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BRIEF REPORT

Differentiation of Severe Fever With Thrombocytopenia Syndrome From Scrub Typhus

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We developed a scoring system to differentiate severe fever with thrombocytopenia syndrome (SFTS) in 21 patients with SFTS and 91 with scrub typhus; it provided 100% sensitivity and 97% specificity (score > 1). Criteria included altered mental status, leukopenia, prolonged activated partial thromboplastin time, and normal C-reactive protein (1-point each).

Keywords. severe fever with thrombocytopenia syndrome; scrub typhus; differentiation.

Severe fever with thrombocytopenia syndrome (SFTS) and scrub typhus are endemic zoonoses that are becoming significant public health threats in East Asia [1, 2]. SFTS virus, a novel *Phlebovirus* in the family Bunyaviridae, which is transmitted usually by tick such as *Haemophysalis longicornis*, was first isolated from a patient in central China in 2009 and reported in 2011 [1]. SFTS was first reported in South Korea and Japan in 2013 [1]. Since then, thousands of SFTS cases have been annually reported in central and eastern China (1306 cases in 2016) [3] and hundreds have been reported annually in South Korea (165 cases in 2016) [4]. No effective antiviral therapy has been developed for SFTS, with a mortality rate reported as 6% in China [3] and 32% in Korea [5]. Scrub typhus is caused by *Orientia tsutsugamushi,* classified in the family Rickettsiaceae, which is an intracellular bacterium mediated by chigger mite such as *Leptotrombidium* species [2]. Annually, >10 000 scrub typhus cases are reported (16 050 in 2014 in China, 11 105 in 2016 in South Korea) [4, 6]. The mortality rate of treated scrub typhus is reported to be 1.4% [7]. SFTS occurred in rural areas of South Korea, China, and Japan, where there were epidemiologic overlaps in terms of the prevalent areas of scrub typhus [1, 2].

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Patients with SFTS and scrub typhus present similar clinical manifestations, such as fever, headache, and myalgia. In addition, both diseases share common risk factors such as farming, weed exposure, and outdoor activities, with occasional histories of tick or chigger bite [1–3, 6]. Thus, it has remained problematic to differentiate between SFTS and scrub typhus. Furthermore, early diagnosis of the 2 diseases is critical, because SFTS and scrub typhus may become devastating by multiple organ dysfunction involving lung, kidney, and brain, which are potentially fatal [1, 2]. We therefore assessed the clinical characteristics of SFTS and scrub typhus and developed a SFTS differentiation score to discriminate the 2 diseases in emergency rooms or outpatient clinics.

METHODS

Patients

All adult patients aged ≥ 16 years with suspected tick-transmitted diseases were enrolled in Asan Medical Center, a 2700-bed tertiary hospital in Seoul, South Korea, from January 2014 to December 2016. Asan Medical Center serves as a referral center for a nationwide population as well as the Seoul metropolitan (Seoul and Gyeonggi province) population near the hospital; half of the patients admitted to our hospital are from the Seoul metropolitan population, and the remaining half are from the entire county. Patients without confirmation of SFTS or scrub typhus were excluded. The study protocol was approved by the Institutional Review Board of Asan Medical Center (protocol No. 2016-0046).

Diagnostic Tests

SFTS virus was confirmed through detection of the viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) analysis of a plasma sample, using a DiaStar 2X OneStep RT-PCR Pre-Mix kit (SolGent), as described elsewhere [8]. The diagnosis of scrub typhus was established either through a 4-fold rise in immunoglobulin G (IgG) in the following sample or by a single positive IgG result (titer ≥1:320), both as measured with immunofluorescence assay (IFA; SD Bioline Tsutsugamushi Assay; Standard Diagnostics) [9].

Statistical Analysis

Categorical data were compared using the $\chi 2$ or Fisher exact test, and continuous variables were analyzed using the Mann-Whitney *U* test. The SFTS differentiation score was generated using the FIRTH option of logistic-regression analysis for estimating odds ratios. The receiver operating characteristic (ROC) curve was constructed for the scoring model. Data

manipulation and statistical analyses were conducted using SAS software, version 9.2 (SAS Institute).

RESULTS

A total of 149 patients were initially enrolled. Of these patients, 37 without confirmation of either SFTS or scrub typhus were excluded. Finally, findings were analyzed in 112 patients, including 21 with SFTS and 91 with scrub typhus (Supplementary Figure S1). Clinical characteristics and outcomes in these patients are shown in Table 1.

We created a clinical prediction model to differentiate SFTS from scrub typhus using scoring points. Multiple logistic regression analysis adjusting the relevant differences between SFTS and scrub typhus showed that altered mental status (odds ratio, 44.9; $P = .03$), leukopenia (WBC count, <4000/μL; odds ratio, 40.9; $P = .008$), prolonged activated partial thromboplastin time (39.5; $P = .007$), and normal C-reactive protein (75.3; $P = .001$) were significantly associated with SFTS rather than with scrub typhus (Supplementary Table S1). The following variables were scored to develop the SFTS differentiation score: altered mental status, leukopenia, prolonged activated partial thromboplastin , and normal C-reactive protein level (1 point each); the combination of these 4 parameters created scores ranging from 0 to 4. On the ROC curve obtained for the model, the optimal cutoff was >1. A score >1 had 100% sensitivity (95% confidence interval [CI], 84%–100%) and 97% specificity (90%–99%) for SFTS, with an ROC area under the curve of 0.995 (.957–1.000), (Supplementary Table S2 and Supplementary Figure S2).

We performed a subgroup analysis including 21 patients with SFTS and 53 with scrub typhus in whom 4-fold rise of IgG titer was documented (Supplementary Table S3). This analysis revealed that an SFTS differentiation score >1 had 100% sensitivity (95% CI, 84%–99%) and 94% specificity (84%– 99%). In addition, sensitivity analysis including 21 patients with SFTS and 37 patients without confirmation of either SFTS or scrub typhus who were excluded from the final analysis showed that the score of >1 had 100% sensitivity (95% CI, 84%–100%) and 88% specificity (71%–97%) (Supplementary Table S4).

DISCUSSION

Definitive diagnosis of SFTS and scrub typhus depends on laboratory tests. However, the current diagnostic methods have several limitations, and confirmation of the diseases may take up to a few weeks. Diagnosis of SFTS is established by the detection of viral RNA in a patient's blood using RT-PCR [1]. Unfortunately, RT-PCR for SFTS is neither standardized nor commercially available, so this test is not available in most hospitals in South Korea. Until now, most samples from patients with suspected SFTS were sent to the regional government laboratories of South Korea, and the process has significantly delayed the confirmation of SFTS. Furthermore, early-phase or mild presentations of SFTS may have short or no viremic period that reduce the diagnostic accuracy of RT-PCR [5].

As for scrub typhus, the current reference standard for diagnosis is IFA testing [10]. However, a single IFA measurement is sometimes insufficient for a definite diagnosis, and identification of the dynamic change in IFA titers between paired samples is required [9]. Positive IFA results may also indicate past infection with scrub typhus, especially in endemic regions [10]. Recently, blood PCR, especially performed with buffy coat samples and/or eschar, has been proposed for early diagnosis of scrub typhus [11, 12], but widespread use is limited owing to suboptimal sensitivity and technical expertise such as buffy coat collection depending on clinical samples. Therefore, we assumed that clinical differentiation could play an important role in patients with suspected SFTS or scrub typhus during the wait for laboratory confirmation.

Although there is currently no effective therapy for patients with SFTS, several experimental therapies—such as ribavirin [13], plasma exchange therapy [14], intravenous immunoglobulin plus steroid [15], and convalescent plasma therapy [16]—have been tried in critically ill patients with SFTS. Some therapy, such as plasma exchange therapy, may be beneficial in early-stage disease [14]. Thus, our proposed SFTS differentiation score may help physicians make an early decision on which experimental therapy to use for SFTS. Furthermore, the SFTS differentiation score can be useful for adopting preemptive appropriate precautions for SFTS to prevent transmission to healthcare workers [8].

Our study has a few limitations. First, we included only the patients from a tertiary referral hospital with suspected SFTS or scrub typhus. Thus, there could have been a selection bias toward more severe diseases. Second, there was disparity between the numbers of SFTS of scrub typhus cases, and a sex difference between the 2 patient groups (Table 1). The small number of patients with SFTS relative to the number with scrub typhus reflects the current epidemiologic situation in South Korea (incidence rate per 100 000 population, 0.11/ for SFTS vs 21.52 for scrub typhus) [4, 17]. The epidemiology of SFTS regarding sex distribution was not clearly established, because previous studies showed conflicting findings [5, 18, 19]. Male sex predominance in SFTS might partly be explained by the older age distribution of patients in our study, because SFTS was more common in men older than 50 years than in women older than 50 years in South Korea [17]. The female sex predominance in scrub typhus is consistent with the previous results from South Korea [20]. However, other clinical characteristics and laboratory findings were consistent with those reported from previous studies [5, 18, 19].

Third, some may argue that coinfection of SFTS and scrub typhus was not considered in this study, given that a recent Korean study reported that 7 of 17 patients with confirmed SFTS patients had *O. tsutsugamushi* antibody titers of 1:2560 or seroconversion,

Table 1. Clinical Characteristics and Outcomes of Severe Fever With Thrombocytopenia Syndrome and Scrub Typhus[a]

Variable	SFTS (n = 21)[b]	Scrub Typhus (n = 91)[c]	*P* value
Season			<.001
Spring–summer (March–August)	8 (38)	4 (4)	
Autumn (September–November)	13 (62)	87 (96)	
Geographic distribution: Seoul metropolitan area (Seoul and Gyeonggi province)	10 (48)	23/84 (27)[d]	.07
Age, mean (SD), y	60 (10)	65 (13)	.02
Male sex	12 (57)	32 (35)	.06
Underlying disease			
Previously healthy	14 (67)	51 (56)	.37
Diabetes	3 (14)	14 (15)	>.99
Cardiovascular or cerebrovascular disease	4 (19)	14 (15)	.74
Solid tumor	0	14 (15)	.07
Chronic liver disease	0	9 (10)	.20
Chronic kidney disease	0	2 (2)	>.99
Rheumatologic disease	1 (5)	2 (2)	.47
Hematologic malignancy	0	1 (1)	>.99
Transplant recipient	0	4 (4)	>.99
Immunosuppressive condition[e]	0	24 (26)	.006
Symptom duration before hospital visit, mean (SD), d	5.8 (4.0)	9.0 (5.8)	.07
Delay before diagnosis, mean (SD), d	13.4 (6.8)[f]	6.4 (3.1)[g]	<.001
Clinical characteristics			
Fever	21 (100)	99 (100)	>.99
Febrile period, mean (SD), d	5.0 (3.7)	2.6 (1.6)	.003
Tick or chigger bite wound	8 (38)	66 (73)	.003
Typical eschar	1 (5)	59 (65)	<.001
Rash	3 (14)	63 (69)	<.001
Bleeding events	2 (10)	0	.03
Myalgia	10 (48)	33 (36)	.34
Lymphadenopathy	7 (33)	13 (14)	.057
General weakness	14 (67)	31 (34)	.006
Nausea/vomiting	7 (33)	22 (24)	.39
Abdominal pain	2 (10)	22 (24)	.24
Diarrhea	10 (48)	4 (4)	<.001
Cough/sputum/dyspnea	3 (14)	25 (28)	.21
Headache	9 (43)	33 (36)	.57
Altered mental status	9 (43)	8 (9)	<.001
Leukopenia (WBC count <4000/μL)	17 (81)	11 (12)	<.001
Leukocytosis (WBC count >10000/μL)	1 (5)	29 (32)	.01
WBC count, mean (SD), WBCs/μL	2600 (2200)	8800 (5800)	<.001
Neutrophils, mean (SD), %	55 (19)	68 (16)	.005
Lymphocytes, mean (SD), %	37 (17)	24 (14)	<.001
Monocytes, mean (SD), %	6.7 (4.8)	6.8 (3.7)	.56
Thrombocytopenia (platelet count $<150 \times 10^3$/μL)	21 (100)	55 (60)	<.001
Platelet count, mean (SD), $\times 10^3$/μL	62 (22)	152 (74)	<.001
Duration of thrombocytopenia, mean (SD), d	8.6 (4.8)	2.4 (2.8)	<.001
Hemoglobin, mean (SD) g/dL	14.2 (1.8)	12.6 (1.5)	<.001
Prolonged PT	8 (38)	31/86 (36)[h]	.86
INR, mean (SD)	1.10 (0.13)	1.11 (0.21)	.95
Prolonged aPTT (>35 s)	18 (86)	18/86 (21)[h]	<.001
aPTT, mean (SD), s	51 (20)	34 (10)	<.001
Normal CRP level (≤ 1.0 mg/dL)	18 (86)	5 (5)	<.001
CRP, mean (SD), mg/dL	0.63 (0.77)	8.98 (6.54)	<.001
Renal dysfunction	6 (29)	14 (15)	.20
Blood urea nitrogen, mean (SD), mg/dL	17.8 (13.2)	18.8 (13.1)	.43
Creatinine, mean (SD), mg/dL	1.09 (0.77)	1.02 (0.76)	.73
Abnormal LFT (AST or ALT >40 IU/L)	20 (95)	80 (88)	.46
AST, mean (SD), IU/L	558 (1098)	154 (205)	.007
ALT, mean (SD), IU/L	161 (198)	133 (194)	.56
Alkaline phosphatase, mean (SD), IU/L	118 (152)	134 (92)	.01
Total bilirubin, mean (SD), mg/dL	0.6 (0.7)	3.7 (22.7)	.01
Rhabdomyolysis feature			
Creatine kinase, mean (SD), IU/L	3233 (4574)	201 (454)	<.001
Lactate dehydrogenase, mean (SD), IU/L	1426 (1652)	464 (181)	.005
Myoglobin, mean (SD), ng/dL	1130 (2113)	175 (193)	.008
Central nerve system involvement	11 (52)	19 (21)	.003
Lung involvement	6 (29)	30 (33)	.70
Shock	7 (33)	8 (9)	.007
Concomitant *Aspergillus* infection	3 (14)	1 (1)	.02
Clinical course			
Intensive care unit admission	9 (43)	8 (9)	.001
Mechanical ventilation	7 (33)	5 (6)	.001
In-hospital death	3 (14)	1 (1)	.02
Hospital stay, mean (SD), d	13.4 (15.3)	6.6 (8.7)	.001
Treatment			
Doxycycline	15 (71)	88 (97)	.001
Ribavirin	9 (43)	1 (1)	<.001
Supportive care	7 (33)	0	<.001
Plasmapheresis	11 (52)	1 (1)	<.001
Plasmatherapy	2 (10)	0	.03
Azithromycin	0	11 (12)	.12

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; INR, international normalized ratio; LFT, liver function test; PT, prothrombin time; SD, standard deviation; SFTS, severe fever with thrombocytopenia syndrome; WBC, white blood cell.

[a]All clinical characteristics and laboratory data were evaluated when the patients initially visited the emergency room or outpatient clinic. Data represent No, (%) of patients unless otherwise specified.

[b]All patients with severe fever with thrombocytopenia syndrome had diagnoses confirmed by reverse-transcriptase polymerase chain reaction analysis of plasma samples.

[c]Of the 91 patients with scrub typhus, 53 (58%) had a 4-fold rising immunoglobulin G (IgG) titer shown by immunofluorescence assay (IFA) in paired samples. The remaining 38 patients had a single high IgG titer measured with IFA: 28 patients (31%) had a titer ≥1:1280; 8 (9%), 1:640; and 2 patients (2%), 1:320.

[d]Regions where the 8 patients with scrub typhus had been infected could not be identified.

[e]Immunosuppressive condition is defined as the presence of underlying diseases, such as human immunodeficiency virus infection, malignancy, liver cirrhosis, or chronic renal failure, and/or receipt of immunosuppressive treatment.

[f]Diagnostic confirmation with reverse-transcriptase polymerase chain reaction was performed by the Korea Center for Disease Control and Prevention.

[g]The delay in diagnosis was 7.7 (3.4) days in patients with scrub typhus with a 4-fold rise in IgG titers with paired IFA, and 4.8 (1.4) days in those with a single positive IgG titer ≥1:320.

[h]The PT and aPTT were not available in 5 patients with scrub typhus.

suggesting coinfection of SFTS and scrub typhus [21]. In our study, of the 91 patients with scrub typhus and the 21 with SFTS, 38 (42%) with scrub typhus and 21 (100%) with SFTS underwent

both RT-PCR for SFTS and IFA for scrub typhus owing to the diagnostic uncertainty. All 38 patients with scrub typhus had negative RT-PCR results for SFTS. However, of the 21 with SFTS, 1 patient had a high IFA titer for scrub typhus (1:2560). Further studies are needed on the coinfection of SFTS and scrub typhus. Finally, the scoring system was not validated in another cohort; therefore, further study is needed to evaluate the application of our scoring system in Korea as well as in China and Japan, where SFTS and scrub typhus are endemic. In conclusion, patients with SFTS presented with several distinct and characteristic clinical features, and our SFTS differentiation score using those features could help differentiate early between SFTS and scrub typhus.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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