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Original Article

# Clinical features of fatal severe fever with thrombocytopenia syndrome that is complicated by invasive pulmonary aspergillosis

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ABSTRACT

*Introduction:* Severe fever with thrombocytopenia syndrome (SFTS) has been prevalent in parts of Asia during recent years. However, SFTS with invasive pulmonary aspergillosis (IPA) is rare, and it is important to understand its clinical features.
*Materials and methods:* Total four cases of SFTS with IPA are reviewed and detailing the disease progression, treatment options, and prognosis were summarized and analyzed.
*Results:* The patients with SFTS-associated IPA first presented with fever, gastrointestinal symptoms, thrombocytopenia, leukopenia, and multiple organ failure. After 1–2 weeks, the patients developed mild polypnea and wheezing rales, and quickly developed dyspnea and respiratory failure. Tracheal intubation was usually performed, but did not relieve the intractable airway spasm and pulmonary ventilation failure. Bronchoscopy confirmed that the antifungal treatment was ineffective and the aspergillosis had worsened. All patients died of type 2 respiratory failure caused by continued airway obstruction and spasticity.
*Conclusions:* Given the high mortality rate in this series, there is a need for increased awareness of SFTS-associated IPA. Additional examinations should be performed in these cases, and early-stage antifungal treatment with organ support may be helpful.


## 1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an infection that is caused by a novel phlebovirus, characterized by unexplained fever, thrombocytopenia, leukopenia, gastrointestinal symptoms (e.g., nausea, celiodynia, and diarrhea), and multiple organ failures. This disease is mainly prevalent in the agricultural and mountainous regions of China, Japan, and South Korea [1]. A bunyavirus that is associated with the disease has been named the SFTS virus (SFTSV), and its RNA was isolated and identified in 2011 [2]. SFTS-related mortality is caused by multiple organ failures, which can involve significant thrombocytopenia, severe coagulopathy, central nervous system damage, and respiratory failure [3]. However, we are not aware of any reports that have examined the association of SFTS with invasive pulmonary aspergillosis (IPA).

IPA is the most common type of invasive aspergillosis, and usually develops in immunocompromised patients who have experienced neutropenia, hematological malignancy, transplantation, prolonged treatment with corticosteroids, or lung destruction [4]. The primary disease is usually masked by equivocal symptoms of IPA, such as fever, cough, chest pain, and hemoptysis [5].

We report the clinical characteristics and treatments from four cases of SFTS-associated IPA, in order to help improve the clinical outcomes among these critically ill patients.

## 2. Materials and methods

This retrospective study examined data from 48 patients with SFTS who were treated at the Nanjing Drum Tower Hospital between July 2010 and July 2017. Four patients were found to have SFTS with IPA. The study's retrospective protocol was approved by the Ethics Committee of the Nanjing Drum Tower Hospital, and all data were anonymized. The patients' medical records were searched to obtain clinical and demographic data, such as underlying medical conditions, clinical signs and symptoms, and laboratory test results, as well as any relevant follow-up data.

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The SFTS diagnoses were confirmed based on (a) acute fever, (b) thrombocytopenia, (c) detection of SFTSV RNA using polymerase chain reaction, (d) detection of IgM to the SFTSV, or (e) seroconversion or a >4-fold increase in IgG to SFTSV when the acute and convalescent serum samples were compared [6]. The IPA diagnoses were based on the revised definitions of invasive fungal infections from the European Organization for the Research and Treatment of Cancer/Mycosis Study Group [7]. A diagnosis of IPA is considered probable if the patient has appropriate clinical manifestations, positive cultures, and a positive result from the serum galactomannan antigen test for aspergillosis. However, a diagnosis of proven IPA requires direct histopathological evidence.

## 3. Results

The initiation and progression of disease for four cases of SFTS with IPA are summarized as follows:

### 3.1. Case 1

A 72-year-old woman who performed agricultural work presented to a local hospital with a 3-day history of fever (>38.5 °C), nausea, and vomiting. Laboratory tests revealed leukopenia (white blood cell [WBC] count: 1700/μL, normal: 4000–10000/μL), thrombocytopenia (platelet [PLT] count: 0.36 × $10^4$/μL, normal: 1–3 × $10^4$/μL), acute liver injury (aspartate aminotransferase [AST] level: 93 U/L, normal: 8–40 U/L; alanine aminotransferase [ALT] level: 319 U/L, normal: 5–40 U/L), and acute renal injury (creatinine [Cr] level: 1.58 mg/dL, normal: 0.50–1.20 mg/dL; blood urea nitrogen (BUN) level: 44.23 mg/dL, normal: 8.12–21.01 mg/dL). She was treated using antibiotics (cephalosporin) and antipyretics, which included dexamethasone and nonsteroidal anti-inflammatory drugs. However, her fever did not improve and she gradually became somnolent before being referred to our hospital for additional treatment. The laboratory test results from her admission to our hospital were a PLT count of 0.38 × $10^4$/μL, an activated partial thromboplastin time (APTT) of 57.1 s (normal: 20–40 s), and a thrombin time (TT) of 110 s (normal: 13–21 s). After she was admitted to our infectious disease ward, she received antiviral treatment (ribavirin and ganciclovir), an antibiotic (minocycline), plasma, cryoprecipitate, and a gamma globulin infusion based on a suspicion of SFTS. Fourteen days after the onset of disease, she slipped into a coma and developed dyspnea with acute left heart failure, and was subsequently transferred to our intensive care unit (ICU). The patient underwent endotracheal intubation with simultaneous intermittent mechanical ventilation and continuous renal replacement therapy (CRRT) to improve the acute renal injury and fluid overload.

During this period, the patient tested positive for bunyavirus RNA, which confirmed the diagnosis of SFTS. In addition, her sputum culture was positive for *Aspergillus flavus*, and she had a serum galactomannan (GM) level of 5.4 (normal cut-off index:0–0.5) and a (1 → 3)-β-D-glucan level of 617.4 pg/mL (normal: 0–100.5 pg/mL). Chest radiography revealed bilateral lung infiltration and computed tomography (CT) revealed scattered nodular or patchy shadows with obscure borders on both sides of the lungs. Bronchoscopy revealed that the right airway was obstructed by yellowish white mold, and the left airway had scattered yellowish-white mold. The airway mucosa was edematous and bled easily. Pathological examination of the airway tissue revealed necrotic fibrous tissue and fungal filaments, which confirmed an Aspergillus infection (Fig. 1). The patient received voriconazole (6 mg/kg every 12 h for first day, then 4 mg/kg every 12 h, intravenous) based on suspected IPA. But serious airway spasms persisted despite treatment using bronchial and muscle relaxants. Arterial blood gas analysis revealed a persistently increasing partial pressure of carbon dioxide ($PCO_2$), and the patient ultimately died because of pulmonary function failure and a severe coagulation disorder.

### 3.2. Case 2

A 42-year-old female farmer developed fever (>38 °C), fatigue, anorexia, and muscle pain. A community hospital treated her using antipyretics (acetaminophen and dexamethasone, 5 mg, twice) and an antibiotic (ceftriaxone), although these treatments did not improve her symptoms. On day 7, the patient experienced hyperspasmia with loss of consciousness for 1 min. On day 8, the patient experienced another episode of hyperspasmia and continued drowsiness, and was subsequently admitted to our hospital. After being admitted to an emergency ICU, she underwent endotracheal intubation and ventilator-assisted breathing. Laboratory testing revealed a WBC count of 3800/μL, a PLT count of 0.36 × $10^4$/μL, an AST level of 3510 U/L, an ALT level of 745 U/L, and a Cr level of 5.03 mg/dL. The patient subsequently received antiviral treatment (ribavirin), an antibiotic (ceftizoxime), an immune globulin infusion, a transfusion, and CRRT. Bunyavirus RNA was detected, which supported a diagnosis of SFTS. Two weeks later, the patient developed progressively worsening shortness of breath, and multiple sputum cultures tested positive for *Aspergillus fumigatus*, with a serum GM level of 5.6 and a serum (1 → 3)-β-D-glucan level of 134.1 pg/mL. Radiography revealed bilateral lung infiltrations and CT revealed a globular shadow along the bronchi tree, which supported a probable diagnosis of IPA. The patient received caspofungin (70 mg/day for first day, then 50 mg/day, intravenous) and voriconazole (6 mg/kg every 12 h for first day, then 4 mg/kg every 12 h, intravenous), although her partial $PCO_2$ continued to rise (to 100 mmHg) and CT revealed multiple cavities with serious bilateral consolidation. Thus, she was transferred to our ICU (Fig. 2).

Bronchoscopy revealed yellowish-white mold that was partially obstructing the entire airway. The airway mucosa was edematous and bled easily. Pathological examination of the airway tissue revealed fungal filaments (Fig. 3). The patient's pulmonary function improve slightly after the ventilator parameters were adjusted and she received bronchial and muscle relaxants. In addition, the patient received intravenous antifungal treatment (voriconazole and caspofungin) with inhaled amphotericin B (10 mg, every 8 h, inhaled). However, the patient's asthma and dyspnea worsened on day 23, and her partial $PCO_2$ rose to 105 mmHg. Bronchoscopy revealed diffuse yellowish-white mold throughout the entire airway, which obstructed the subsegmental bronchi. Oxygenation could not be maintained using mechanical ventilation because of the patient's respiratory failure, and venovenous extracorporeal membrane oxygenation (ECMO) was used. The IPA had progressed despite 11 days of voriconazole and caspofungin treatment, the antifungal therapy was changed to intravenous voriconazole, intravenous amphotericin B liposome (3 mg/kg, every day) and inhaled amphotericin B. The 9-day ECMO treatment maintained oxygenation at a normal level, but the airway spasms and obstruction did not improve. Repeated bronchoscopy also confirmed that the mold was not controlled by the treatments. The patient subsequently slipped into a deep coma after developing serious coagulopathy, aggravated liver failure, and complete dependence on ECMO for oxygenation. She eventually died because of SFTS with IPA.

### 3.3. Case 3

A 58-year-old female farmer developed a fever (>39 °C), fatigue, anorexia, dizziness, and vomiting. She was initially treated using dexamethasone and intravenous fluids, although 3 days later she

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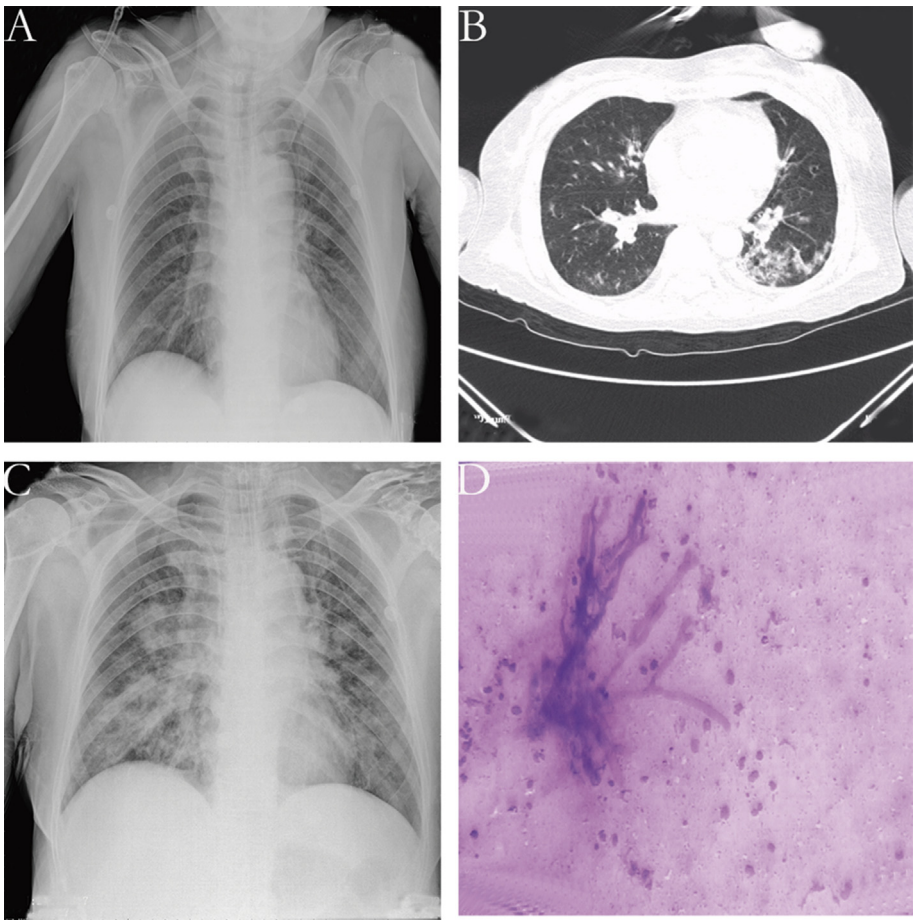


**Fig. 1.** Case 1. (A) A chest radiograph from day 10 after the onset of illness. (B) Computed tomography revealed a globular shadow along with bronchi tree on day 13 when the patient was transferred to the intensive care unit. (C) Chest radiography revealed increased infiltration on both sides of the lung on day 17, when the patient's airway spasm was more severe. (D) Pathological examination of the protected specimen brush reveals fungal hyphae (×400).

began experiencing intervals of drowsiness and unconsciousness. A CT scan at a local hospital revealed no obvious abnormalities in her head, and blood testing revealed a WBC count of 1290/μL and a PLT count of 0.51 × $10^4$/μL. Five days later, she was admitted to our hospital while unconscious and in shock, with gingival hemorrhage and dermal ecchymosis. A wheezing rale could be auscultated in her left lung. Blood testing revealed a WBC of count 3800/μL, a PLT count of 0.3 × $10^4$/μL, an APTT of 106.4 s, a TT of 114.8 s, a fibrinogen level of 1.6 g/L, an AST level of 1823 U/L, an ALT level of 633 U/L, a BUN level of 36.02 mg/dL, and a Cr level of 2.75 mg/dL. Arterial blood gas analysis revealed 102.2 mmHg as the partial pressure of oxygen ($PO_2$; oxygen mask for oxygen inhalation, 10 L/min) with a buffer excess of 6.5 mmol/L and a lactate level of 4.4 mmol/L. In addition, CT revealed consolidation in part of the left lung with an infiltrative shadow. The patient was admitted to our ICU, where she immediately underwent intubation, received ventilator-assisted breathing, and was treated using an antiviral drug (ribavirin), an antibiotic (biapenem), a transfusion, and CRRT. Additional examinations revealed a serum GM level of 5.22 and a (1 → 3)-β-D-glucan level of 243.3 pg/mL. A sputum culture from after the endotracheal intubation tested positive for *Aspergillus flavus*, which supported a diagnosis of IPA, and detection of bunyavirus RNA confirmed the diagnosis of SFTS. The patient rapidly developed severe circulatory disturbances, and her blood pressure could not be maintained using high doses of norepinephrine. The patient exhibited clear coagulation dysfunction and ultimately died on day 7.

### 3.4. Case 4

A 65-year-old man had a history of field work and a 5-year history of chronic obstructive pulmonary disease. He presented to a local hospital with a 3-day history of fever (>38 °C), diarrhea, malaise, anorexia, and vomiting. Blood testing revealed a WBC count of 1700/μL, a PLT count of 0.48 × $10^4$/μL, a BUN level of 45.52 mg/dL, and a Cr level of 1.78 mg/dL. The specific treatment that he received at that hospital was unclear. After 2 days, the patient still had a temperature of 39.6 °C and came to our hospital. Blood testing revealed a WBC count of 1700/μL, a PLT count of 0.25 × $10^4$/μL, a BUN level of 33.14 mg/dL, a Cr level of 1.75 mg/dL, an APTT of 50.3 s, a TT of 23.7 s, an AST level of 139 U/L, an ALT level of 72.3 U/L, and a fibrinogen level of 1.8 g/L. CT revealed signs of emphysema and a physical examination detected bilateral scattered wheezing rales and scattered red petechiae on his abdomen. The patient received antiviral treatment (ribavirin), an antibiotic (cefazolin), and granulocyte colony-stimulating factor based on a suspicion of SFTS. One day after being hospitalized, he began to experience ecphysesis and dyspnea, with a marked increase in the wheezing rales. Arterial blood gas analysis revealed a pH of 7.182, a $PO_2$ of 82 mmHg, and a $PCO_2$ of 47.4 mmHg (noninvasive ventilator-assisted ventilation, $FiO_2$: 60%). The patient underwent emergency endotracheal intubation and received ventilator-assisted breathing. Additional examinations revealed a serum GM level of 4.3 and a (1 → 3)-β-D-glucan level of 461.8 pg/mL. A sputum culture from after the

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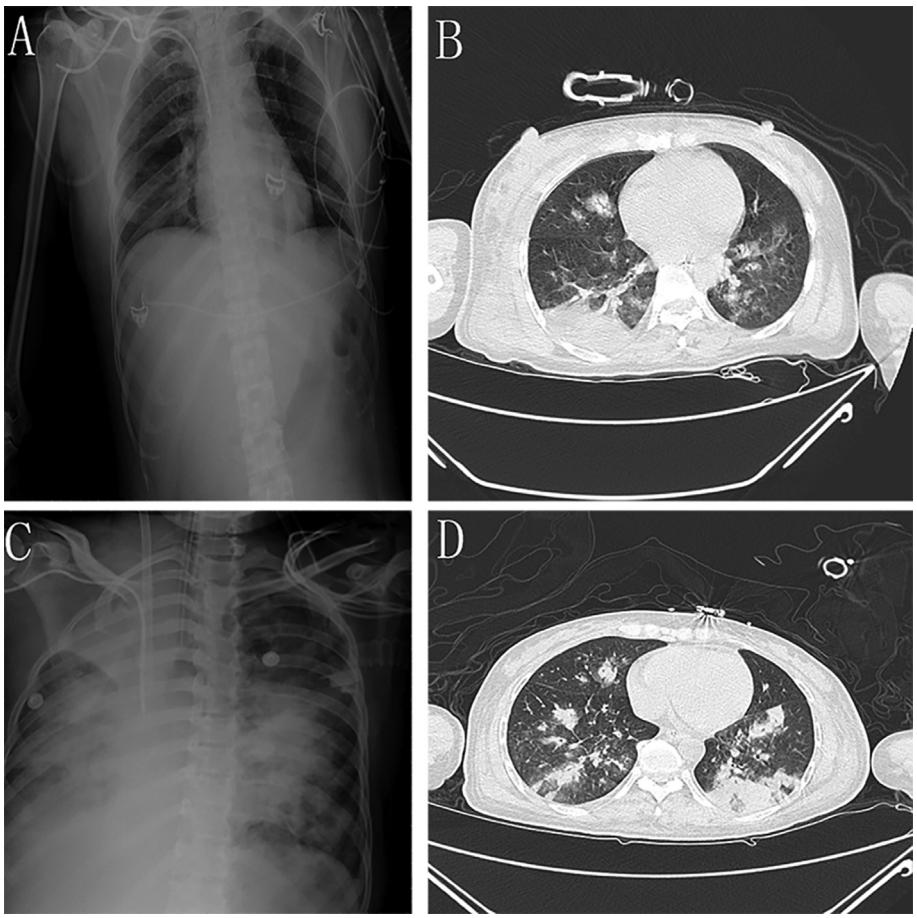


**Fig. 2.** Case 2. (A) Chest radiography from day 10 after the onset of illness revealed slight infiltration of the left lung. (B) Chest computed tomography from day 12 revealed a globular mass and shadow along with bronchi tree, when the patient began to experience shortness of breath. (C) Chest radiography from day 28 revealed significantly increased infiltration on both sides of the lungs, with more serious infiltration on the left lung. (D) Computed tomography from day 22, before the start of extracorporeal membrane oxygenation, revealed multiple small cavities and bilateral consolidation.

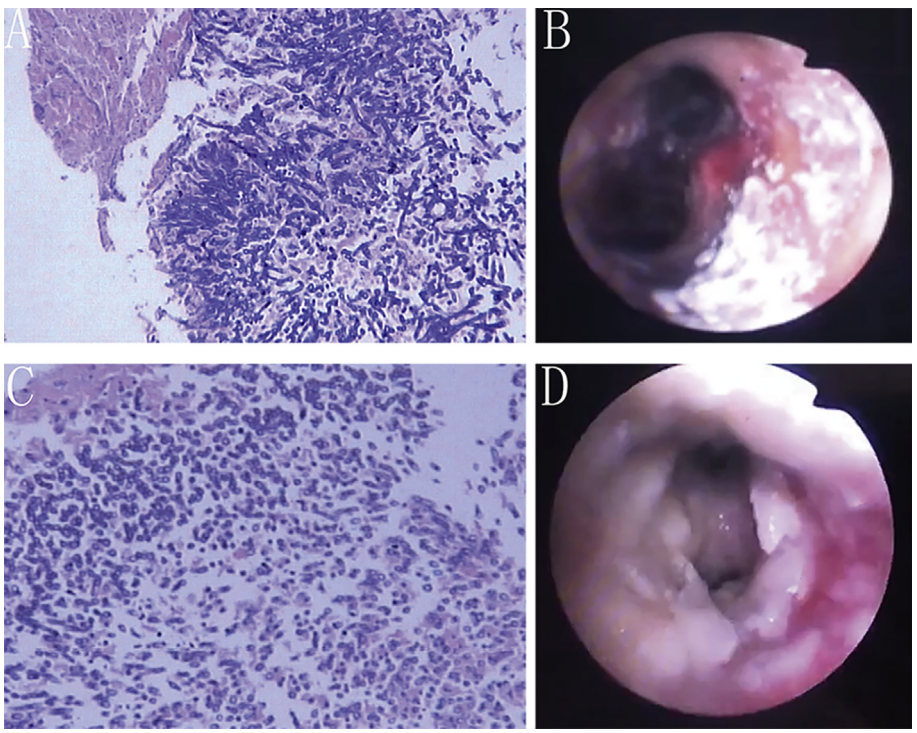


**Fig. 3.** Pathological examination of the airway mass from Case 1 (A) and Case 2 (C) revealed fibrous necrotic tissue and fungal filaments, which confirmed an Aspergillus infection (×100). Bronchoscopy of Case 1 (B) and Case 2 (D) revealed yellowish-white mold that was partially obstructing the entire airway.

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**Table 1**
Clinical manifestations of the four patients with SFTS-associated IPA.

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Patient | 72-year-old woman | 42-year-old woman | 58-year-old woman | 65-year-old man |
| Current/ex-smoker | No | No | No | Yes |
| Underlying disease | Hypertension | None | None | COPD |
| Farm or field worker | Yes | Yes | Yes | Yes |
| Total disease course | 19 days | 29 days | 7 days | 10 days |
| Systemic steroid before the diagnosis | Dexamethasone (5 mg, once) | Dexamethasone (5 mg, twice) | Dexamethasone (5 mg, twice) | None |
| Lowest neutrophil count (/μL, time <5 × $10^9$/L) | 1700, 16 days | 3800, 14 days | 1290, 5 days | 1700, 10 days |
| Lowest platelet count (×$10^4$/μL, subnormal time) | 0.19, 18 days | 0.26, 23 days | 0.26, 7 days | 0.25, 10 days |
| AST/ALT (minimum, U/L) | 818/111 | 3510/745 | 1823/633 | 335/72 |
| Coagulopathy (minimum APTT, subnormal time) | 129.1, 19 days | 96.8, 8 days | 119.7, 7 days | 99.2, 9 days |
| AKI (KDIGO) | 2 | 3 | 3 | 1 |
| Status at ICU admission | Coma | Coma | Coma | Languid |
| APACHE II score at ICU admission | 24 | 30 | 28 | 22 |
| Days to wheezing rales | 13th day | 19th day | 5th day | 8th day |
| Days to dyspnea | 14th day | 20th day | 6th day | 9th day |
| Days to intubation | 15th day | 10th day | 6th day | 9th day |
| Diagnosis of IPA | Proven | Proven | Probable | Probable |
| CT scan results | Consolidation | Cavity | Left lung infiltration | Consolidation |
| Bronchoscopic classification | Pseudomembranous | Pseudomembranous | – | – |
| *Aspergillus* spp. | *A. flavus* | *A.fumigatus* | *A. flavus* | *A.fumigatus* |
| Serum G (pg/mL) | 617.4 | 134.8 | 243.3 | 461.8 |
| Serum GM | 5.4 | 5.6 | 5.22 | 4.3 |
| Antifungal therapy | Voriconazole | Voriconazole, caspofungin, L-AmB | Voriconazole | None |
| Co-infection with bacteria | – | *Acinetobacter Baumannii* | *Staphylococcus epidermidis* | – |
| Outcome | Death | Death | Death | Death |

APACHE II: Acute Physiology and Chronic Health Evaluation II; *A. flavus*: *Aspergillus flavus*; *A.fumigatus*: *Aspergillus fumigatus*; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AKI: acute kidney injury; COPD: chronic obstructive pulmonary disease; CT: computed tomography; GM: galactomannan test; G: (1 → 3)-β-D-glucan test; KDIGO: Kidney Disease Improving Global Outcomes; ICU: intensive care unit; IPA: invasive pulmonary aspergillosis; L-AmB: Amphotericin B Liposome; SFTS: severe fever with thrombocytopenia syndrome.

endotracheal intubation tested positive for *Aspergillus fumigatus*, which supported a diagnosis of IPA, and the SFTS diagnosis was confirmed after detecting bunyavirus RNA. The patient's symptoms and type 2 respiratory failure did not improve within 2 days, then his family insisted on leaving the hospital because of financial reasons. The patient was discharged with severe airway spasm and bilateral wheezing sounds, and eventually died on day 10 (see Table 1).

## 4. Discussion

SFTS is a new viral infection that has emerged during recent years, which is mainly transmitted by ticks [8]. This infection has become a significant public health problem because of its high fatality rate and rapid evolution. As we are unaware of any English-language reports of SFTS with IPA, we have reported the diagnosis, disease course, treatment, and prognosis of four cases of SFTS with IPA at our hospital.

All patients exhibited the typical symptoms at the onset of SFTS, which included prolonged thrombocytopenia and leukopenia with multiple organ failures. During the first 1–2 weeks, the patients developed scattered wheezing rales that were detected during lung auscultation, and then rapidly developed asthma, dyspnea, and respiratory failure. Two patients underwent tracheal intubation and antifungal treatment, which were unable to relieve their airway spasm and pulmonary ventilation function. Furthermore, bronchoscopy revealed that the antifungal treatment was ineffective, as the mold spread and worsened. All four patients eventually died because of type 2 respiratory failure with continuing airway obstruction and spasticity. Moreover, ECMO was ineffective for improving the oxygenation function of 1 patient.

The typical features of SFTS are hyperpyrexia, grave inflammatory reactions, thrombocytopenia, and leukopenia that is induced by the viral infection. The risk factors for IPA include neutropenia, organ transplantation, liver cirrhosis, and destruction of the lungs' physiological structure [9]. A dramatic increase in the incidence of IPA has been observed among patients in the ICU, which is related to their multiple organ failures, prolonged antibiotic treatment, and various invasive procedures (especially tracheal intubation) [9]. There appear to be several factors that can predispose patients to SFTS with IPA. The first is virus-induced leukopenia and thrombocytopenia, as the combination of these conditions with corticosteroid treatment reduces the body's ability to prevent Aspergillus invasion and replication. Second, there appears to be immune suppression caused by a degenerative feedback mechanism, which is in response to the fierce inflammatory reaction at the onset of SFTS. Third, multi-organ failure, a compromised nervous system, and tracheal intubation can lead to airway barrier damage, which allows Aspergillus to attach, invade, and proliferate in the bronchial airways.

The standard diagnostic work-up for IPA includes a clinical assessment, CT, biopsies, microscopic imaging, and tissue specimen cultures [10]. When IPA is suspected or diagnosed, an antifungal treatment should have been started immediately, and voriconazole is a standard first-line choice. Isavuconazole is another useful and well-tolerated drug, while it is not approved or used in China [11]. Caspofungin is a commonly used echinocandin that has been approved for salvage treatment of invasive aspergillosis, although its fungistatic activity is only 33% efficient. Amphotericin B is also treatment choose but usually with severe side effects, amphotericin B liposome improved the poor tolerability of amphotericin B and been used more widely for severely ill patients now [12,13]. A combination of two categories of antifungal therapy is recommended for refractory Aspergillus infections, although this approach may not provide a clear effect [14,15].

Patients who are infected with SFTSV have an average mortality rate of 5.3% [16]. Furthermore, the mortality rate for IPA is 42–64%, despite advances in diagnostic technology and antifungal treatment [4]. Moreover, the overall in-hospital mortality rate is 93.5% for invasive fungal tracheobronchitis with respiratory failure, which is a subtype of IPA [17]. These findings are consistent with our data regarding patients with SFTS and IPA, which indicate a poor treatment response and very low overall survival rate [18].

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This retrospective study has two limitations. First, we only identified 4 patients and the sample size is insufficient to investigate all of their features. However, we believe that ours is the first report of this rare illness. Second, our center is at a regional critical care hospital, and patients with relatively mild illnesses would not normally present to or be hospitalized at our center.

## 5. Conclusions

Our results indicate that SFTS is a predisposing factor for aspergillosis, especially among patients with multiple organ failures and tracheal intubation. In cases with asthma, wheezing sounds, and poor infection control, clinicians should suspect IPA co-infection and perform early examinations that include sputum cultures, serum (1 → 3)-β-D-glucan and galactomannan testing, radiography, bronchoscopy, and histopathological examinations. These examinations may facilitate early antifungal therapy that can inhibit the growth of Aspergillus and improve the patient's prognosis. Furthermore, appropriate organ support is crucial and ECMO may be an option for patients with severe pneumonia, although further clinical studies are needed to confirm whether this approach is effective.

## Ethics statement

The study's retrospective protocol was approved by the Ethics Committee of the Nanjing Drum Tower Hospital.

## Authorship statement

All authors meet the ICMJE authorship criteria.

We wish to confirm that there are no known conflicts of interest associated with this publication. We received financial support from the National Natural Science Foundation of China (No. 81701953).

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

## Contributions

| | |
|---|---|
| Xiancheng Chen | Study design and writing |
| Zhuxi Yu | Study design and writing |
| Yajun Qian | Data collection |
| Danjiang Dong | Data analysis |
| Yingying Hao | Providing patients |
| Ning Liu | Analyzed the data |
| Qin Gu | Revise and conceived |

## Conflicts of interest

The authors do not have any conflicts of interest.

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