of IPA, single center, and sample size) create limitations in interpreting published data. In fact, before the guidelines of coronavirus disease-19 associated IPA, nonclinical relevant colonization in patients with mycological evidence had been described. Thus, early identification of IPFI in patients with pulmonary infection is important for early antifungal treatment.

Therefore, we conducted this multicentre study in central China to systematically investigate the prevalence, outcomes, risk factors and laboratory characteristics of pulmonary infection in patients with SFTS. Furthermore, we reported the high prevalence and risk factors of IPFI in SFTS patients. Particularly, the predictive parameters for IPFI in patients with pulmonary infection were also identified.

2 | METHODS AND MATERIALS

2.1 | Study design and data collection

From April 2019 to October 2021, this multicenter, observational study was conducted in the top three large tertiary hospitals in Anhui Province (The First Affiliated Hospital of Anhui Medical University, The Second Affiliated Hospital of Anhui Medical University and The First Affiliated Hospital of USTC). All hospitalized adult patients (aged ≥18-year-old) were considered for enrollment if they were diagnosed as SFTS confirmed by reverse transcript polymerase chain reaction. The detailed inclusion and exclusion protocol was presented in Figure 1.

Epidemiological, demographic, clinical, laboratory, treatment and outcome data were collected anonymously from electronic medical records. All data were checked by two physicians (Z. Y. and W. H.) and a third researcher (H. J.) adjudicated any difference in interpretation between the two primary reviewers.

2.2 | Case definitions

Laboratory and clinical data of all patients enrolled were reviewed and re-assessed. The diagnosis of pulmonary infection is based on guidelines in terms of symptoms, signs, laboratory and imaging findings. Chronic pulmonary inflammation or pulmonary infection that was clearly preceded by the onset of SFTS or history of tick bite were excluded. Notably, the diagnosis of infection rather than colonization was confirmed according to Infectious Disease Society of America/American Thoracic Society (IDSA) guidelines.[14] Notably, antibiotics and antiviral treatment were defined as the use of any drug that has been continuously used for >3 days.

Invasive pulmonary fungal disease was defined according to European Organization for Research and Treatment of Cancer (EORTC)/Mycosis Study Group (MSG) criteria in patients with underlying immunosuppressive conditions.[15] As for the SFTS patients lack of typical host factors, we categorized putative IPA using a modified AspICU algorithm as previously described.[16,17] Briefly, the putative IPA definition was based on clinical, radiological, and mycological criteria: compatible signs and symptoms, abnormal image

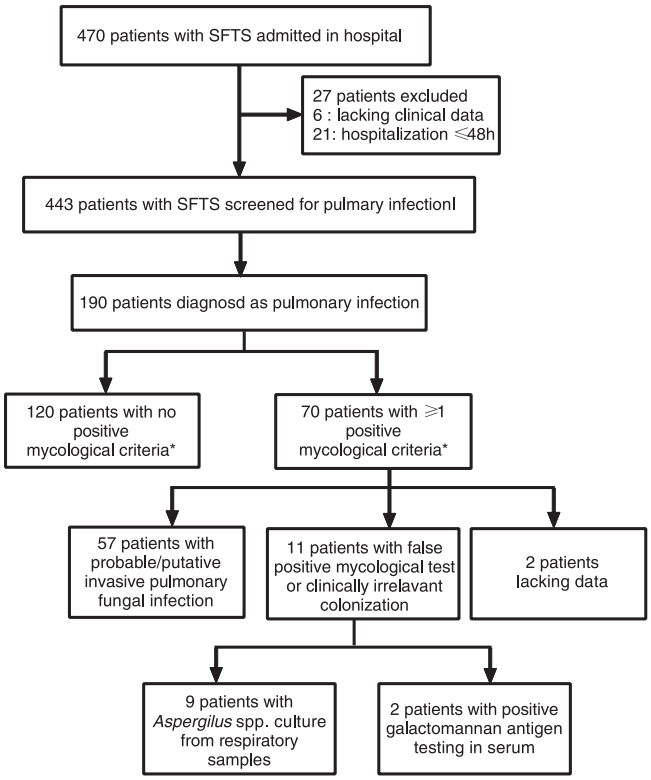

FIGURE 1 Study flowchart. *Candida spp. recovered from samples of respiratory tract was not included and in diagnosis for invasive pulmonary mold infection, β-glucan positive testing was also not considered. SFTS, severe fever with thrombocytopenia syndrome.

findings and mycological criteria such as histopathologic evidence, positive culture from a sputum, broncho alveolar lavage (BAL) or bronchial brush, galactomannan (GM) index in BAL ≥ 1, or GM index in serum ≥0.5.

2.3 | Laboratory procedure

The hematology and coagulation assay, the functions of the liver, kidney and myocardial enzymes, C-reactive protein, procalcitonin, galactomannan, and[1,3]-β-D-glucan were detected by routine tests after patient admission. The laboratory was certified by ISO 15189. Inflammatory mediators were measured in plasma samples using MILLIPLEX MAP human cytokine/chemokine magnetic bead panel kits (Merck Millipore) on a Luminex 200 System (Life Technologies). Peripheral EDTA blood was stained with the following mouse anti-human monoclonal antibodies CD45-krome orange, CD3-fluorescein isothiocyanate, CD4-phycoerythrin, CD8-allophycocyanin, and then analyzed on a Beckman Coulter Navios flow cytometer (Beckman Coulter). Clinical samples for microbiology culture and their frequency were depending on diagnosis of treating physicians. The strain identification was performed by MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry; BioMérieux).

2.4 | Statistical analysis

Continuous variables that were in line with normal distribution were presented as the means ($\bar{x}$) ± standard deviation (SD) and compared by *t* test, while those that were not in line with normal distribution were presented as medians (interquartile range [IQR]) and compared by Mann–Whitney U test. Categorical variables were described as *n* (%) and compared by χ^2 or Fisher's exact test. The multivariate analysis of variables with $p < 0.1$ in univariate analysis was performed by binary logistic regression model, with results being expressed as odds ratios (*OR*) values and 95% confidence intervals (*95% CI*). For analysis for outcomes, we used Kaplan–Meier survival analysis and the log-rank test to make initial comparisons between the groups and conduct a Cox regression model for multivariate prognostic analysis. The prediction accuracy was evaluated using the area under the receiver operating characteristic (ROC) curves. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 16.0 (SPSS Inc), and a 2-tailed $p < 0.05$ was considered significant for all analyses.

3 | RESULTS

3.1 | Characteristics of patients

After exclusion of 6 cases with no clinical data available and 21 cases with hospital stay ≤48 h, we finally included 443 patients (205 cases from First Affiliated Hospital of Anhui Medical University, 130 cases from Second Affiliated Hospital of Anhui Medical University and 108 cases from The First Affiliated Hospital of USTC) in this study.

The baseline clinical characteristics of patients enrolled were presented in Table 1. Among them, 229 (51.7%) patients were male. The mean age was 65.0-year-old (IQR, 55.0–71.0 years). A total of 179 (40.4%) patients were in severe status of SFTS. The median time from disease onset to admission was 5.0 days (IQR, 3.0–7.0 days), and the median hospitalization stay was 10.0 days (IQR, 7.0–14.0 days). A total of 396 (89.4%) patients started with fever, and other common symptoms included fatigue (283/443, 63.9%) and gastrointestinal tract symptoms (188/443, 42.4%). The most common comorbid disease in SFTS patients was hypertension (105/443, 23.7%), followed by diabetes (69/443, 15.6%). Moreover, during hospital stay, 347 (78.3%) patients and 303 (68.4%) patients received initial antiviral treatment with ribavirin and intravenous immunoglobin respectively, while 34 (7.7%) patients received early systemic corticosteroids, and all of them were diagnosed as SFTS. 88 (19.9%) patients died during hospitalization. The median laboratory findings at admission of patients were also shown in Table 1.

TABLE 1 Demography, clinical and laboratory findings and outcomes between the SFTS patients with or without pulmonary infection.

Variables	All patients (n = 443)	Patients with pulmonary infection (n = 190)	Patients without pulmonary infection (n = 253)	p Value
Demography				
Sex at birth				
Male	229 (51.7)	97 (51.1)	132 (52.2)	0.815
Female	214 (48.3)	93 (48.9)	121 (27.3)	
Age, years	65.0 (55.0–71.0)	69.0 (61.0–74.0)	63.0 (54.0–69.5)	<0.001
Smoking history	34 (7.7)	20 (10.5)	14 (5.5)	0.051
Drinking history	42 (9.5)	22 (11.6)	20 (7.9)	0.191
Time from onset to admission, days	5.0 (3.0–7.0)	5.0 (4.0–7.0)	5.0 (3.0–6.0)	0.001
Severe status at admission	179 (40.4)	114 (60.0)	65 (25.7)	<0.001
Baseline diseases				
Diabetes	69 (15.6)	37 (19.5)	32 (12.6)	0.050
Hypertension	105 (23.7)	53 (27.9)	52 (20.6)	0.072
Dyslipidaemia	15 (3.4)	8 (4.2)	7 (2.8)	0.406
Autoimmunity disease	10 (2.3)	7 (3.7)	3 (1.2)	0.153
Heart dysfunction	23 (5.2)	13 (6.8)	10 (4.0)	0.175
Neurologic disease	43 (9.7)	26 (13.7)	17 (6.7)	0.014
Malignancy	12 (2.7)	3 (1.6)	9 (3.6)	0.330
COPD	13 (2.9)	9 (4.7)	4 (1.6)	0.096
Others	45 (10.2)	22 (11.6)	23 (9.1)	0.391
Symptoms at admission				
Fever	396 (89.4)	169 (88.9)	227 (89.7)	0.793
Fatigue	283 (63.9)	135 (71.1)	148 (58.5)	0.006
Rigor	178 (40.2)	89 (46.8)	89 (35.2)	0.013
Gastrointestinal tract symptoms	188 (42.4)	85 (44.7)	103 (40.7)	0.396
Muscular soreness	108 (24.4)	49 (25.8)	59 (23.3)	0.549
Skin change	38 (8.6)	25 (13.2)	13 (5.1)	0.003
CNS symptoms	78 (17.6)	48 (25.3)	30 (11.9)	<0.001
Antiviral treatment before				
Ribavirin	347 (78.3)	156 (82.1)	191 (75.5)	0.095
Intravenous immunoglobin	303 (68.4)	153 (80.5)	150 (59.3)	<0.001
Systemic corticosteroids	34 (7.7)	16 (8.4)	18 (7.1)	0.609
Laboratory findings at admission				
White blood cell count, $\times 10^9$ per L	2.7 (1.7–4.5)	2.7 (1.6–4.5)	2.6 (1.7–4.5)	0.693
Lymphocyte count, $\times 10^9$ per L	0.7 (0.4–1.1)	0.6 (0.4–1.0)	0.8 (0.5–1.2)	0.006
Neutrophils count, $\times 10^9$ per L	1.5 (0.9–2.9)	1.6 (1.0–3.1)	1.4 (0.9–2.9)	0.550
Platelet count, $\times 10^9$ per L	47.0 (32.0–70.0)	41.5 (30.0–58.3)	53.0 (36.0–77.5)	<0.001
APTT, s	48.1 (39.8–57.5)	50.1 (39.2–60.5)	46.9 (40.0–55.1)	0.126
Prothrombin time, s	12.8 (11.6–13.6)	12.7 (11.5–13.7)	12.8 (11.6–13.6)	0.973
D-dimer, μg/mL	2.4 (1.2–4.4)	3.1 (1.5–6.0)	1.9 (0.9–3.9)	<0.001

TABLE 1 (Continued)

Variables	All patients ($n = 443$)	Patients with pulmonary infection ($n = 190$)	Patients without pulmonary infection ($n = 253$)	p Value
AST, U/L	156.0 (81.0–310.0)	206.0 (98.8–383.5)	127.0 (66.5–262.5)	<0.001
Lactate dehydrogenase, U/L	679.0 (412.5–1260.0)	875.0 (522.0–1566.8)	576.0 (357.0–1049.0)	<0.001
C-reactive proteins, pg/mL	4.0 (1.3–11.8)	6.6 (2.1–16.8)	3 (1.1–8.3)	<0.001
Procalcitonin, ng/mL	0.2 (0.1–0.4)	0.3 (0.1–0.9)	0.1 (0.1–0.3)	<0.001
Outcomes				
Length of hospital stay, days	10.0 (7.0–14.0)	13.0 (8.0–19.0)	9.0 (7.0–12.0)	<0.001
Intensive care unit transfer	113 (25.5)	82 (43.2)	31 (12.3)	<0.001
Medical costs, dollars	4205.0 (1655.0–6633.0)	6102.0 (3420.5–9438.8)	3192.0 (1273.0–4943.0)	<0.001
Crude in-hospital mortality	88 (19.9)	58 (30.5)	30 (11.9)	<0.001
30-day mortality	84 (19.0)	54 (28.4)	30 (11.9)	<0.001

Note: Data are median (interquartile range) or n (%). p Values were calculated by Mann–Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.
Abbreviations: APTT, Activated partial thromboplastin time; AST, aspartate aminotransferase; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; SFTS, severe fever with thrombocytopenia syndrome.

3.2 | Prevalence and clinical characteristics of pulmonary infection in patients with SFTS

After review and re-assess, a total of 190 (42.9%) patients were diagnosed as pulmonary infection, and all of them have positive CT evidence. Among them, 70 (36.8%), 38 (20%), 2 (1.1%), and 1 (0.5%) of patients with pulmonary infection were defined as IPFI, bacterial pneumonia, atypical pathogens infection (*Mycoplasma pneumoniae* and *Legionella pneumophila*) and virus infection (parainfluenza virus) respectively, while others had unspecified pneumonia with no positive culture.

The results of comparative analysis between the groups of patients with and without pulmonary infection showed that patients with pulmonary infection have significantly increased age ($p < 0.001$), time from onset to admission ($p = 0.001$), frequency of having severe status as admission ($p < 0.001$), symptoms of skin change ($p = 0.003$) ($p < 0.001$) at admission and receiving initial intravenous immunoglobin treatment ($p < 0.001$). Other results of the clinical characteristics between the two groups were also presented in Table 1.

3.3 | Laboratory findings and outcomes of pulmonary infection in patients with SFTS

The comparison of laboratory findings also showed the significantly decreased lymphocyte count ($p = 0.006$) and platelet count ($p < 0.001$) and increased D-dimer ($p < 0.001$), aspartate aminotransferase ($p < 0.001$), lactate dehydrogenase ($p < 0.001$), C-reactive proteins ($p < 0.001$), and procalcitonin ($p < 0.001$) in SFTS patients with pulmonary infection (Table 1).

In addition, due to the qualitative analysis in majority patients, the data on viral loads was only obtained in 73 cases (43 cases without pulmonary infection and 30 cases with it) in this study. The comparative analysis suggested that the significantly increased Log_{10} copies/mL of SFTSV ($p = 0.025$) were found in the group of patients with pulmonary infection, when compared with those without pulmonary infection.

As for the outcomes, significantly increased length of hospital stay, intensive care unit transfer, medical costs, crude in-hospital mortality and 30-day mortality (all $p < 0.001$) were found in group of patients with pulmonary infection (Table 1). Additionally, as shown in Figure 2A, pulmonary infection was associated with decreased survival time in SFTS patients ($p < 0.0001$ by log-rank test). Moreover, a multivariate Cox regression analysis was performed and the results suggested that pulmonary infection (adjusted hazard ratio (aHR) 1.729 [95% CI, 1.076–2.780], $p = 0.024$) could independently predict the prognosis of SFTS patients, after adjusted by age, sex, time from onset to admission, history of smoking and drink, symptoms and baseline diseases.

3.4 | Risk factors for the occurrence of pulmonary infection in SFTS patients

We put the variables of clinical characteristics that have $p < 0.1$ in Table 1 into the further logistic regression analysis, and the results were presented in Table 2. The results of multivariate analysis exhibited that older age (OR 1.040 [95% CI, 1.019–1.062], $p < 0.001$), longer time from onset to admission (OR 1.163 [95% CI, 1.070–1.264], $p < 0.001$), severe status at admission (OR 3.166 [95% CI, 2.020–4.962], $p < 0.001$), having symptoms of skin change at admission (OR 2.361 [96% CI, 1.049–5.316], $p < 0.001$) and receiving intravenous immunoglobin for antiviral treatment (OR 2.185 [96% CI, 1.337–3.569], $p = 0.002$) were independently associated with the increased risk for the occurrence of pulmonary infection in SFTS patients.

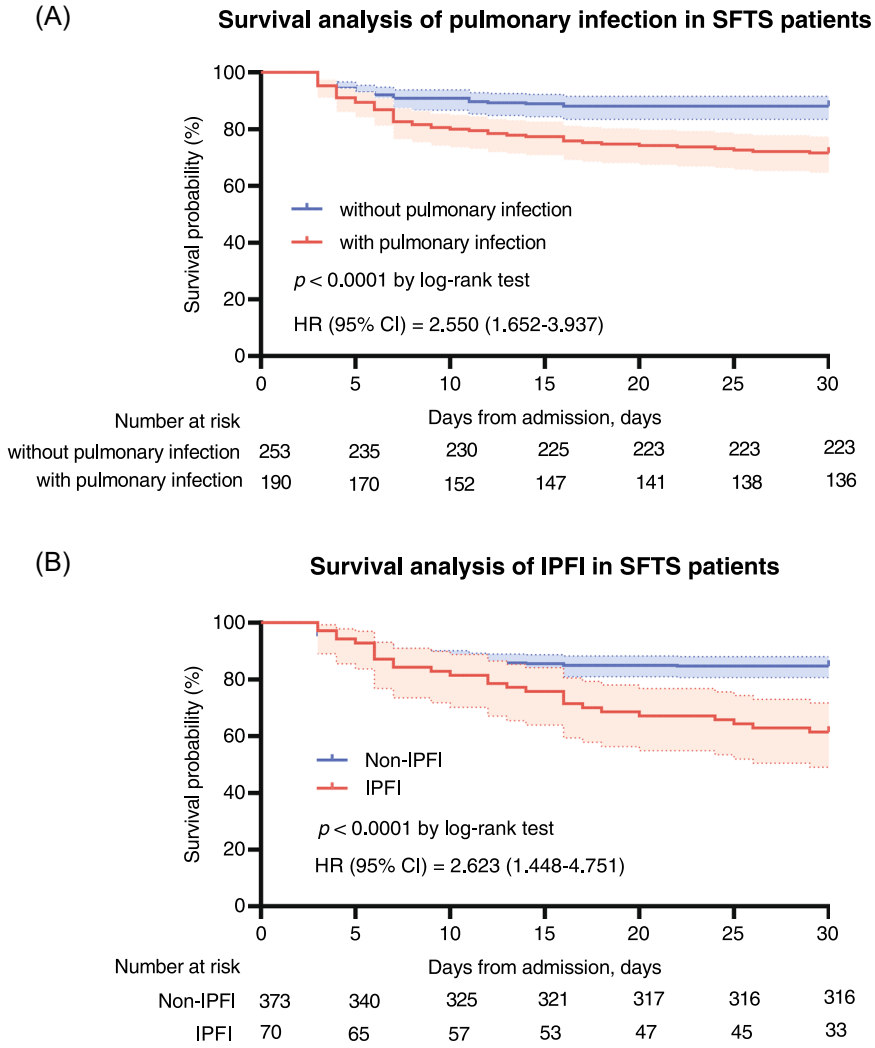

FIGURE 2 Survival proportion of patients according to infection status. (A) Cumulative survival proportion of SFTS patients with pulmonary infection versus without, by days from admission. (B) Cumulative survival proportion of SFTS patients with IPFI versus without, by days from admission. IPFI, invasive pulmonary fungal infection; SFTS, severe fever with thrombocytopenia syndrome.

3.5 | Prevalence of IPFI in patients with SFTS

Regarding to respiratory and serum samples, among 190 SFTS patients with pulmonary infection, 70 of them had ≥1 positive mycological test and among them, 3 patients could be defined as possible IPFI, while 67 cases could be defined as putative IPA. In other word, 70 (15.8%) of 443 patients enrolled were diagnosed with probable or putative IPFI.

Among the 70 IPFI patients, 40 (57.1%) cases were diagnosed in acute stage of disease, while 17 (24.3%) and 13 (18.6%) cases were diagnosed in initial stage of fever and recovery stage respectively. 31 (44.3%) of them have noneffective treatment outcomes (stable or deterioration) for pulmonary infection at discharge or death. Compared to non-IPFI patients with pulmonary infection, the frequency of noneffective infection treatment outcomes was significant higher in IPFI patients ($p = 0.047$), while the difference in infection stage do not have statistical significance ($p = 0.503$). Among the 70 IPFI patients, 44 were treated with voriconazole, 10 with fluconazole, 8 with caspofungin, 1 with amphotericin B, and 1 with isavuconazole. Interestingly, 11 of them were found to have favorable outcomes despite the absence of specific antifungal treatment.

3.6 | Clinical characteristics and outcomes of SFTS patients with IPFI

The comparison of clinical characteristics between the patients with or without IPFI demonstrated that patients with IPFI have longer time from onset to admission ($p = 0.004$), increased frequency of having smoking history ($p = 0.024$), severe status at admission ($p < 0.001$), comorbidities of autoimmunity disease ($p < 0.001$), receiving intravenous immunoglobin ($p < 0.001$) treatment. Other clinical characteristics between the two groups were also exhibited in Table 3.

Significantly increased length of hospital stay ($p < 0.001$), medical costs ($p < 0.001$), crude in-hospital mortality ($p < 0.001$) were found in group of patients with IPFI (Table 3). Furthermore, as shown in Figure 2B, the results of log-rank test showed the significant reduced survival time of SFTS patients with IPFI ($p < 0.0001$).

TABLE 2 Risk factors associated with the occurrence of pulmonary infection in SFTS patients.

Variables	Univariate OR (95% CI)	*p* Value	Multivariate OR (95% CI)	*p* Value
Demography				
Male sex	0.956 (0.656–1.393)	0.815		
Age	1.050 (1.031–1.069)	<0.001	1.040 (1.019–1.062)	<0.001
Time from onset to admission	1.143 (1.060–1.233)	<0.001	1.163 (1.070–1.264)	<0.001
Severe status at admission	4.338 (2.895–6.503)	<0.001	3.166 (2.020–4.962)	<0.001
Baseline diseases				
Diabetes	1.670 (0.997–2.798)	0.051		
Hypertension	1.495 (0.963–2.322)	0.073		
Neurologic disease	2.201 (1.157–4.186)	0.016		
COPD	3.095 (0.999–10.208)	0.063		
Symptoms at admission				
Skin change	2.797 (1.391–5.627)	0.004	2.361 (1.049–5.316)	0.038
Fatigue	1.741 (1.166–2.601)	0.007		
Rigor	1.624 (1.106–2.6385)	0.013		
CNS symptoms	2.513 (1.520–4.152)	<0.001		
Antiviral treatment before				
Ribavirin	1.489 (0.932–2.380)	0.096		
Intravenous immunoglobin	2.389 (1.832–4.400)	<0.001	2.185 (1.337–3.569)	0.002

Abbreviations: CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; OR, odds ratio; SFTS, severe fever with thrombocytopenia syndrome.

3.7 | Risk factors for the occurrence of IPFI in patients with SFTS

Similarly, the variables of clinical characteristics that have $p < 0.1$ in Table 3 were further analyzed by the method of multivariate logistic regression analysis (Table 4). The results demonstrated that having smoking history (OR 3.178 [95% CI, 1.251–8.070], $p = 0.015$), longer time from onset to admission (OR 1.117 [95% CI, 1.016–1.229], $p = 0.022$), severe status at admission (OR 5.737 [95% CI, 3.054–10.779], $p < 0.001$), complicating with autoimmunity disease (OR 7.855 [96% CI, 1.632–37.796], $p = 0.010$) and receiving intravenous immunoglobin for antiviral treatment (OR 3.270 [96% CI, 1.424–7.508], $p = 0.005$) were independently associated with a risk of IPFI in SFTS patients.

3.8 | Laboratory parameters of SFTS patients with IPFI

Univariate analysis was conducted between the patients with or without IPFI to identify the possible predict parameters of IPFI. As shown in Table 5, the decreased white blood cell count ($p < 0.001$), lymphocyte count ($p < 0.001$), monocyte count ($p = 0.041$), neutrophils count ($p = 0.002$), $CD3^+CD4^+$ T cell count ($p < 0.001$) and $CD3^+CD8^+$ T cell count ($p < 0.001$) were associated with co-infection with IPFI. OR value of these variables and statistical value of other parameters were presented in Table 5.

3.9 | Predictors of IPFI in SFTS patients with pulmonary infection

To further explore the predictors of IPFI in patients with pulmonary infection, we included predictive laboratory parameters in Table 5 into a univariate analysis, and the OR and p value of each variable was exhibited in Table 6. Variables were then included in a multivariate analysis to be adjusted by sex, age, time from onset to admission, having smoking history, severe status, autoimmunity disease, and intravenous immunoglobin treatment. The results showed that decreased white blood cell count ($p = 0.001$), lymphocyte count ($p = 0.013$), monocyte count ($p = 0.046$), neutrophils count ($p < 0.001$), $CD3^+CD4^+$ T cell count ($p = 0.001$) and $CD3^+CD8^+$ T cell count ($p = 0.028$) were independently associated the decreased risk of IPFI in SFTS patients with pulmonary infection. Adjusted OR value of these variables and statistical value of other parameters were also presented in Table 6.

The results of ROC curve analysis included above independent associated parameters demonstrated that white blood count

TABLE 3 Demography, clinical and laboratory findings and outcomes between the SFTS patients with or without IPFI.

Variables	IPFI ($n = 70$)	Non-IPFI patients ($n = 373$)	p Value
Demography			
Male sex at birth	36 (51.4)	193 (51.7)	0.962
Age, years	69.0 (63.0–74.0)	64.0 (54.0–71.0)	<0.001
Smoking history	10 (14.3)	24 (6.4)	0.024
Time from onset to admission	6.0 (4.07–.0)	5.0 (3.0–7.0)	0.004
Severe status at admission	54 (77.1)	125 (33.5)	<0.001
Baseline diseases			
Diabetes	19 (27.1)	50 (13.4)	0.004
Hypertension	24 (34.3)	81 (21.7)	0.023
Autoimmunity disease	5 (7.1)	5 (1.3)	0.003
Neurologic disease	10 (14.3)	33 (8.8)	0.158
COPD	4 (5.7)	9 (2.4)	0.264
Symptoms at admission			
Fatigue	50 (71.4)	233 (62.5)	0.152
Rigor	30 (42.9)	148 (39.7)	0.619
Gastrointestinal tract symptoms	36 (51.4)	152 (40.8)	0.097
Skin change	10 (14.3)	28 (7.5)	0.063
CNS symptoms	22 (31.4)	56 (15.0)	0.001
Antiviral treatment before			
Ribavirin	63 (90.0)	284 (76.1)	0.010
Intravenous immunoglobin	61 (87.1)	242 (64.9)	<0.001
Systemic corticosteroids	9 (12.9)	25 (6.7)	0.076
Outcomes			
Length of hospital stay, days	16.0 (10.0–24.0)	10.0 (7.0–13.0)	<0.001
Medical costs, dollars	8940.5 (6115.0–14060.3)	3540.0 (1439.5–5764.5)	<0.001
Crude in-hospital mortality	30 (42.9)	58 (15.5)	<0.001

Note: Data are median (interquartile range) or n (%). p Values were calculated by Mann–Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.
Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; IPFI, invasive pulmonary fungal infection; SFTS, severe fever with thrombocytopenia syndrome.

$<2.09 \times 10^9$ per L (AUC value 0.759 [95% CI, 0.687–0.830]) and $CD3^+CD4^+$ T cell count <104.0 per μL (AUC value 0.733 [95% CI, 0.643–0.824]) could effectively predict IPFI, with sensitivity of 80.0% and 64.7%, respectively and with specificity of 75.0% and 64.3% respectively, when comparing with other predictors. We also put the independent risk factors identified in univariate analysis in Table 4 and the predictive parameters into multivariate analysis, and results also suggested the independently predict value of white blood count $<2.09 \times 10^9$ per L (OR 11.064 [96% CI, 3.708–33.012], $p < 0.001$) and $CD3^+CD4^+$ T cell count <104.0 per μL (OR 10.429 [96% CI, 3.395–32.038], $p < 0.001$) for IPFI in SFTS patients with pulmonary infection (Table 7).

4 | DISCUSSIONS

To our acknowledgment, this study is the first cohort study to date to investigate the prevalence of pulmonary infection in hospitalized SFTS patients, with assessment of the outcomes, risk factors and predictive parameters for such secondary infections. We determined the high prevalence of pulmonary infection in patients hospitalized with SFTS. In particular, age, time from onset to admission, severe status, with symptoms of skin change and receiving intravenous immunoglobin were associated with the higher odds of pulmonary infection. Moreover, pulmonary infection was associated with decreased survival time in both the univariate and multivariate

TABLE 4 Risk factors associated with the occurrence of IPFI in SFTS patients.

Variables	Univariate OR (95% CI)	*p* Value	Multivariate OR (95% CI)	*p* Value
Demography				
Male sex	0.988 (0.593–1.646)	0.962		
Age	1.044 (1.018–1.070)	0.001		
Smoking history	2.424 (1.103–5.324)	0.027	3.178 (1.251–8.070)	0.015
Time from onset to admission	1.114 (1.021–1.216)	0.015	1.117 (1.016–1.229)	0.022
Severe status at admission	6.696 (3.683–12.175)	<0.001	5.737 (3.054–10.779)	<0.001
Baseline diseases				
Diabetes	2.407 (1.314–4.408)	0.004		
Hypertension	1.881 (1.084–3.265)	0.025		
Autoimmunity disease	5.662 (1.594–20.106)	0.007	7.855 (1.632–37.796)	0.010
Symptoms at admission				
Gastrointestinal tract symptoms	1.539 (0.922–2.569)	0.099		
Skin changes	2.054 (0.949–4.446)	0.068		
CNS symptoms	2.594 (1.454–4.612)	0.001		
Antiviral treatment before				
Ribavirin	4.416 (1.461–11.765)	0.008	2.299 (0.963–5.487)	0.061
Intravenous immunoglobin	3.669 (1.766–7.624)	<0.001	3.270 (1.424–7.508)	0.005
Systemic corticosteroids	2.054 (0.915–4.612)	0.081		

Abbreviations: CI, confidence interval; CNS, central nervous system; IPFI, invasive pulmonary fungal infection; OR, odds ratio; SFTS, severe fever with thrombocytopenia syndrome.

analysis. Importantly, this is the largest study to investigate the prevalence of IPFI in SFTS patients until now. Among the enrolled 443 patients, we recorded 70 IPFI cases. Time from onset to admission, severe status, having smoking history, autoimmunity disease, receiving intravenous immunoglobin were independent risk factors for the occurrence of IPFI. Furthermore, white blood count and $CD4^+$ T cell count were also identified to predict IPFI in patients with pulmonary infection, which may provide a basis for clinical management of fungal treatment timing.

We observed a prevalence of up to 42.9% of pulmonary infection in patients hospitalized with SFTS. The prominent features of SFTS patients, namely thrombocytopenia and leukopenia, may increase the risk of secondary infection.[18] The high prevalence observed in this study might be related with the rigorous monitoring, especially the early CT and laboratory test. An interesting finding was that bacteriological confirmation of an infecting pathogens was not found in a high percentage of SFTS patients with pulmonary infection. We speculated that the priority and frequency of microbiological testing and early antibiotic treatment received for differential diagnoses of SFTS, such as rickettsial infection, may help to explain it to some extent. However, further prospective study is needed to provide robust data support on this issue.

We identified several risk factors associated with pulmonary infection by multivariate analysis. Patients with pulmonary infection were significantly older and had more severe status of the disease at admission. Additionally, symptoms of skin change may also indicate a more severe bleeding tendency in patients.[19] Increased risk for pulmonary infection, caused by the longer time from onset to admission, may be attributed to the delayed diagnosis and treatment of infections. Furthermore, to explore the stress or internal interaction, antiviral treatment was set as variables into analysis. Patients with pulmonary infection more frequently received the initial intravenous immunoglobin (IVIG) treatment. In fact, severe patients with virus infection may get benefit due to the regulated effect of IVIG on host immune response.[20] Systematic inflammatory response syndrome has been widely reported in severe SFTS patients, and they were considered to receive IVIG in real world.[2,9] However, both the followed compensatory anti-inflammatory response syndrome and the influence of IVIG in inactive auto-reactive T-cells increased susceptibility to secondary infection.[21,22]

A main finding of this study was the prevalence of IPFI in SFTS patients. In fact, only small cohort studies previously reported the highly variable IPA prevalence estimated in SFTS patients, ranging from 31.9% to 56.0%.[9,11,13] The rigor of criteria and the monocentric nature of these studies, with variable local environment and low numbers of patients may help explain such varying prevalence. However, lack of host factors was suggested by all of these studies, which makes the diagnosis of SAPA challenging.[9,11] Similar results were also found in this study and these findings made SFTS

TABLE 5 Univariate analysis of laboratory parameters between the SFTS patients with or without IPFI.

Variables	IPFI patients (n = 70)	Non-IPFI patients (n = 373)	Univariate OR (95% CI)	p Value
White blood cell count, $\times10^9$ per L	1.7 (1.2–2.8)	2.9 (1.8–4.7)	0.736 (0.624–0.868)	<0.001
Lymphocyte count, $\times10^9$ per L	0.4 (0.3–0.7)	0.8 (0.5–1.2)	0.292 (0.151–0.565)	<0.001
Monocyte count, $\times10^9$ per L	0.1 (0.1–0.3)	0.2 (0.1–0.4)	0.293 (0.090–0.949)	0.041
Neutrophils, count $\times10^9$ per L	1.2 (0.7–1.7)	1.6 (1.0–3.2)	0.735 (0.606–0.893)	0.002
NLR	2.2 (1.3–3.8)	2.3 (1.3–4.5)	0.953 (0.880–1.032)	0.236
Platelet count, $\times10^9$ per L	38.0 (30.0–50.5)	48.0 (34.0–73.0)	0.993 (0.985–1.000)	0.066
PLR	87.3 (43.3–151.8)	74.0 (38.3–121.6)	1.003 (1.000–1.006)	0.028
APTT, s	51.2 (42.8–64.9)	47.2 (39.4–56.6)	1.008 (0.993–1.022)	0.233
PT, s	12.7 (11.4–13.9)	12.8 (11.6–13.6)	1.063 (0.961–1.175)	0.234
D-dimer, μg/mL	4.0 (2.2–8.3)	2.1 (1.1–3.9)	1.021 (0.990–1.053)	0.182
AST, U/L	206.0 (105.5–380.8)	142.0 (76.0–300.5)	1.000	0.655
Lactate dehydrogenase, U/L	979.0 (585.5–1941.0)	629.0 (396.0–1179.0)	1.000	0.093
C-reactive proteins, pg/mL	7.7 (3.1–17.0)	3.5 (1.2–10.3)	1.001 (0.996–1.006)	0.808
$CD3^+CD4^+$ T cell count per μL	91.0 (54.0–139.0)	201.0 (114.0–365.0)	0.989 (0.985–0.994)	<0.001
$CD3^+CD8^+$ T cell count per μL	84.0 (39.0–130.0)	154.0 (84.0–289.5)	0.993 (0.989–0.997)	<0.001
$CD4^+/CD8^+$ ratio	1.2 (0.7–1.8)	1.3 (0.9–1.9)	0.922 (0.699–1.218)	0.569
TNF-α, pg/mL	15.7 (9.6–24.9)	16.7 (8.9–24.3)	0.993 (0.984–1.009)	0.550
IL-6, pg/mL	58.3 (12.2–194.7)	12.9 (6.1–32.6)	1.001 (1.000–1.002)	0.086
IL-10, pg/mL	67.7 (45.6–107.0)	23.3 (8.0–65.5)	1.001 (0.998–1.004)	0.455
IL-8, pg/mL	29.0 (20.2–42.2)	21.3 (14.3–37.2)	1.001 (0.993–1.010)	0.735
IL-2R, pg/mL	1264.0 (1058.0–1466.0)	1064.0 (702.3–1386.3)	1.000 (1.000–1.001)	0.323
IL-1B, pg/mL	7.4 (5.0–15.1)	7.4 (5.0–15.4)	0.998 (0.991–1.006)	0.666

Note: Data are median (interquartile range).

Abbreviations: APTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; CI, confidence interval; IL-1B, interleukin-1B; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IPFI, invasive pulmonary fungal infection; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PT, Prothrombin time; SFTS, severe fever with thrombocytopenia syndrome; TNF-α, tumor necrosis factor-alpha.

TABLE 6 Associated laboratory parameters with IPFI in SFTS patients with pulmonary infection.

Variables	Univariate OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
White blood cell count	0.685 (0.568–0.828)	<0.001	0.714 (0.588–0.867)	0.001
Lymphocyte count	0.352 (0.179–0.691)	0.002	0.428 (0.220–0.833)	0.013
Monocyte count	0.265 (0.075–0.932)	0.038	0.269 (0.074–0.978)	0.046
Neutrophils count	0.650 (0.513–0.823)	<0.001	0.664 (0.517–0.852)	0.001
PLR	1.003 (1.000–1.006)	0.051		
$CD3^+CD4^+$ T cell count	0.989 (0.983–0.995)	0.001	0.990 (0.984–0.996)	0.001
$CD3^+CD8^+$ T cell count	0.993 (0.988–0.998)	0.007	0.995 (0.991–1.000)	0.028

Note: Adjusted by sex, age, time from onset to admission, having smoking history, severe status, autoimmunity disease and intravenous immunoglobin treatment.

Abbreviations: CI, confidence interval; IPFI, invasive pulmonary fungal infection; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; SFTS, severe fever with thrombocytopenia syndrome.

TABLE 7 Predictors for IPFI in SFTS patients.

Variables	β	SE	Wald	p Value	OR	95% CI
Severe status at admission	1.388	0.572	5.890	0.015	4.008	1.306–12.296
Time from onset to admission	0.224	0.093	5.848	0.016	1.252	1.043–1.501
White blood count $<2.09 \times 10^9$ per L	2.404	0.558	18.572	<0.001	11.064	3.708–33.012
$CD3^+CD4^+$ T cell count <104.0 per μL	2.345	0.573	16.763	<0.001	10.429	3.395–32.038

Abbreviations: CI, confidence interval; IPFI, invasive pulmonary fungal infection; OR, odds ratio; SFTS, severe fever with thrombocytopenia syndrome.

reasonable as a host factor for IPFI. The second point accompanied with this phenomenon was the confirmation of clinical relevance and invasiveness. In present study, it worth to note that some patients meeting the criteria of IPFI exhibit favorable outcomes without any antifungal treatment. However, it may also be related with best host immunological status or more adequate treatments.

The risk factors for IPFI in SFTS patients were also determined in our work. Severe status of disease was an independent risk factor for IPFI, and possible attribute may be the severe dysfunction of immune responses. In fact, initial IVIG treatment was also associated with the occurrence of IPFI. Importantly, the treatment included was only occurred before the diagnosis of the focused event (pulmonary infection or IPFI). Autoimmunity disease was identified as a risk factor for IPFI. Patients having autoimmunity disease usually have a chronic immunosuppression condition and corticoids treatment.[23] Smoking history could also increase the risk of IPFI in SFTS. Previous studies have revealed that smoking can dysfunction immunity and microbial adhesion to increase the risk of pneumonia.[24,25] Overall, the risk factors for IPFI identified in our work primarily indicated more severe disease. Therefore, it would be suggested that patients who were appear to have more advanced illness at admission should be carefully ruled out for concurrent or subsequent development of IPFI.

Identification of early predictive parameters for IPFI in SFTS patients with pulmonary infection were important, because the diagnosis is difficult in these patients due to the nonspecific CT and clinical evidence. According to the ROC curve and multivariate analysis, we determined the independent predictors for IPFI. In fact, the general immunosuppressive condition in SFTS patients with pulmonary infection, which weakened the predict role of typical risk factors for invasive fungal infection. Natural antifungal defense is based on the normal function of macrophage and neutrophil.[18] Fungal infection has been reported to be associated with impaired cell-mediated immunity.[18] $CD4^+$ T cell loss was observed to be associated with severity of SFTS.[8] Hu et al. also reported the predict value of $CD4^+$ T cell in SFTS patients for IPA.[11] Similarly, in our work, it was also confirmed to be a useful predictor with high sensitivities and specificities of cut-off value. Whatever, a complex change in immune function in SFTS patients with pulmonary infection and high prevalence of IPFI imply the importance of early diagnosis and robust monitoring of IPFI.

Our study has several limitations. First, the frequency of microbiological tests was determined by the clinical physicians which may cause the underestimate of the infection. Second, the risk and predictive factors identified in this study lacked efficient external validation, which might limit the interpretation of our findings. Third, the data of levels of serum immunoglobin were lacked because the test of it before IVIG treatment were rarely conducted in patients enrolled in this study. Finally, the information of antiviral treatment was insufficient to some extent as the clinical significance was difficult to determine.

This study systematically described detailed information of pulmonary infection in SFTS, with high prevalence and associated high mortality. We found that older age, time from onset to admission, severe status, with symptoms of skin change and receiving intravenous immunoglobin were risk factors for the occurrence of pulmonary infection. In addition, time from onset to admission, severe status, having smoking history, autoimmunity disease, receiving intravenous immunoglobin were independent risk factors for the occurrence of IPFI. White blood count and $CD4^+$ T cell count help predict IPFIs in SFTS patients with pulmonary infection. Overall, these findings highlight the need for implementation of active surveillance of high-risk patients.

AUTHOR CONTRIBUTIONS

Yan Zuo: Methodology; investigation; data curation and analysis and writing. **Heming Wang**: Data curation and writing. **Jiaxiang Huang**: Validation and analysis. **Fang Zhang**: Formal analysis. **Dongmei Lv**: Formal analysis. **Tao Meng**: Data curation. **Asma Bibi**: Data curation. **Lianzi Wang**: Methodology and writing—review. **Zhongxin Wang**: Methodology and writing—review. **Yuanhong Xu**: Methodology; supervision; funding acquisition and writing—review.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The present study was conducted according to the Declaration of Helsinki and was approved by Ethics Committee of the First Affiliated

Hospital of Anhui Medical University, The Second Affiliated Hospital of Anhui Medical University and The First Affiliated Hospital of USTC. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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