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Clinical Score System to Differentiate Severe Fever with Thrombocytopenia Syndrome Patients from Patients with Scrub Typhus or Hemorrhagic Fever with Renal Syndrome in Korea

Dae-Hyuk Heo [1*†], Yu Min Kang [2*†], Kyoung-Ho Song [1,3], Jun-Won Seo [1†], Jeong-Han Kim [1†], June Young Chun [1†], Kang Il Jun [4], Chang Kyung Kang [3,4], Song Mi Moon [1†], Pyoeng Gyun Choe [3,4], Wan Beom Park [3,4], Ji Hwan Bang [3,5], Eu Suk Kim [1,3], Hong Bin Kim [1,3], Sang-Won Park [3,5], Won Sup Oh [2], Nam Joong Kim [3,4] and Myoung-don Oh [3,4]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea
[3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[5]Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

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Address for Correspondence:
Kyoung-Ho Song, MD, PhD
Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro, 173-beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea.
E-mail: khsongmd@snu.ac.kr

*Dae-Hyuk Heo and Yu Min Kang contributed equally to this work.

†Present address: Dae-Hyuk Heo, Department of Internal Medicine, Yuseong Sun Hospital, Daejeon, Korea; Yu Min Kang, Department of Medical Education, Seoul National University College of Medicine, Seoul, Korea; Jun-Won Seo, Department of Internal Medicine, Chosun University College of Medicine, Gwangju, Korea; Jeong-Han Kim, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Korea; June Young Chun, Department of Internal Medicine, National Cancer Center, Goyang, Korea; Song Mi Moon, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea.

ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease with high mortality in East Asia. This study aimed to develop, for primary care providers, a prediction score using initial symptoms and basic laboratory blood tests to differentiate between SFTS and other endemic zoonoses in Korea.
Methods: Patients aged ≥ 18 years diagnosed with endemic zoonoses during a 3-year period (between January 2015 and December 2017) were retrospectively enrolled from 4 tertiary university hospitals. A prediction score was built based on multivariate logistic regression analyses.
Results: Of 84 patients, 35 with SFTS and 49 with other endemic zoonoses were enrolled. In multivariate logistic regression analysis, independent predictors of SFTS included neurologic symptoms (odds ratio [OR], 12.915; 95% confidence interval [CI], 2.173–76.747), diarrhea (OR, 10.306; 95% CI, 1.588–66.895), leukopenia (< 4,000/mm^3) (OR, 19.400; 95% CI, 3.290–114.408), and normal C-reactive protein (< 0.5 mg/dL) (OR, 24.739; 95% CI, 1.812–337.742). We set up a prediction score by assigning one point to each of these four predictors. A score of ≥ 2 had 82.9% sensitivity (95% CI, 71.7%–87.5%) and 95.9% specificity (95% CI, 88.0%–99.2%). The area under the curve of the clinical prediction score was 0.950 (95% CI, 0.903–0.997).
Conclusion: This study finding suggests a simple and useful scoring system to predict SFTS in patients with endemic zoonoses. We expect this strategic approach to facilitate early differentiation of SFTS from other endemic zoonoses, especially by primary care providers, and to improve the clinical outcomes.

Keywords: Severe Fever with Thrombocytopenia Syndrome; Prediction; Differential Diagnosis; Scrub Typhus; Hemorrhagic Fever with Renal Syndrome

ORCID iDs
Dae-Hyuk Heo
https://orcid.org/0000-0002-7306-0149
Yu Min Kang
https://orcid.org/0000-0002-4368-9878
Kyoung-Ho Song
https://orcid.org/0000-0002-4517-3840
Jun-Won Seo
https://orcid.org/0000-0002-2806-1863
Jeong-Han Kim
https://orcid.org/0000-0001-5117-4893
June Young Chun
https://orcid.org/0000-0001-9345-6645
Kang Il Jun
https://orcid.org/0000-0002-6019-1238
Chang Kyung Kang
https://orcid.org/0000-0003-1952-072X
Song Mi Moon
https://orcid.org/0000-0003-1241-4895
Pyoeng Gyun Choe
https://orcid.org/0000-0001-6794-7918
Wan Beom Park
https://orcid.org/0000-0003-0022-9625
Ji Hwan Bang
https://orcid.org/0000-0002-7628-1182
Eu Suk Kim
https://orcid.org/0000-0001-7132-0157
Hong Bin Kim
https://orcid.org/0000-0001-6262-372X
Sang-Won Park
https://orcid.org/0000-0002-0550-1897
Won Sup Oh
https://orcid.org/0000-0002-4992-4787
Nam Joong Kim
https://orcid.org/0000-0001-6793-9467
Myoung-don Oh
https://orcid.org/0000-0002-2344-7695

Presentation
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Disclosure
The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by the novel bunyavirus, called SFTS virus, which was first reported in China in 2011[1] and Korea and Japan in 2013.[2,3] The virus is transmitted by ticks such as *Haemaphysalis longicornis*.[1] The clinical manifestations of SFTS are nonspecific and include fever, myalgia, vomiting, and diarrhea. In critically ill patients, multi-organ failure may occur.[4] There is no effective antiviral therapy, and the mortality ranges from 6.3% to 30%.[5,6] Because SFTS is a disease with a rapidly progressive deterioration and high mortality rate, early diagnosis is important for survival of patients and preventing transmission of infection.[6,7]

Although the number of SFTS cases has increased steadily, with 259 patients with SFTS in 2018, other endemic zoonoses, such as scrub typhus (6,682 patients), hemorrhagic fever with renal syndrome (HFRS) (433), and leptospirosis (118) were more prevalent in Korea.[8] Moreover, early clinical manifestations of SFTS are similar to those of other endemic zoonoses; therefore, SFTS needs to be differentiated from these diseases. Although the quantitative real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay is a reliable method for early diagnosis of SFTS,[9] this test could not be performed by most primary care providers at local clinics.

Therefore, we aimed to derive a clinical prediction scoring system with initial symptoms and basic laboratory blood tests that could be useful for primary care providers to differentiate SFTS from other endemic zoonoses. We also evaluated the predictability of the score, reassessed 2 days after admission in patients with low probability of SFTS.

METHODS

Patients and data collection

Patients aged 18 years or older diagnosed with endemic zoonoses during the 3-year period from January 2015 to December 2017 were enrolled from 4 university hospitals in Korea: Seoul National University Bundang Hospital (1,300 beds), Boramae Medical Center (800 beds), Seoul National University Hospital (1,700 beds), and Kangwon National University Hospital (600 beds). Endemic zoonoses included SFTS, scrub typhus, HFRS, leptospirosis, Q fever, and human granulocytic anaplasmosis (HGA). All patients with a diagnosis code and/or confirmatory test results of endemic zoonoses were screened.

SFTS was confirmed by detecting the M segment gene of the viral ribonucleic acid (RNA) with RT-PCR as described in a previous study.[10] Scrub typhus was diagnosed by a single titer ≥ 1:160[11] or a ≥ 4-fold rise in indirect immunofluorescent assay (IFA) titer in paired serum samples. HFRS was diagnosed by a single titer ≥ 1:80, ≥ 4-fold rise in IFA titer in paired serum samples, or positive RT-PCR test. Considering the incidence and importance of these endemic zoonoses in Korea, we included only the patients with all three of the above results in this study. Leptospirosis was diagnosed by ≥ 4-fold rise in IFA titer in paired serum samples or an antibody titer ≥ 1:800 in one serum sample by the microscopic agglutination test. Q fever was diagnosed by ≥ 4-fold rise an antiphase II antigen immunoglobulin G titer in paired serum samples. HGA was diagnosed by ≥ 4-fold rise in IFA titer in paired serum samples or positive PCR test. We excluded patients with bacteremia or co-infections between endemic zoonoses.

Author Contributions

Conceptualization: Heo DH, Kang YM, Song KH, Kim ES, Kim HB. Data curation: Heo DH, Kang YM, Song KH, Seo JW, Kim JH, Chun JY, Jun KI, Kang CK, Moon SM, Choe PG, Park WB, Bang JH. Formal analysis: Heo DH, Kang YM, Choe PG, Park WB, Song KH. Methodology: Kim ES, Kim HB, Park SW, Oh WS, Kim NJ, Oh MD. Writing - original draft: Heo DH, Kang YM, Song KH. Writing - review & editing: Heo DH, Kang YM, Song KH, Moon SM, Kim ES, Kim HB, Kim NJ, Oh MD.

We retrospectively reviewed the demographic and clinical data of the patients, including age, gender, occupation, comorbidities, presence of symptoms, and laboratory findings, to analyze the differentiating factors between SFTS and other endemic zoonoses.

Neurologic symptoms included altered mentality, for which Glasgow coma scale score is < 15, and tremor, motor weakness, and dysarthria, which were based on the information in the physician or nurse's medical records. Diarrhea was defined as three or more unformed stools per day, and we also considered that diarrhea was present when the attending physician described diarrhea symptoms in the patient's medical record. Leukopenia was defined as white blood cell count < 4,000/mm^3. Thrombocytopenia was defined as blood platelet count < 150 × 10^3/mm^3. Normal C-reactive protein (CRP) was defined as < 0.5 mg/dL.

Statistical analysis

Categorical variables were compared using χ^2 or Fisher's exact tests, and continuous variables were compared using *t*-test or Mann-Whitney U test. Multivariate logistic regression analysis was performed using the significant differentiating factors ($P < 0.05$) between SFTS and other endemic zoonoses in univariate analysis and adjusted for the duration from the onset of illness to the initial presentation. We excluded some variables that could be influenced by recall bias or had insufficient description (e.g., insect bite wound) from the multivariate analysis. For possible overlapping variables (e.g., anemia and bleeding), we constructed separate models. Variables without all patients' data were excluded from multivariate regression model. The prediction score for SFTS was built based on the final multivariate regression model. The receiver operating characteristic (ROC) curve was constructed for scoring model. Statistical analyses were performed using SPSS for Windows (version 18 software package; SPSS, Inc., Chicago, IL, USA).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (B-1801/445-112), which waived the need to obtain informed consent from the patients. All the other institutions participating in this study also obtained approvals from their IRBs. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

RESULTS

A total of 202 patients were diagnosed with endemic zoonoses clinically and/or by laboratory tests during the 3-year period including 49 patients with SFTS, 132 with scrub typhus, 18 with HFRS, 2 with Q fever, and 1 with leptospirosis. Of these, 118 patients (without the test results for the following three, SFTS, scrub typhus, and HFRS, or with other bacterial infection) were excluded. Finally, 84 patients including 35 with SFTS and 49 with other endemic zoonoses (40 scrub typhus and 9 HFRS) were enrolled in this study (**Supplementary Fig. 1**). None of the patients clinically diagnosed with leptospirosis, Q fever, or HGA met the enrollment criteria. Patients' demographic and clinical characteristics are described in **Table 1**. At the initial presentation, diarrhea and neurologic symptoms were more common in SFTS patients than in other endemic zoonoses patients. In the laboratory findings, the elevation of aspartate aminotransferase (AST), creatinine kinase, and ferritin were also more common in SFTS patients than in others. White blood cell (WBC), CRP, and procalcitonin were rarely elevated in SFTS. In addition, on comparing the three diseases, younger men were more common in the HFRS group, and no rash was observed. Diarrhea, neurologic symptoms, and normal CRP were more common in the SFTS group (**Supplementary Table 1**).

Table 1. Comparison of patients' baseline clinical characteristics and laboratory results between SFTS and other endemic zoonoses

Variables	SFTS (n = 35)	Other endemic zoonoses[a] (n = 49)	*P* value
Age, yr	64.5 ± 11.0	62.5 ± 19.7	0.640
Gender, men	23 (65.7)	25 (51.0)	0.180
Occupation			
Farmers	14 (40.0)	20 (40.8)	0.940
Underlying disease			
Diabetes	7 (20.0)	6 (12.2)	0.333
Cerebrovascular disease	1 (2.9)	2 (4.1)	1.000
Chronic kidney disease	0 (0)	1 (2.0)	1.000
Chronic lung disease	0 (0)	2 (4.1)	0.508
Chronic liver disease	0 (0)	1 (2.0)	1.000
Solid tumor	0 (0)	3 (6.1)	0.262
Onset to admission, day	5.7 ± 2.5	5.7 ± 3.2	0.996
Clinical characteristics			
Fever	30 (85.7)	41 (85.4)	0.970
Rash	7 (20.0)	15 (30.6)	0.275
Insect bite wound	11 (31.4)	26 (53.1)	0.049
Lymphadenopathy	5 (14.3)	1 (2.0)	0.078
Myalgia	21 (60.0)	33 (67.3)	0.488
Nausea/vomiting	14 (40.0)	13 (26.5)	0.193
Diarrhea	19 (54.3)	6 (12.2)	< 0.001
Abdominal pain	13 (37.1)	13 (26.5)	0.300
Bleeding	9 (25.7)	5 (10.2)	0.060
Cough/sputum/dyspnea	10 (28.6)	20 (40.8)	0.248
Headache	13 (37.1)	12 (24.5)	0.211
Neurologic symptoms	21 (60.0)	8 (16.3)	< 0.001
Leukopenia, WBC < 4,000/mm^3	28 (80.0)	5 (10.2)	< 0.001
Leukocytosis, WBC > 10,000/mm^3	1 (2.9)	17 (34.7)	< 0.001
WBC, /mm^3	3,095 ± 2,101	10,056 ± 7,867	< 0.001
Neutrophil, %	54 ± 19	71 ± 16	< 0.001
Lymphocyte, %	32 ± 15	18 ± 11	< 0.001
Monocyte, %	8.5 ± 8.5	7.4 ± 6.7	0.676
Anemia, hemoglobin < 11 g/dL	0 (0)	6 (12.2)	0.038
Hemoglobin, g/dL	14.2 ± 1.5	13.3 ± 2.7	0.007
Thrombocytopenia, platelet < 150 × 10^3/mm^3	33 (94.3)	40 (81.6)	0.111
Platelet, × 10^3/mm^3	78 ± 40	97 ± 64	0.276
PT, INR	1.01 ± 0.12	1.10 ± 0.18	0.004
aPTT, sec	57 ± 21	44 ± 18	< 0.001
Fibrinogen, mg/dL[b]	261 ± 52	345 ± 126	0.004
Abnormal LFT, AST or ALT > 40 IU/L	31 (88.6)	47 (95.9)	0.229
AST, IU/L	530 ± 899	147 ± 175	0.014
ALT, IU/L	161 ± 167	94 ± 102	0.142
ALP, IU/L	119 ± 106	128 ± 71	0.013
Total bilirubin, mg/dL	0.5 ± 0.2	1.0 ± 0.8	< 0.001
BUN, mg/dL	22.3 ± 18.3	24.5 ± 18.4	0.295
Creatinine, mg/dL	1.0 ± 0.5	1.2 ± 1.2	0.967
ESR, mm/hr[b]	10 ± 11	28 ± 25	0.267
Normal CRP, < 0.5 mg/dL	17 (48.6)	2 (4.1)	< 0.001
CRP, mg/dL	1.40 ± 1.77	11.13 ± 7.75	< 0.001
LDH, IU/L[b]	1,297 ± 1,229	833 ± 426	0.205
Creatine kinase, IU/L[b]	1,249 ± 1,502	187 ± 354	< 0.001
Ferritin, ng/mL[b]	14,942 ± 26,706	324 ± 37	0.026
Procalcitonin, ng/mL[b]	0.16 ± 0.05	2.97 ± 5.26	0.001

Data are presented as mean ± standard deviation or number (%).
SFTS = severe fever with thrombocytopenia syndrome, WBC = white blood cell, PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time, LFT = liver function test, AST = aspartate aminotransferase, ALT = alanine aminotransferase, IU =international unit, ALP = alkaline phosphatase, BUN =blood urea nitrogen, ESR =erythrocyte sedimentation rate, CRP = C-reactive protein, LDH = lactate dehydrogenase.
[a]Number of patients with other endemic zoonoses: scrub typhus 40, hemorrhagic fever with renal syndrome 9; [b]Number of patients with the biomarkers results: Fibrinogen (SFTS 19, other endemic zoonoses 20), ESR (SFTS 2, other endemic zoonoses 4), LDH (SFTS 28, other endemic zoonoses 32), Creatinine kinase (SFTS 34, other endemic zoonoses 42), Ferritin (SFTS 11, other endemic zoonoses 2), and Procalcitonin (SFTS 4, other endemic zoonoses 11).

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Table 2. Results of univariate and multivariate logistic regression analyses of the clinical and laboratory factors associated with SFTS

Variables	OR	95% CI	*P* value
Univariate			
Age	1.007	0.981–1.035	0.590
Gender, men	0.543	0.222–1.330	0.182
Farmers	1.034	0.427–2.505	0.940
Diabetes	1.792	0.545–5.888	0.337
Cerebrovascular disease	0.691	0.060–7.935	0.767
Onset of illness	0.998	0.859–1.159	0.979
Fever	1.024	0.296–3.542	0.970
Rash	0.567	0.203–1.583	0.278
Insect bite wound	0.405	0.164–1.005	0.051
Lymphadenopathy	8.000	0.891–71.837	0.063
Myalgia	0.727	0.295–1.793	0.489
Nausea/vomiting	1.846	0.731–4.666	0.195
Diarrhea	8.510	2.883–25.124	< 0.001
Abdominal pain	1.636	0.643–4.164	0.301
Bleeding	3.046	0.921–10.072	0.068
Cough/sputum/dyspnea	0.580	0.229–1.468	0.250
Headache	1.822	0.708–4.690	0.214
Neurologic symptoms	7.687	2.785–21.223	< 0.001
Leukopenia	35.200	10.170–121.832	< 0.001
Leukocytosis	0.055	0.007–0.440	0.006
WBC	0.999	0.999–1.000	< 0.001
Neutrophil	0.947	0.920–0.976	< 0.001
Lymphocyte	1.079	1.037–1.123	< 0.001
Monocyte	1.019	0.962–1.079	0.529
Hemoglobin	1.195	0.974–1.465	0.088
Thrombocytopenia	3.712	0.750–18.388	0.108
Platelet	0.994	0.985–1.002	0.132
PT	0.006	0–0.382	0.015
aPTT	1.038	1.009–1.069	0.011
Fibrinogen	0.991	0.983–0.999	0.020
Abnormal LFT	0.330	0.057–1.911	0.216
AST	1.003	1.001–1.005	0.013
ALT	1.004	1.000–1.008	0.041
ALP	0.999	0.994–1.004	0.667
Total bilirubin	0.038	0.006–0.234	< 0.001
BUN	0.993	0.969–1.018	0.588
Creatinine	0.798	0.479–1.331	0.387
ESR	0.923	0.775–1.099	0.367
Normal CRP	22.194	4.652–105.899	< 0.001
CRP	0.572	0.433–0.756	< 0.001
LDH	1.001	1.000–1.002	0.077
Creatine kinase	1.002	1.001–1.003	0.003
Ferritin	1.177	0.010–141.933	0.947
Multivariate			
Neurologic symptoms	12.915	2.173–76.747	0.005
Diarrhea	10.306	1.588–66.895	0.015
Bleeding	1.848	0.205–16.636	0.584
Leukopenia	19.400	3.290–114.408	0.001
Normal CRP	24.739	1.812–337.742	0.016
Onset of illness	0.855	0.631–1.160	0.315

SFTS = severe fever with thrombocytopenia syndrome, OR = odds ratio, CI = confidence interval, WBC = white blood cell, PT = prothrombin time, aPTT = activated partial thromboplastin time, LFT = liver function test, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, BUN = blood urea nitrogen, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, LDH = lactate dehydrogenase.

In the multivariate logistic regression analysis, neurologic symptoms, diarrhea, leukopenia, and normal CRP were significantly associated with SFTS rather than with other endemic zoonoses (**Table 2**).

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Table 3. Diagnostic performance of the SFTS prediction score system[a]

Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
1	0.971 (0.857–0.999)	0.612 (0.531–0.632)	0.642 (0.566–0.659)	0.968 (0.839–0.998)	2.505 (1.828–2.710)	0.047 (0.002–0.268)
2	0.829 (0.717–0.875)	0.959 (0.880–0.992)	0.935 (0.810–0.988)	0.887 (0.813–0.918)	20.300 (5.966–116.491)	0.179 (0.126–0.321)
3	0.429 (0.330–0.429)	1.000 (0.930–1.000)	1.000 (0.770–1.000)	0.710 (0.660–0.710)	NA	0.571 (0.571–0.721)
4	0.200 (0.116–0.200)	1.000 (0.940–1.000)	1.000 (0.579–1.000)	0.636 (0.598–0.636)	NA	0.800 (0.800–0.941)

SFTS = severe fever with thrombocytopenia syndrome, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR− = negative likelihood ratio, NA = not available.
[a]Prediction score system = (1 × neurologic symptoms) + (1 × diarrhea) + (1 ×leukopenia) + (1 × normal CRP).

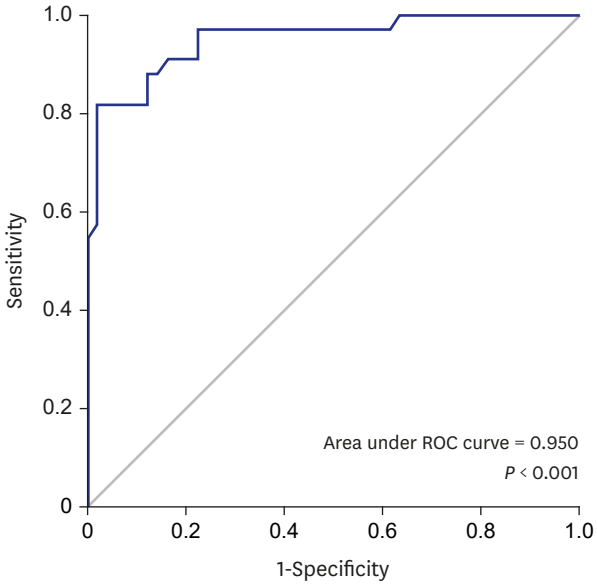

Fig. 1. ROC curve of the clinical prediction score for SFTS in patients with endemic zoonoses.
ROC = receiver operating characteristic, SFTS = severe fever with thrombocytopenia syndrome.

A prediction score for SFTS in comparison with other endemic zoonoses was generated using the combination of those 4 parameters (using 1 point each for neurologic symptoms, diarrhea, leukopenia, and normal CRP) and the total sum ranged from 0 to 4. On the ROC curve obtained for the model, the optimal cut-off was ≥ 2 points. A score of ≥ 2 had 82.9% sensitivity (95% confidence interval [CI], 71.7%–87.5%) and 95.9% specificity (95% CI, 88.0%–99.2%) for SFTS with ROC area under the curve of 0.950 (95% CI, 0.903–0.997) (**Table 3** and **Fig. 1**).

When we applied this prediction score according to the cut-off ≥ 2, 29 patients had SFTS and 2 patients had other endemic zoonoses (**Supplementary Fig. 1**). Among 53 patients with a prediction score of 0 or 1, 27 patients had clinical data on the 4 parameters 2 days after admission. Of the 22 patients with other endemic zoonoses and a score of 0 or 1, only 4 patients had diarrhea, and none had neurologic symptoms, leukopenia, or normal CRP. A score ≥ 2 had 100.0% positive predictive value (95% CI, 55.0%–100.0%) (**Supplementary Table 2**).

DISCUSSION

The present study identified the predictors of SFTS and suggested a clinical scoring system to distinguish SFTS patients from patients with other endemic zoonoses. This system

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consists of easily applicable clinical parameters, including neurologic symptoms, diarrhea, leukopenia, and normal CRP. This scoring system would be useful for early differentiation of SFTS from other endemic zoonoses.

SFTS is already an endemic disease in Korea. Han et al.[12] reported an SFTS virus seroprevalence of 4.1% among residents of rural areas in Korea. Most SFTS cases occur from April to November in Korea.[6] Scrub typhus and HFRS are common zoonotic diseases in Korea, and are prevalent during autumn. Most of the scrub typhus cases occur between October and November.[13] Similarly, HFRS predominantly occurs during the last quarter of the calendar year.[14] It is important to differentiate between SFTS and these endemic zoonoses because of their overlapping epidemic seasons.

Recently, two studies addressing the differentiation of SFTS from scrub typhus were published.[15,16] In particular, Park et al.[16] proposed a prediction scoring tool to differentiate SFTS from eschar- or skin rash- negative scrub typhus, as it involves diagnostic uncertainty. Furthermore, there has been a report of the usefulness of ferritin as a diagnostic marker to distinguish between SFTS and bacteremia with thrombocytopenia.[17] However, there was no previous study that has differentiated SFTS from other endemic zoonoses in Korea.

Our clinical score system to predict SFTS used four variables (neurologic symptoms, diarrhea, leukopenia, and normal CRP), which could easily be available in the primary care settings. Although no specific therapy is available for SFTS, and symptomatic and supportive care is the mainstay of treatment,[5] several rescue therapies such as ribavirin and plasma exchange[18] or intravenous immunoglobulin and corticosteroid[19] may be effective in treating rapidly progressive SFTS. Our clinical score system could help clinicians to stratify the patients so that they can decide on whether to try these therapies or make an early referral, particularly in primary care settings.[16]

However, SFTS can spread via human-to-human transmission through blood contact, unlike other endemic zoonoses including scrub typhus.[20] Kim et al.[21] reported in Korea that of the 27 healthcare workers who had contact with a severely ill SFTS patient, the 4 who were involved in cardiopulmonary resuscitation were diagnosed with SFTS via seroconversion. Using our clinical score system could facilitate early referral of patients suspected of having SFTS to the tertiary hospital, with possible consideration of nosocomial transmission of SFTS, pending the availability of the confirmatory test result.

This study has several limitations. First, although this study included endemic zoonoses in Korea other than scrub typhus or HFRS, such as leptospirosis, Q fever, or HGA, no patient with these diseases met the enrollment criteria. We included 6 HFRS patients diagnosed with a single high titer. However, incorrect diagnosis was not probable as these patients not only had positive serologic results but also had clinical manifestations and an exposure history relevant to HFRS. Second, there have been recent reports of co-infection of SFTS with other zoonoses.[22,23] The patients with all three (SFTS, scrub typhus, and HFRS) test results were enrolled; thus, it is likely that co-infected cases occurred among those patients that were excluded from this study. We also excluded bacteremia from this study, but some types of bacteremia may be associated with endemic zoonoses. Although we excluded such co-infections to develop a clear predictive scoring system, further study is needed to determine how to distinguish co-infected cases from others. Third, the comparative group did not contain a homogenous population. However, clinicians need a prediction tool to differentiate

severe disease among heterogenous populations, and the results of this study confirm the unique clinical findings of SFTS, which may be useful for primary care providers. Finally, we planned to re-evaluate for the likelihood of SFTS 2 days after admission in patients with low predictive scores at the time of admission. However, we could only apply the prediction score 2 days after admission in 27 patients; this was due to the lack of clinical information. Thus, we could not reach a conclusion from this study. Prospective validation study of this prediction score at the time of admission and a study to evaluate the usefulness of early reassessment for SFTS are warranted.

In summary, our study suggests a simple and useful scoring system to predict SFTS in patients suspected of having endemic zoonoses in Korea. We expect that this strategic approach would be helpful for primary care providers in early differentiation of SFTS from other endemic zoonoses and for improving the clinical outcomes in patients with SFTS.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline clinical characteristics and laboratory results of the subjects

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Supplementary Table 2

Diagnostic performance of the severe fever with thrombocytopenia syndrome prediction score system after 2 days of admission

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Supplementary Fig. 1

Flow chart of the study.

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