Comparison of chest radiographic findings between severe fever with thrombocytopenia syndrome and scrub typhus

Single center observational cross-sectional study in South Korea

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Abstract

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by SFTS virus (SFTSV) which involves multiple organ systems, including lungs. There is limited data on lung involvement of SFTS. Therefore, the present study investigated the chest radiographic findings of SFTS, including computed tomography (CT), and compared these with those of scrub typhus, which is the most common tick-borne illness in South Korea and share risk factors and occur in similar settings.

Medical records of patients with confirmed SFTS and scrub typhus in a tertiary hospital in Seoul (South Korea), between January 2014 and June 2018, were reviewed. Initial chest radiography and CT were reviewed by 2 experienced radiologists. A total of 39 patients with SFTS and 101 patients with scrub typhus were analyzed. All patients except 3 patients with scrub typhus in both groups received chest radiography. Cardiomegaly (90%) and patchy consolidation with ground glass opacity (GGO) pattern (31%) were more common in SFTS group than scrub typhus group (20%, P < .001 and 2%, P < .001, respectively). About half of each group received chest CT. Consolidation (29%) and pericardial effusion (24%) were more common in SFTS group than scrub typhus group (6%, P = .02 and 4%, P = .008, respectively). Interstitial thickening in chest radiography (58%) and chest CT (65%) was more frequent in scrub typhus group than SFTS group (18%, P < .001 and 19%, P < .001, respectively).

Cardiomegaly with/without pericardial effusion and patchy consolidation with GGO pattern were more frequent in SFTS group, whereas interstitial thickening was more frequent in scrub typhus group. These findings will assist the early differentiation of SFTS from scrub typhus.

Abbreviations: aPTT = activated partial thromboplastin time, CRP = C-reactive protein, CT = computed tomography, GGO = ground glass opacity, IFA = immunofluorescence assay, IgG = immunoglobulin G, LFT = liver function test, RT-PCR = reverse transcription-polymerase chain reaction, SFTS = severe fever with thrombocytopenia syndrome, SFTSV = severe fever with thrombocytopenia syndrome virus.

Keywords: chest radiographic findings, computed tomography, scrub typhus, severe fever with thrombocytopenia syndrome

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by novel bunyavirus, SFTS virus (SFTSV), which was first identified in China in 2011.[1] SFTS causes a characteristic clinical presentation which includes fever, thrombocytopenia, lymphadenopathy, bleeding tendency, vomiting, diarrhea, and multiple organ impairment.[1-7] Patients present with symptoms ~4 to 15 days following exposure to
SFTS.
2.5. Statistical analysis

SPSS version 21.0 (SPSS, Inc., Chicago, IL) was used to analyze data. Categorical variables were analyzed using the chi-squared test or Fisher exact test and continuous variables were analyzed using Student t test. All tests were 2-tailed and differences were considered significant at $P < .05$.

3. Results

3.1. Study populations

A total of 39 patients with SFTS and 101 patients with scrub typhus were analyzed in the present study. All patients with SFTS were confirmed by RT-PCR analysis. All patients with scrub typhus were confirmed by IFA, which was used to test antibodies. Among patients with scrub typhus, 58 patients (57%) exhibited a rise in IgG titer $>4$-folds in paired samples and 43 patients (43%) had IgG titer $>1:320$ at initial test; 3 patients (3%) with $1:640$, 9 patients (9%) with $1:1280$, and 33 patients (33%) with $1:2560$.

3.2. Baseline characteristics and clinical features

Table 1 shows the baseline characteristics between patients with SFTS and patients with scrub typhus. There were no significant differences in age, geographic distribution, or underlying diseases (Table S1). Differences in age, geographic distribution, and underlying diseases were seen between the two groups. SFTS was more common in men (22 [56%]) and occurred more frequently in the spring-summer season (19 [49%]) than March and August, than scrub typhus (35 [35%], $P = .02$ and 5 [5%], $P < .001$, respectively). Patients with SFTS complained of general weakness (28 [72%]) and myalgia (20 [51%]) more frequently than scrub typhus patients. Bleeding episodes, including epistaxis, bruising, petechiae, and gum bleeding, were observed in 6 (15%) of the patients with SFTS ($P < .001$). Respiratory symptoms, including a cough, sputum, and dyspnea, were similar between the 2 groups (9 [23%] in SFTS, vs 25 [25%] in scrub typhus, $P = .84$).

3.3. Laboratory findings, treatments, and outcomes

Tables 1 and 2 show comparison of laboratory findings, treatments, and outcomes between 2 groups. Leukopenia and thrombocytopenia were more common in the SFTS group than in the scrub typhus group ($P < .001$), and leukocytosis was more common in the scrub typhus group than in the SFTS group ($P < .001$). The proportion of patients with abnormal liver function tests (LFT) and renal function tests was similar between the 2 groups. Increases in cardiac markers, including creatine kinase-muscle/brain and troponin-I, were more common in the SFTS group (10 [32%]) than in the scrub typhus group (5 [13%], $P = .049$). The levels of creatine kinase and lactate dehydrogenase were higher in the SFTS group than in the scrub typhus group ($P = .003$ and $P = .002$, respectively). A normal range of CRP and prolonged activated prothrombin time (aPTT) were observed more frequently in the SFTS group than in the scrub typhus group ($P = .001$ and $P < .001$, respectively).

The provision of care in an intensive care unit and use of a ventilator were more frequent in the SFTS group than in the scrub typhus group ($P < .001$). Mortality rate was higher in the SFTS group (18%) than in the scrub typhus group (1%, $P = .001$).

3.4. Radiologic findings

All of the patients with SFTS and 98 (97%) of the patients with scrub typhus underwent chest radiography. Time from symptoms onset to chest x-ray and time from admission to chest x-ray were comparable between 2 groups ($P = .12$ and $P = .80$, respectively) (Table 3). Antero-posterior portable bedside radiographs were obtained in 22 (56%) patients of SFTS group and in 55 (56%) patients of scrub typhus group and the remained had posteroanterior projection radiographic images. The findings of chest radiography are summarized in Table 3 and shown in Figs. 1 and 2. In both groups, $\sim$60% of patients presented with abnormal initial chest radiographic findings. Cardiomegaly was

### Table 1

| Variables | SFTS (n = 39) | Scrub typhus (n = 101) | $P$ value |
|-----------|--------------|------------------------|---------|
| Age, mean years±SD | 61±10 | 64±13 | .22 |
| Gender, male | 22 (56) | 35 (35) | .02 |
| Seasons, (months) | | | |
| Spring-Summer (March-August) | 19 (49) | 5 (5) | .001 |
| Autumn (September-November) | 19 (49) | 96 (95) | .99 |
| Geographic distribution: Seoul metropolitan area | | | |
| | 18 (46) | 65/94 (69) | .09 |
| Underlying disease | | | |
| Diabetes mellitus | 9 (23) | 14 (14) | .19 |
| Cardiovascular and cerebrovascular disease | 7 (18) | 14 (14) | .54 |
| Chronic lung disease | 5 (13) | 6 (6) | .18 |
| Chronic renal disease | 0 | 2 (2) | .001 |
| Chronic liver disease | 1 (3) | 9 (9) | .28 |
| Autoimmune disease | 3 (8) | 3 (3) | .35 |
| Solid tumor | 2 (5) | 16 (16) | .001 |
| Hematologic malignancy | 0 | 2 (2) | .001 |
| Transplant recipient | 0 | 4 (4) | .58 |

### Table 2

| Clinical features | SFTS | Scrub typhus | $P$ value |
|------------------|------|-------------|---------|
| Fever | 39 (100) | 100 (99) | .99 |
| Febrile period, mean days±SD | 4.4±4.5 | 2.5±1.6 | .01 |
| General weakness | 28 (72) | 35 (35) | <.001 |
| Myalgia | 20 (51) | 37 (37) | .11 |
| Bleeding | 6 (15) | 0 | .001 |
| Respiratory symptoms | 9 (23) | 25 (25) | .14 |
| Abdominal pain | 7 (18) | 21 (21) | .71 |
| Nausea and vomiting | 19 (49) | 25 (25) | .006 |
| Diarrhea | 18 (46) | 8 (8) | <.001 |
| Headache | 14 (36) | 33 (33) | .72 |
| Altered mentality | 16 (41) | 8 (8) | <.001 |
| Skin rash | 6 (20) | 67 (66) | <.001 |
| Eschar | 10 (26) | 75 (74) | <.001 |
| Lymphadenopathy | 10 (26) | 15 (15) | .14 |
| Treatment | | | |
| Doxycycline | 28 (72) | 98 (97) | <.001 |
| Azithromycin | 1 (3) | 8 (8) | .44 |
| Ribavirin | 11 (28) | 1 (1) | <.001 |
| Plasmapheresis | 18 (46) | 1 (1) | <.001 |
| Plasmapheresis | 3 (8) | 0 | .02 |
| Intensive care unit care | 15 (39) | 9 (9) | <.001 |
| Ventilator care | 12 (31) | 4 (4) | <.001 |
| Mortality | 7 (18) | 1 (1) | .001 |

Data are no. (%) of patients, unless otherwise indicated. SD = standard deviation, SFTS = severe fever with thrombocytopenia syndrome.
the most common chest radiographic pattern of the SFTS group and was more common in the SFTS group (90%) than in the scrub typhus group (20%, P < .001).

Chest CT was performed in 21 (54%) patients of SFTS group and 49 (49%) patients of scrub typhus group. Time from symptoms onset to chest CT and time from admission to chest CT were comparable between 2 groups (P = .07 and P = .27, respectively) (Table 4). The CT findings are summarized in Table 4 and shown in Figs. 2 and 3. Lobar or segmental consolidation was the most common CT finding of the SFTS group (6/21 [29%]) and was more frequently observed in the SFTS group than in the scrub typhus group (3/49 [6%], P = .02). Most consolidation involved bilateral lungs (4/6 [67%]), and lower lobes (5/6 [83%]) (Supplement Table 1, http://links.lww.com/MD/D361).

4. Discussion
In the present study, SFTS was found to develop more frequently in men and during the spring-summer seasons than scrub typhus. Clinical features, including general weakness, bleeding, nausea and vomiting, diarrhea, and altered mentality were more common in patients with SFTS than in patients with scrub typhus. The rate of symptoms was similar to the previous studies.[9,10,15] Skin rash and eschar were more common in patient with scrub typhus than in patients with SFTS. These findings were also compatible with the previous study.[16] In laboratory findings, leukopenia, thrombocytopenia, increased cardiac marker, and prolonged aPTT were more frequent in SFTS patients than in scrub typhus patients. Neutropenia and thrombocytopenia were marked findings of SFTS and observed in most of SFTS patients in previous study.[9,10,15] Normal

### Table 2
Laboratory findings of patients with severe fever with thrombocytopenia syndrome (SFTS) and patients with scrub typhus.

| Variables                        | SFTS (n=39) | Scrub typhus (n=101) | P value |
|----------------------------------|-------------|---------------------|---------|
| Laboratory findings              |             |                     |         |
| Leukocytosis (WBC >10,000/mm³)   | 1 (3)       | 32 (32)             | <.001   |
| Leukopenia (WBC <4000/mm³)       | 32 (82)     | 14 (14)             | <.001   |
| Hemoglobin, g/dL ± SD            | 13.8 ± 2.0  | 12.5 ± 1.7          | <.001   |
| Thrombocytopenia (platelets <150 × 10³/mm³) | 38 (87) | 64 (63)             | <.001   |
| Duration of thrombocytopenia, mean days ± SD | 8.2 ± 6.2 | 2.5 ± 2.8          | <.001   |
| Abnormal LFT (AST or ALT >40 UI/L) | 38 (87) | 88 (87)             | .11     |
| Alkaline phosphatase, IU/L ± SD  | 122 ± 129   | 133 ± 93            | .56     |
| Total bilirubin, mg/dL ± SD      | 0.6 ± 0.6   | 0.8 ± 0.8           | .10     |
| Renal dysfunction (eGFR <60 mL/min/1.73 m²) | 11 (21) | 24 (24)             | .59     |
| Increased cardiac marker (CK-MB >5 ng/mL or troponin-I >1.5 ng/mL) | 10/31† (32) | 5/39† (13) | .049 |
| Rhabdomyolysis features          |             |                     |         |
| Creatine kinase, IU/L ± SD       | 2114 ± 3542 | 181 ± 434           | .003    |
| Lactate dehydrogenase, IU/L ± SD | 1298 ± 1507 | 479 ± 184           | .002    |
| Myoglobin, mg/dL ± SD            | 729 ± 1568  | 158 ± 166           | .24     |
| Normal C-reactive protein        | 30 (77)     | 6 (6)               | .001    |
| Prolonged prothrombin time       | 12 (31)     | 36/96‡ (38)         | .46     |
| Prolonged aPTT (aPTT >35 second) | 34 (87)    | 23/93‡ (25)         | <.001   |

Data are no. (%) of patients, unless otherwise indicated.

ALT = aspartate aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, CK-MB = creatine kinase-muscle/brain, eGFR = estimated glomerular filtration rate, LFT = liver function test, SD = standard deviation, SFTS = severe fever with thrombocytopenia syndrome, WBC = white blood cells.

† Results of creatine kinase were available in 35/39 patients with SFTS and 52/101 patients with scrub typhus.

‡ Results of lactate dehydrogenase were available in all of patients with SFTS and 93/101 patients with scrub typhus.

§ No. of patients with a positive test result/number of patients tested.

### Table 3
Chest radiographic findings of patients with severe fever with thrombocytopenia syndrome (SFTS) and patients with scrub typhus.

| Findings                              | SFTS (n=39) | Scrub typhus (n=96) | P value |
|---------------------------------------|-------------|---------------------|---------|
| Time from symptoms onset to chest x-ray, days ± SD | 8.5 ± 8.7 | 6.5 ± 4.7 | .12     |
| Time from admission to chest x-ray, days ± SD | 0.5 ± 1.3 | 0.6 ± 1.4 | .80     |
| Abnormal chest x-ray findings         | 25 (64)     | 59 (60)             | .67     |
| Patch consolidation with GGO pattern  | 12 (31)     | 2 (2)               | <.001   |
| Interstitial pattern                  | 7 (18)      | 57 (58)             | <.001   |
| Lobar consolidation pattern           | 4 (10)      | 0                   | .006    |
| Diffuse ground glass opacity pattern  | 2 (5)       | 0                   | .08     |
| Cardiomegaly                          | 35 (61)     | 20 (20)             | <.001   |

Data are no. (%) of patients, unless otherwise indicated.

GGO = ground glass opacity, SD = standard deviation, SFTS = severe fever with thrombocytopenia syndrome.

4. Discussion
In the present study, SFTS was found to develop more frequently in men and during the spring-summer seasons than scrub typhus. Clinical features, including general weakness, bleeding, nausea and vomiting, diarrhea, and altered mentality were more common in patients with SFTS than in patients with scrub typhus. The rate of symptoms was similar to the previous studies.[9,10,15] Skin rash and eschar were more common in patient with scrub typhus than in patients with SFTS. These findings were also compatible with the previous study.[16] In laboratory findings, leukopenia, thrombocytopenia, increased cardiac marker, and prolonged aPTT were more frequent in SFTS patients than in scrub typhus patients. Neutropenia and thrombocytopenia were marked findings of SFTS and observed in most of SFTS patients in previous study.[9,10,15] Normal
range of CRP was more common in SFTS patients than in scrub typhus patients. Despite the differences in epidemiologic and clinical characteristics between the SFTS and scrub typhus groups, overlapping of seasonality and similarities in the risks of exposure and clinical presentations sometimes make it difficult to distinguish SFTS from scrub typhus. So, rapid available conventional clinical tests may provide further clinical clues for the differentiation between 2 diseases. However, there are limited data on radiologic findings between 2 diseases.

Figure 1. Chest radiography of a patient with severe fever with thrombocytopenia syndrome. A. Bilateral patchy consolidation with ground glass opacity in both upper lung zone and right lower lung zone are present. Cardiomegaly is also present. B. Following resolution of symptoms, the abnormal findings are no longer apparent.

Figure 2. Chest radiography and CT of a patient with scrub typhus. A. Chest radiograph shows diffuse and mild interstitial thickening in the bilateral lungs. A small amount of bilateral pleural effusion is noted. B. Axial chest CT shows smooth interlobular septal line thickening, axial interstitial thickening, and bilateral pleural effusion. CT = computed tomography.
Of note, the majority (90%) of patients with SFTS presented with cardiomegaly on chest radiographs, and this was more common in the SFTS group compared with the scrub typhus group. However, only 25% of patients with SFTS who underwent chest CT presented with pericardial effusion and one-third of patients with SFTS had elevated cardiac enzymes (Table 2). Therefore, these findings are not sufficient to explain the remaining patients with SFTS with cardiomegaly. Further investigations on this area are required.

Patchy consolidation with GGO pattern was the most common chest radiographic pattern of lung involvement in the SFTS group and patchy consolidation was the most common CT finding in SFTS group. These radiologic findings are nonspecific and can be manifestations of several diseases, including bacterial or viral infection. However, these findings may be distinguished from the typical radiologic findings of scrub typhus. Typical chest CT findings of scrub typhus have been reported as interlobular septal thickening and lymphadenopathy.12,23 And the chest radiographic and CT findings of scrub typhus in the present study were consistent with those of previous reports. Therefore, the radiologic findings of SFTS may assist the physician to early differentiate SFTS from scrub typhus.

The proportion of patients with SFTS who had abnormal chest radiography, 64% in chest radiography and 62% in chest CT, was higher than in previous studies (29%–45%).13,16 Patchy shadowing was observed in 21/44 (48%) SFTS patients with abnormal chest radiography in a previous study.13 This finding is consistent with the present study who identified patchy consolidation with GGO in 12/25 (48%) SFTS patients with abnormal chest radiography. However, pleural effusion and pericardial effusion were more frequently observed in the present study (38% and 24%, respectively) than in the previous study (23% and 14%, respectively).13 This may be associated with differences in modalities, disease severity, and the experience of the thoracic radiologists.

The present study has some limitations. First, the study was performed retrospectively. There were missing data in laboratory findings, including cardiac markers. In total, ~50% of patients with SFTS and scrub typhus initially underwent chest CT scans because chest CT was performed to evaluate the other causes of fever in the patient with severe disease or abnormal chest x-ray, and/or no obvious fever focus. If the patients had typical clinical presentation of scrub typhus or SFTS, chest CT was not performed in patients with suspected SFTS and scrub typhus. Therefore, our estimates on abnormal chest CT findings might be overestimated. Although we did not access whether CT findings affected clinical decision in patients with suspected SFTS of scrub typhus, further studies are needed on the clinical impact of chest CT on the differential diagnosis of SFTS and scrub typhus, especially in patients who had atypical presentation of scrub typhus or SFTS. Second, the present study was conducted in a tertiary center in South Korea. So, some kind of selection bias toward more severe disease might occur. Third, although the majority of CT scans were performed in the emergency department, CT scans at heterogeneous clinical stages of patients with SFTS and scrub typhus were analyzed as hospital visits varied following symptom onset. Despite these limitations, to the best of our knowledge, the present study is the first to systemically evaluate the differences in chest radiography and chest CT findings between SFTS and scrub typhus, which are the most common tick-borne illness in South Korea.

5. Conclusions
Cardiomegaly with/without pericardial effusion, patchy consolidation with GGO pattern, and lobar consolidation were more frequent in patients with SFTS, whereas interstitial thickening was more frequent in patients with scrub typhus. These findings will assist in the early differentiation of SFTS from scrub typhus.
Author contributions

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Figure 3. Chest CT of a patient with severe fever with thrombocytopenia syndrome. A. Multifocal patchy consolidations are present in both upper lobes (▼). B. Multifocal patchy consolidations are present in right upper, middle (▼), and both lower lobes. C. Multifocal patchy consolidations are present in both lower lobes (▼). D. A small amount of right pleural effusion (▲) is present, whereas no pericardial effusion is noted. CT = computed tomography.
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