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Research article

Viral shedding pattern of severe fever with thrombocytopenia syndrome virus in severely ill patients: A prospective, Multicenter cohort study

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ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is spreading rapidly in Asia. The pathway of SFTS virus shedding from patient and specific use of personal protective equipments (PPEs) against viral transmission have rarely been reported. The study was to determine SFTS virus (SFTSV) shedding pattern from the respiratory, digestive and urinary tract to outside in patients. Methods: Patients were divided into mild and severe groups in three sentinel hospitals for SFTS in Anhui province from April 2020 to October 2022. SFTSV level from blood, throat swabs, fecal/anal swabs, urine and bedside environment swabs of SFTS patients were detected by qRT-PCR. Specific PPEs were applied in healthcare workers contacting with the patients who had oropharyngeal virus shedding and hemorrhagic signs.

Results: A total of 189 SFTSV-confirmed patients were included in the study, 54 patients died (case fatality rate, 28.57 %). Positive SFTSV in throat swabs (T-SFTSV), fecal/anal swabs (F-SFTSV) and urine (U-SFTSV) were detected in 121 (64.02 %), 91 (48.15 %) and 65 (34.4 %) severely ill patients, respectively. The levels of T-SFTSV, F-SFTSV and U-SFTSV were positively correlated with the load of SFTSV in blood. We firstly revealed that SFTSV positive rate of throat swabs were correlated with occurrence of pneumonia and case fatality rate of patients ($P < 0.0001$). Specific precaution measures were applied by healthcare workers in participating cardiopulmonary resuscitation and orotracheal intubation for severely ill patients with positive T-SFTSV, no event of SFTSV human-to-human transmission occurred after application of effective PPEs.

Conclusions: Our research demonstrated SFTSV could shed out from blood, oropharynx, feces and urine in severely ill patients. The excretion of SFTSV from these parts was positively correlated with viral load in the blood. Effective prevention measures against SFTSV human-to-human transmission are needed.

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1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne zoonotic disease caused by SFTS virus (SFTSV) belonging to Bunyavirales order, Pheniviridae family, Bandavirus genus [1,2].

Severe fever with thrombocytopenia syndrome virus (SFTSV) renamed as *Dabie bandavirus* (DBV) belongs to Bunyavirales order, Pheniviridae family, Bandavirus genus [1,2], which was the pathogen of severe fever with thrombocytopenia syndrome(SFTS). In recent years, SFTS has been rapidly spreading in Asia including China, Japan, South Korea, Vietnam, Pakistan, and Myanmar [3–8]. *Haemaphysalis longicornis* (*H. longicornis*) tick is the main reservoir and vector of SFTSV, which although native to East Asia, has established populations in the Australasian and Western Pacific Regions [9]. SFTS is an acute-onset disease characterized by fever, thrombocytopenia, leukocytopenia, gastrointestinal symptoms, neural disorders and multiple organ damage [10]. Although most persons with SFTS experience nonspecific influenza-like symptoms, more severe and prolonged disease can occur in severe ill patients with high-grade viremia and excessive inflammatory response, further leading to organ damage, nervous system disorders, blood clotting abnormalities, and secondary infection in severe patient. The case fatality rate of critically ill patients is up to 10%–50 % in hospitalized patients [11–14]. Due to its high fatality and the possibility of causing pandemic transmission, SFTS was listed among the top 10 priority infectious disease with urgent need for research by the World Health Organization in 2017 [15].

In addition to tick transmission, events about human-to-human transmission of SFTS had been widely reported [16–34]. A strong risk factor linked to SFTSV human-to-human spread is contact with infected bodily fluids. However, there is still a dearth of knowledge regarding related factors that might affect the human-to-human transmission of SFTSV. Research on the viral shedding pattern and specific precaution measures against SFTSV human-to-human transmission are becoming impending demand.

In the present study, SFTSV shedding pattern from the respiratory, digestive and urinary tract to the outside in severely ill patients were evaluated. Precaution measures were applied for healthcare workers (HCWs) exposed to critically ill SFTS patients except the 7 persons involved in human-to-human transmission event at the beginning of the study. The relationship between viral shedding with comorbidities of patients and human-to-human transmission events were analyzed. The result would be important for early prediction of complications and effective control strategies against SFTSV human-to-human transmission.

2. Materials and methods

2.1. Study Design and Participants

A prospective cohort study was performed in three sentinel hospitals for SFTS in Anhui province, including the First Affiliated Hospital of Anhui Medical University, the Chaohu Affiliated Hospital of Anhui Medical University and Lu'an People's Hospital of Anhui Medical University from April 2020 to October 2022. We enrolled patients ($\geq$18 years and $<$80 years of age) who were hospitalized and confirmed as SFTSV infection by positive polymerase-chain reaction (PCR) detection of blood samples. Patients of younger than 18 years old, with chronic respiratory disease, gastrointestinal diseases and chronic kidney disease were excluded, which may affect the diagnosis of complications. The patients were divided into mild and severe groups based on the presence of shock, neural disorders, hemorrhage, coinfection or severe organ impairment with renal damage. All the SFTS patients underwent chest radiography or chest computed tomography (CT) during the disease course. The study protocol was approved by the Human Ethics Committee of Anhui Medical University (20200980). Informed consent was obtained from all patients, in accordance with the Declaration of Helsinki.

2.2. Virological Investigations

SFTSV infection was confirmed in all patients by testing serum specimens with a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. At the extreme stage of disease progression, the blood, throat swab, anal swab, urine and bedside environment swab samples of the patients were collected for SFTSV detection. RNA was extracted from these samples using the high-purity viral RNA kit (Omega, Guangzhou, China) according to the manufacturer's instructions. SFTSV RNA was amplified using specific primers and probes by real-time RT-PCR under conditions previously described using the SFTSV nucleic acid quantitative detection Kit (DaAn Gene Co, Guangzhou, China) [35]. The standard curve was generated using different standard RNA concentrations ranging from 1.0×10^7 to 1.0×10^3 copies/μL obtained by 10-fold serial dilutions.

2.3. Personal protective equipment use of healthcare workers

Different PPEs were applied in HCWs according to exposure risks. The single-use medical masks were used in HCWs contacting with mild SFTS patients. The gloves and surgical mask with face shield were used in HCWs exposed to SFTS patients with hemorrhagic manifestations and positive T-SFTSV. The gloves, surgical mask or medical protective mask and face shield were applied by HCWs participation in cardiopulmonary resuscitation (CPR). The disposable hat, latex gloves, medical protective mask with face shield were applied by HCWs in participation of orotracheal intubation for severely ill patients with positive T-SFTSV. Besides, mask oxygen inhalation was used in severelly ill patients with positive T-SFTSV or bloody secretions when patients need oxygen inhalation. The ward environment was disinfected with 1000 mg/L chlorine and ultraviolet radiation for more than 30 min after the patient was discharged according to the guidelines for the prevention and control of SFTS by the Chinese Center for Disease Control and

Prevention."

2.4. Data collection of SFTS patients

Hospital-based data were collected during the hospitalization by using a medical questionnaire. A medical record review was performed to collect information on epidemiologic, clinical manifestations including fever, cough, expectoration, hemoptysis, nausea, vomite, abdominal pain and diarrhea, signs of hemorrhage, laboratory parameters including routine blood test and biochemical examination, result of chest radiography or CT. Personal protective equipment (PPE) use of HCWs and occurrence of SFTSV human-to-human event among the patients were also recorded.

2.5. Statistical analysis

Data were analyzed using SPSS, version 20.0 (SPSS Inc., USA). Quantitative variables were expressed as means ± standard deviation (SD) or as medians (interquartile range), categorical variables were expressed as the number (percentage). Student's t-test was applied under normality assumptions, otherwise, the equivalent non-parametric test was used. A chi-square test was used to examine the difference in the percentage of categorical variables. Graphpad prism 5 software was used to compare values in groups and calculate the correlation coefficients and significance values of two variables. The correlation analysis of Log10 (SFTSV) level in blood with that from other samples was calculated using the methods of the Pearson correlation coefficient. A two-sided p-value< 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of viral shedding from SFTS patients

One hundred and eighty-nine SFTS patients were included in the study, the median age was 62.5 years, 83 (43.9 %) patients were male and 106 (56.1 %) were female. Fifty-four patients died (case fatality rate, 28.57 %). The median SFTSV load in blood (B-SFTSV) was 8.3×10^5 copies/mL [interquartile range (IQR) 1×10^5 - 5.2×10^6] in blood (B-SFTSV) in 166 severely ill patients, higher than 9.6×10^3 copies/mL [interquartile range (IQR) 3.6×10^3 - 1.6×10^4] in 23 mild patients ($p = 0.001$). Positive SFTSV in throat swabs (T-SFTSV) were detected in 121 (64.02 %) severely ill patients with median load 2.1×10^3 copies/mL (IQR 1.2×10^3 - 8.1×10^3). Positive SFTSV in fecal/anal swabs (F-SFTSV) were detected in 91 (48.15 %) severely ill patients with median load 1.3×10^3 copies/mL (IQR 1.0×10^3 - 3.0×10^3). Positive SFTSV in urine (U-SFTSV) were detected in 65 (34.4 %) severely ill patients with median load 1.5×10^3 copies/mL (IQR 1.0×10^3 - 2.8×10^3). No positive T-SFTSV, F-SFTSV and U-SFTSV were detected in 23 mild SFTS patients.

In 121 patients with positive T-SFTSV, 91 patients with positive F-SFTSV and 65 patients with positive U-SFTSV, the B-SFTSV load was significantly higher than T-SFTSV, F-SFTSV and U-SFTSV load ($P < 0.0001$), respectively. Positive correlations of SFTSV levels in blood with throat swabs ($r = 0.4535$, $P < 0.0001$), anal swabs ($r = 0.3263$, $P = 0.0016$), and urine ($r = 0.4102$, $P = 0.0007$) were found (Fig. 1 A, B, C, respectively). It is noteworthy that positive SFTSV of bedside environment swab was detected in two fatal patients with pneumonia, besides, one had oral hemorrhage, the other one had cough and expectoration. Our research demonstrated SFTSV could shed out not only the blood, but from oropharynx, feces and urine in severely ill patients with high viral load (Fig. 2). The SFTSV positive rate of throat swabs was 84.9 % in pneumonia patients, significantly higher than 43.7 % in non-pneumonia patients ($P < 0.0001$). The SFTSV positive rate of anal swabs was 62.2 % in diarrhea patients, significantly higher than 28.2 % in non-diarrhea patients ($P < 0.0001$). The SFTSV positive rate of urine was 62.2 % in patients with acute kidney injury (AKI), significantly higher than 28.2 % in non-AKI patients ($P < 0.0001$) (Fig. 3). The levels of estimated glomerular filtration rate (eGFR) in patients with SFTSV in urine were significantly lower than that in negative-SFTSV urine group (52.1 ± 28.8 *vs* 91.3 ± 22.2, $p < 0.0001$).

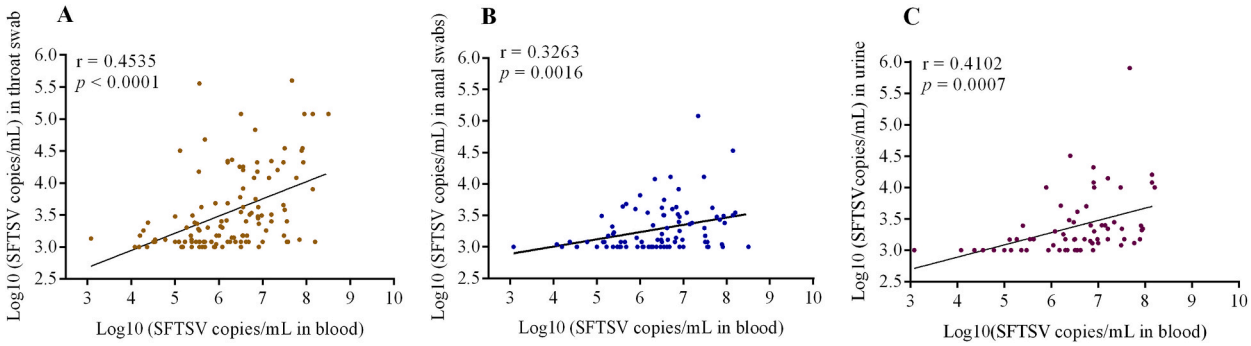

Fig. 1. Correlations of SFTSV load in blood with throat swabs, anal swabs and urine in patients with severe fever with thrombocytopenia syndrome. (A) Correlations of SFTSV levels in blood with throat swabs. **(B)** Correlations of SFTSV levels in blood with anal swabs. **(C)** Correlations of SFTSV levels in blood with urine. The viral levels were in the format of Log10 viral RNA copies/mL. ***$P < 0.0001$. SFTSV: severe fever with thrombocytopenia syndrome virus.

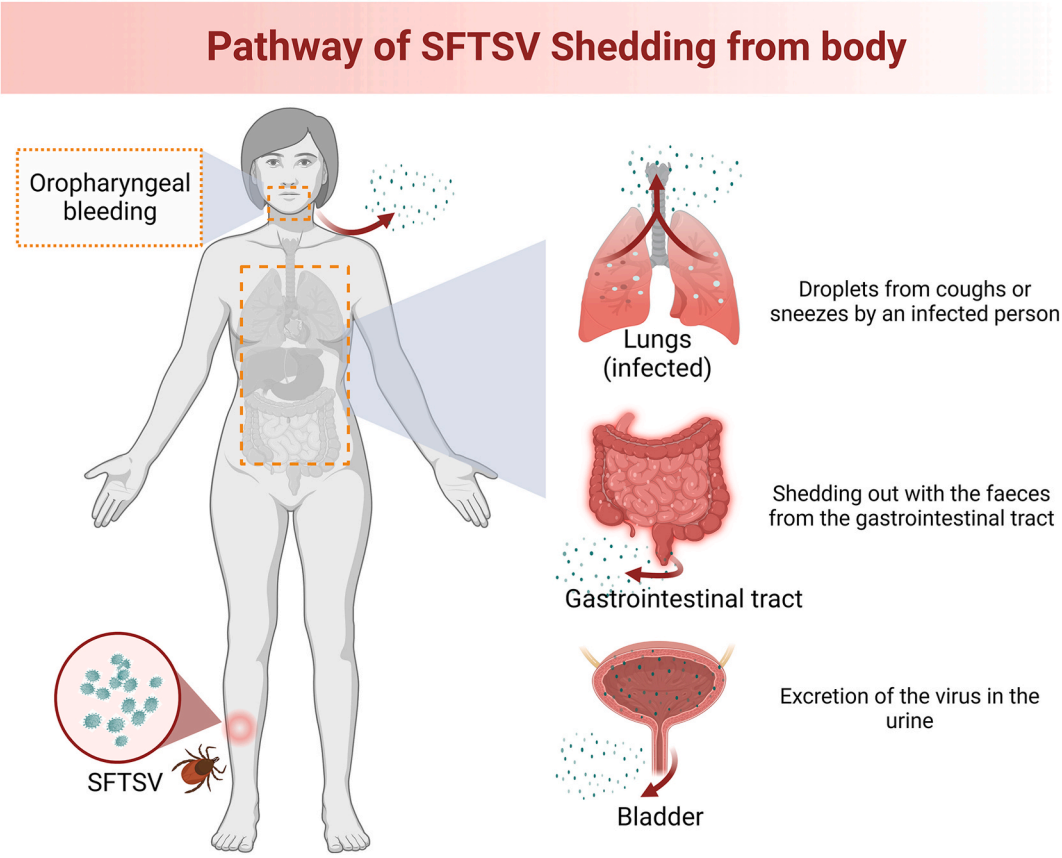

Fig. 2. Pathway of SFTSV shedding from severely ill patients with severe fever with thrombocytopenia syndrome.

Among the 166 severely ill patients, 43 patients had cough, 13 patients had hemoptysis and 26 patients had oropharyngeal bleeding. All the patients with cough and oral or nasal bleeding had positive SFTSV of throat swabs, which is significantly higher than the patients without these presence (100 % *vs* 58.2 %, $p < 0.0001$).

3.2. *Correlation between case fatality rate and SFTSV shedding in patients*

Among 54 patients who developed fatal outcome, the median SFTSV load was 7.2×10^6 copies/mL [interquartile range (IQR) 1.6×10^6 - 3.2×10^7] in blood, which was higher than that in non-fatal patients with 1.4×10^5 copies/mL [interquartile range (IQR) $1.2 \times$

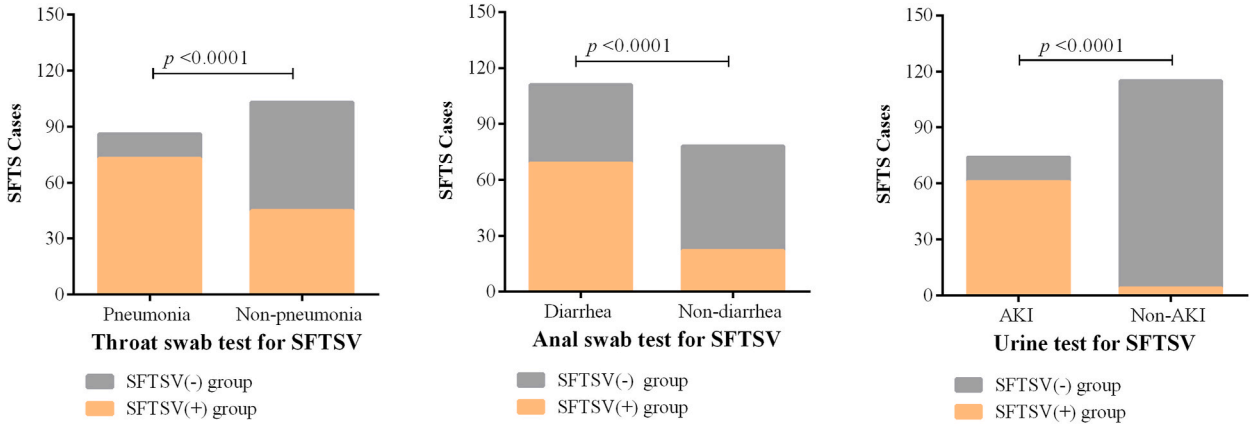

Fig. 3. Correlations between comorbidities and SFTSV shedding in severely ill patients with severe fever with thrombocytopenia syndrome. SFTSV: severe fever with thrombocytopenia syndrome virus.AKI: Acute kidney injury.

10^4- 1.0×10^6] ($P < 0.001$). Positive SFTSV detection was determined in all (54) of throat swabs, 88.89 % (48/54) of anal swabs, 79.63 % (43/54) of the urine samples, all significantly higher than the positive rate obtained from the non-fatal cases (0 %, 31.85 % and 16.29 %, respectively, all $P < 0.0001$) (Fig. 4). Among 61 patients who had simultaneously positive results in all throat swabs, anal swabs and urine samples, 43 fatal patients had positive SFTSV for all sample types, which is significantly higher than the survived patients.

3.3. Precaution measures and incidence of SFTSV human-to-human transmission

In this research, the first patient caused a nosocomial human-to-human transmission event involved in 7 patients. The index case had SFTSV load of 9×10^6 copies/mL in plasma sample, 1.2×10^5 copies/mL in the throat swab, 2.4×10^3 copies/mL in the anal swab, and 2.2×10^3 copies/mL in urine. Among the eight persons exposure to the hemorrhagic patient with cardiopulmonary resuscitation (CPR) and orotracheal intubation bleeding, six persons were infected without tick exposure history. None of the six infected patients worn face shield as personal protective equipment. By contrast, two HCWs who had close contact with the index case including sputum suction and bleeding treatment were all samples test negative for SFTSV, one had worn double surgical masks with face shield, the other one wearing N95 mask in cardiopulmonary resuscitation (CPR) for more than 1 h.

As in Fig. 5, among the severely ill SFTS patients, 25 patients with oropharyngeal bleeding and positive T-SFTSV were received oxygen inhalation through masks when they needed oxygen, HCWs wore gloves and surgical mask with face shield in direct contact to them. Twenty-two patients with positive T-SFTSV received extensive cardiopulmonary resuscitation, HCWs have worn gloves, medical surgical masks with face shield in participation of cardiopulmonary resuscitation of these patients. Eleven patients with positive T-SFTSV were performed orotracheal intubation, disposable hat, latex gloves, medical protective mask with face shield were applied in HCWs in participation of orotracheal intubation. The ward environment was disinfected with 1000 mg/L chlorine and ultraviolet radiation for more than 30 min after the severely ill patient was discharged. No human-to-human transmission incidents occurred again by precaution measures applied.

4. Discussion

Severe fever with thrombocytopenia syndrome is transmitted primarily by tick bites and potentially interpersonal transmission. Contacting with blood or body fluid of SFTS patients were confirmed to cause nosocomial and intrafamily transmission of SFTSV [16–34]. Potential SFTSV aerosol transmission was also proposed in previous research [16,17,20,21,36,37]. Whereas the specific PPEs use against SFTSV human-to-human transmission have rarely been reported. A nosocomial SFTSV infection via human-to-human transmission occurred in our hospital, which showed high viral load, blood or bloody secretions, long exposure time (≥1 h) and face-to-face exposure (≤50 cm) were the risk factors of interpersonal transmission [15], which has promoted to kick start the study on precaution measures against human-to-human transmission of SFTSV. Besides, this is the first analysis about SFTSV RNA shedding level from the respiratory, digestive and urinary tract to external environment by relatively large samples.

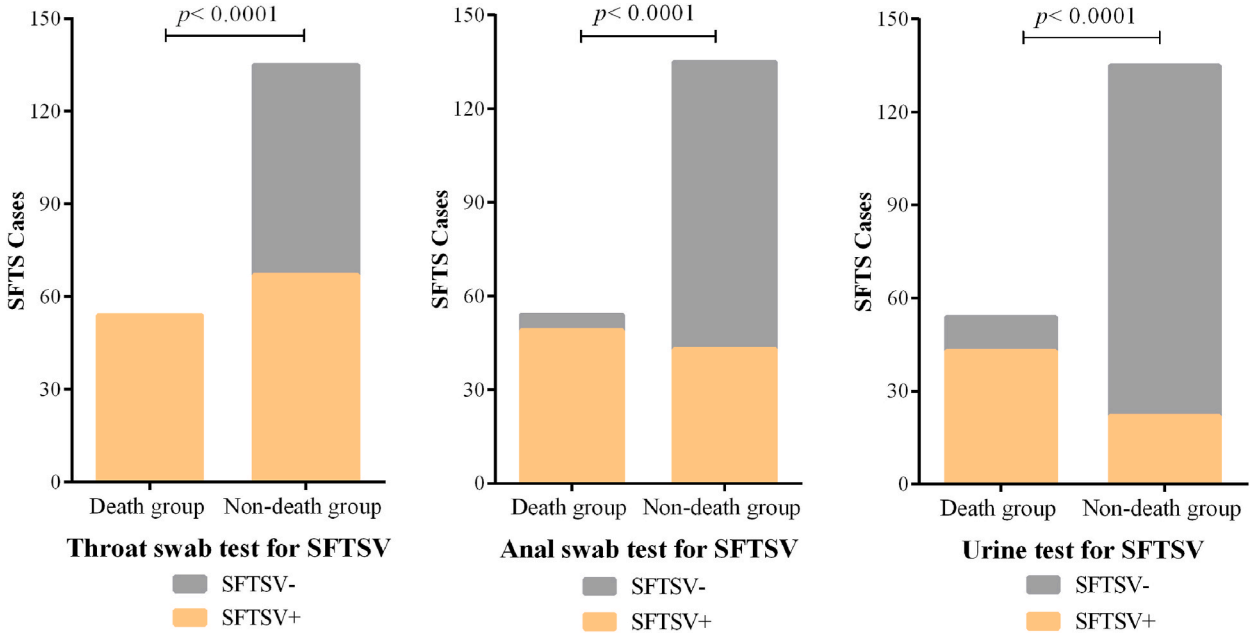

Fig. 4. Difference of SFTSV shedding between death group and non-death group in severe ill SFTS patients.SFTSV: severe fever with thrombocytopenia syndrome virus.

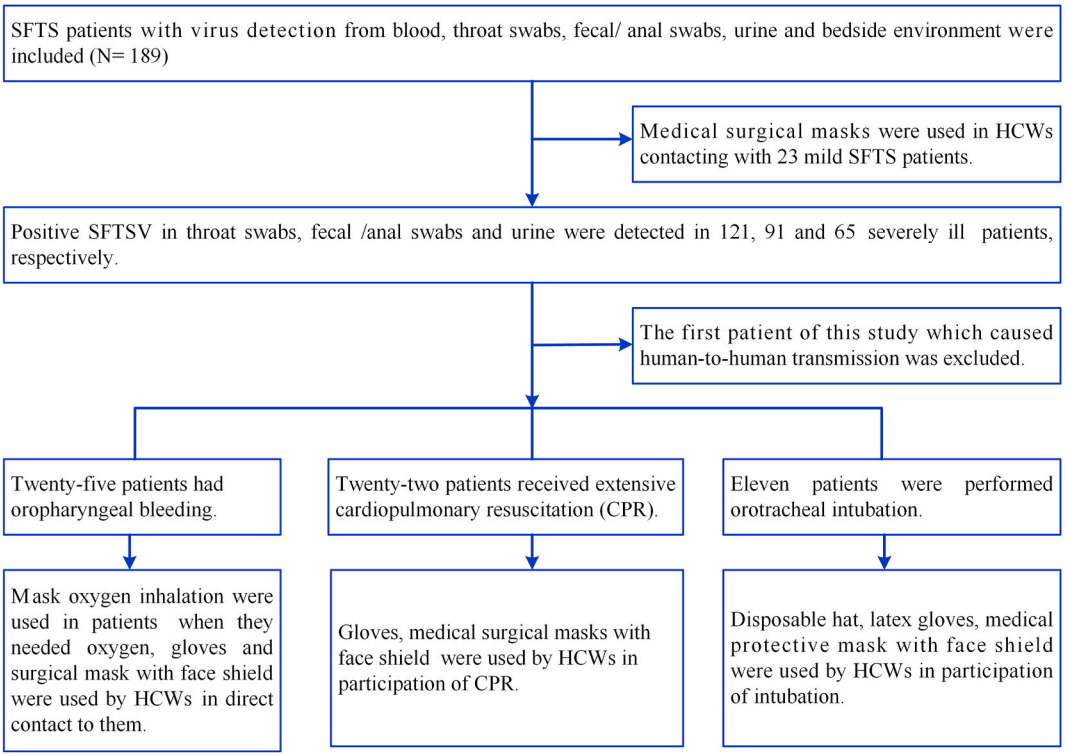

Fig. 5. Diagram flow of personal protective equipment used in healthcare workers in this research.SFTSV: severe fever with thrombocytopenia syndrome virus.

Human-to-human events of SFTSV have attracted urgent public health concern [16–34]. Research about SFTSV excretion from patient's body and PPEs application of HCWs against human-to-human transmission was sparsely investigated. In three case reports, it has been demonstrated that SFTSV could be detected in blood, sputum, gastric juice, urine, semen and cerebrospinal fluid [38–40]. In the present study, our findings indicated SFTSV could shed out from respiratory tract, digestive tract and urinary tract of severely ill patients who have high viral load in blood, especially simultaneous shedding from fatal patients. Oropharyngeal virus shedding level was relatively higher than that from stool and urine. Participation in performing endotracheal intubation or cardiopulmonary resuscitation for SFTS patients with oral bleeding were confirmed to be risk factors of SFTSV droplet or possible aerosol transmission [17,34]. Oropharyngeal virus shedding may indicate a risk for SFTSV interpersonal transmission, especially in conducting treatment of orotracheal intubation and cardiopulmonary resuscitation for these patients. In our research, there were 22 critical ill patients who received cardiopulmonary resuscitation, oropharyngeal virus shedding were found among them. To avoid human-to-human transmission incident, HCWs have worn gloves, medical surgical masks with face shield in participation of CPR among the 22 critical ill patients.

Of note, we found that SFTSV was detected in bedside environment of two fatal patients with high viral load. Previous report also demonstrated that positive SFTSV was detected in 21 % swab samples from stethoscopes, doorknobs, television monitors and sink bed guardrails in five rooms of critically ill patients including 3 fatal cases. Television monitors and sink tables were mentioned to be remote from the patients without daily cleaning and disinfection, it's been speculated that aerosolized virus particles could be generated intracheal suction for critically ill patient [36]. Besides, a recent study has reported that mice could be infected by SFTSV aerosols through the nose, mouth and ocular membranes in a confined space [37]. Oropharyngeal virus shedding may contribute to the generation of aerosolized SFTSV particles through sputum aspiration or tracheal intubation. We suggested disinfection of ward air and bed units should be strengthened.

In our research, disposable hat, latex gloves, medical protective mask with face shield were applied in HCWs in participation of orotracheal intubation for patients with oropharyngeal virus shedding against aerosol human-to-human transmission. No human-to-human infection events occurred after the PPEs application in this research. We recommended aerosol and droplet precautions are needed for healthcare workers and caregiving family members exposed to severely ill SFTS patients. To reduce the spread of virus aerosols in severely ill patients with oral or nasal bleeding, mask oxygen inhalation was suggested.

Our research firstly report that positive SFTSV in respiratory, digestive and urinary tracts were associated with occurrence of complications and increased risk of death. SFTSV infection can elicit damage to multiple organ systems including lung. It was reported that lung imaging abnormalities was present in 29–68.1 % of SFTS patients [41]. Pulmonary infection was associated with fatality or increased disease course in SFTS patients [42]. In the present study, SFTSV positive rate of throat swabs in the patients complicating with pneumonia were significantly higher than patients without pneumonia. In addition, we found that positive throat swab SFTSV

RNA indicate occurrence of complicating pneumonia and developing fatal outcome. Pneumonia with mucosal damage, coughing and hemoptysis may aid in virus excretion of SFTS patients. We concluded that detection of oropharyngeal airway SFTSV might be useful to targeted making protective measures, predict pneumonia and disease severity of SFTS patients.

SFTSV can cause gastrointestinal symptoms as diarrhea, nausea/vomiting, anorexia, and abdominal pain, the occurrence of gastrointestinal symptoms at the disease onset are favorably associated with a severe condition [43]. In this research, SFTSV RNA in fecal/anal swabs of SFTS patients was found to be associated with diarrhea, SFTSV RNA levels in fecal/anal swab was dependent on virus levels in patient's blood. Acute kidney injury was confirmed as a predictive biomarker for disease severity and poor prognosis [44]. In the study, the incidence of AKI was 39.2 %, higher than previous reports [44,45]. We confirmed that U-SFTSV in SFTS patients was significantly associated with incidence of AKI, which is in consistent with previous reports [44]. U-SFTSV evaluation can be useful for early diagnosis of AKI in SFTS patients according to this research. Virus shedding from the urine need to be vigilant , however, further research is needed on virus activity and infectivity.

Our study has a few limitations. Firstly, lower limit of virus detection was 1000 copies/mL, viral load <1000 copies/mL was undetectable, but it may be meaningless to outcome. Secondly, we did not perform virus cultures from throat swab, fecal swab, urine and environmental samples on whether viable virus is detected.

5. Conclusion

Our research revealed that SFTSV could shed out from the upper respiratory tract, digestive tract and urinary tract from severely ill patients, SFTSV contamination was present in the environment of severely ill SFTS patients' wards. Aerosol precautions are recommended for healthcare workers in participation of orotracheal intubation or oro/nasopharyngeal suction for severely ill SFTS patients with hemorrhagic signs. This study would be of great significance against SFTSV nosocomial infection. Our findings also suggested that SFTSV shedding from the upper respiratory tract, feces and urine were predictors for disease severity and poor outcome.

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Ethics statement

The study was approved by the Human Ethics Committee of Anhui Medical University (20200980). Informed consent was obtained from all patients, in accordance with the Declaration of Helsinki.

Availability of data and materials

Data associated with the study has not been deposited into a publicly available repository. Data are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Li-Fen Hu: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ting-Ting Bian:** Visualization, Formal analysis, Data curation. **Qiang Chen:** Visualization, Formal analysis, Data curation. **Meng-Yu Liu:** Visualization, Formal analysis, Data curation. **Jia-Jia Li:** Visualization, Formal analysis, Data curation. **Qin-Xiang Kong:** Visualization, Formal analysis, Data curation. **Jian-Kang Zhang:** Visualization, Formal analysis, Data curation. **Jin Wu:** Visualization, Formal analysis, Data curation. **Jun Cheng:** Visualization, Formal analysis, Data curation. **Rui Yu:** Visualization, Formal analysis, Data curation. **Yan-Qin Qiu:** Visualization, Formal analysis, Data curation. **Yu-Feng Gao:** Visualization, Formal analysis, Data curation. **Guo-Sheng Chen:** Visualization, Formal analysis, Data curation. **Ying Ye:** Project administration, Investigation. **Ting Wu:** Writing – review & editing, Writing – original draft, Conceptualization. **Jia-Bin Li:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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