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BRIEF REPORT

The Differential Characteristics Between Severe Fever With Thrombocytopenia Syndrome and Hemorrhagic Fever With Renal Syndrome in the Endemic Regions

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An effective differentiation between severe fever with thrombocytopenia syndrome and hemorrhagic fever with renal syndrome was attained by a model considering patients' age, mouse/tick contact, presence of blush, low back pain, diarrhea, enlarged lymph nodes, and white blood cell count.

Keywords. differential diagnosis; hemorrhagic fever with renal syndrome; severe fever with thrombocytopenia syndrome.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging viral hemorrhagic fever (VHF) caused by SFTS virus (SFTSV). The disease was first discovered in China in 2010 and is mainly transmitted by tick bite and occasionally from person-to-person spread via SFTSV-infected blood or fluid [1, 2]. By the end of 2018, more than 8000 clinically diagnosed SFTS patients were reported in China [3], and over 1000 cases were reported from Japan [4], South Korea [5], and Vietnam [6], with a case fatality rate ranging from 5% [3] to 30% [2]. Another important VHF that is life threatening among large populations is hemorrhagic fever with renal syndrome (HFRS), which is caused by hantavirus and is often carried and transmitted by rodents [7]. Although HFRS cases occur worldwide, approximately 90% of the cases were reported in China, Japan, and South Korea [8, 9], which shows a highly similar geographic distribution to that of SFTS. Epidemiologically, both SFTS and HFRS are prevalent in rural areas, and farmers and outsiders are susceptible to infection through high-risk exposure to vector or host. Clinically, the 2 VHFs shared common features, with atypical and indistinguishable febrile disease observed at acute infection, subsequently followed by a critical or recovery phase. For those with adverse disease outcomes, both infections might rapidly progress into severe illness, which is characterized by hemorrhagic fever or multiple organ dysregulation. All of these features made differential diagnosis difficult in the endemic regions where both diseases are prevalent. A recent study reported the discovery of 4 patients with SFTSV infection out of 55 hantavirus-negative patients in Shandong Province, a long existing endemic region for HFRS [10]. We hypothesize that, similar to SFTS, HFRS can be misdiagnosed. In this report, we conducted a retrospective study in SFTS-endemic and HFRS-endemic regions, respectively, to identify the misdiagnosis of 2 VHF diseases and to attain differential diagnosis based on complete and detailed clinical data recording.

METHODS

The study was performed in 3 regions, where both SFTS and HFRS have been reported (Supplemental Figure 1). The sera sample and epidemiological database of clinically diagnosed HFRS patients had been collected from the Liaoning Center for Disease Control and Prevention (CDC) and Qingdao CDC. The clinically diagnosed patients and laboratory-confirmed patients had been defined by the criteria for SFTS [11] and HFRS [12], respectively, that was released by National Health Commission of the People's Republic of China (also see the Supplemental Material and Methods). The sera sample and epidemiological database of clinically diagnosed SFTS patients had been collected from Liaoning CDC and the People's Liberation Army 990 hospital in Xinyang city, Henan province. All sera samples were collected immediately after hospital admission and tested for hantavirus and SFTSV infection at the acute phase of illness. Data regarding demographic, epidemiological, and pretreatment clinical information were recorded by using a standard questionnaire released by China CDC.

In the current study, by using the available sera sample, we retested clinically diagnosed HFRS patients for SFTSV ribonucleic acid by applying real-time reverse-transcription polymerase chain reaction (RT-PCR) [2] and anti-SFTSV immunoglobulin (Ig)M antibody by applying immunofluorescence assay (IFA),

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and we retested clinically diagnosed SFTS patients for hantavirus by applying real-time RT-PCR and anti-hantavirus IgM antibody by using a commercial ELISA Kit (Wantai Biological Pharmacy, Beijing, China) (Supplemental Material and Methods). The available epidemiological and clinical datasets were retrospectively used for the current analysis. The study protocol was approved by the Review Board of Beijing Institute of Microbiology and Epidemiology. The SFTS and HFRS differentiation was performed using logistic regression model, and the differential factors were identified by using the classification tree with a Chi-square Automatic Interaction Detection (CHAID) model. Receiver operating characteristic (ROC) curves were constructed for evaluation of the scoring model. A 2-sided $P < .05$ was considered statistically significant. All analyses were performed using STATA 14.0 (Stata Corp LLP, College Station, TX) and SPSS version 22 (IBM Corp., Armonk, NY).

RESULTS

A total of 1546 patients were enrolled. In the SFTS-endemic region, 943 clinically diagnosed SFTS patients were screened, and 588 (62.4%) were positive for SFTSV infection, including 5 (0.9%) with hantavirus infection (coinfection group). Among the remaining 355 (38.6%) SFTSV-negative patients, 21 (5.9%) were positive for hantavirus infection (defined as the misdiagnosed group) (Supplemental Table 1). In comparison with SFTSV-positive patients, the misdiagnosed patients had significantly younger age, shorter interval from disease onset to hospital admission, higher frequency of mouse contact, and lower frequency of tick bite (all $P < .05$). Abdominal pain, nausea, and enlarged lymph nodes were less frequently seen among the misdiagnosed patients compared with the SFTSV-positive patients (all $P < .05$). For 2 hallmark laboratory features of SFTS, leukopenia was underrepresented in the misdiagnosed patients ($P < .001$), whereas thrombocytopenia was seen with comparable frequency (Supplemental Table 1).

In the HFRS-endemic regions, 603 clinically diagnosed HFRS patients were screened, and 348 (57.7%) were positive for hantavirus infection, including 4 (1.1%) with SFTSV infection (coinfection group). Among the remaining 255 (42.3%) hantavirus-negative patients, 8 (3.1%) were positive for SFTSV infection (misdiagnosed group). The misdiagnosed SFTS patients had older age, higher frequency of tick bite, higher body temperature, and higher presence of enlarged lymph nodes, thrombocytopenia, and leukopenia (all $P < .05$) (Supplemental Table 2).

The hantavirus-SFTSV coinfection rate (0.6%, 9 of 1546) was lower than the expected rate that was calculated from SFTSV single infection rate multiplied by the hantavirus single infection rate, ie, 36.2% multiplied by 24.2%, indicating a lower tendency of coinfection between the 2 pathogens. The coinfection group did not reveal significantly higher proportions of clinical features than the SFTS alone or HFRS alone group (Supplemental Table 3), indicating no more serious outcome originated from coinfection, which might be biased by the small sample size.

To attain clinical differentiation between 2 diseases, the laboratory-confirmed SFTS (n = 591) and HFRS patients (n = 365) were grouped for the evaluation of 33 variables regarding demographic, epidemiological, and clinical characteristics (Table 1). Most of the variables displayed significant differences between 2 groups, and 18 significant variables showed area under the curve (AUC) >0.600 and were further entered into the multiple logistic regression model to attain better discrimination power. On the ROC curve obtained from the model, the AUC was 0.985 (95% confidence interval [CI], 0.979–0.992), with 92.6% (95% CI, 89.4%–95.1%) sensitivity and 95.4% (95% CI, 93.4%–97.0%) specificity (Supplemental Figure 2). Patients of younger age that had mouse contact history, clinical presence of blush, low back pain, and higher level of white blood cell (WBC) counts ($\geq 4.74 \times 10^9$/L) were significantly associated with hantavirus infection rather than SFTSV infection. Patients of older age that had tick bite history, presented with diarrhea, had enlarged lymph nodes, and had lower level of WBC counts ($<4.74 \times 10^9$/L) were significantly associated with SFTSV infection rather than hantavirus infection (Supplemental Table 4). The classification tree was generated based on the significant variables in the multiple logistic analysis. Patients with WBC $\leq 2.7 \times 10^9$/L without mouse contact history or low back pain (Node 19), or patients with WBC of 2.7×10^9/L–3.4×10^9/L and enlarged lymph nodes (Node 10) were classified as SFTS patients. Patients with WBC of 7.6×10^9/L–8.4×10^9/L (Node 14) and low back pain or patients with both WBC $>8.4 \times 10^9$/L and mouse contact history (Nodes 16 and Node 18) were classified as HFRS patients (Supplemental Figure 3).

DISCUSSION

In rural regions where both HFRS and SFTS circulate, a common dilemma in diagnosis is the lack of molecular or immunological assay in clinical medical care. The current gold standard for diagnosis is IFA or enzyme-linked immunosorbent assay test or molecular test by PCR [10], whereas their widespread use is limited due to lack of instrument or technical expertise in rural areas where disease circulated. Although the case definition of SFTS or HFRS defined by classic clinical features is sufficiently sensitive to capture most of the likely cases, there are other patients with atypical manifestation that was missed by the clinical definition. In this study, we provided evidence showing that a certain proportion of hantavirus infection was found in patients who were initially diagnosed with SFTS, and vice versa a certain proportion of SFTSV infection existed in patients treated for HFRS. The presence of low back pain, orbital pain, neck red and chest red, and headache, which are considered to be typical

Table 1. The Basic and Clinical Differentiation Between the Laboratory-Confirmed SFTS and HFRS Patients

Characteristics	SFTS (n = 591)	HFRS (n = 365)	*P* value	AUC
Age, year, mean ± SD	62 ± 12	46 ± 14	<.001[a]	0.812
<45	55 (9.3)	161 (44.1)	<.001[b]	0.784
45-60	167 (28.3)	152 (41.6)		
≥60	369 (62.4)	52 (14.3)		
Sex, male	279 (47.2)	269 (73.7)	<.001[b]	0.633
Days from onset to admission, median (IQR)	5 (3-6)	4 (2-6)	<.001[c]	0.433
Recent contact with				
Mouse	31 (5.3)	164 (44.9)	<.001[b]	0.698
Mosquito (n = 461)	20 (9.0)	6 (2.5)	.003[b]	0.533
Tick	151 (25.6)	2 (0.6)	<.001[d]	0.625
Mice faeces	10 (4.6)	2 (0.8)	.016[d]	0.519
Clinical Manifestation, n (%)				
Headache	187 (31.6)	253 (69.3)	<.001[b]	0.688
Highest temperature, ℃, mean ± SD	38.9 ± 0.6	39.0 ± 0.6	.010[a]	0.543
Low back pain (n = 634)	81 (28.9)	210 (59.3)	<.001[b]	0.652
Orbital pain (n = 634)	17 (6.1)	100 (28.3)	<.001[b]	0.611
Arthralgia	90 (15.2)	92 (25.2)	<.001[b]	0.550
Pantalgia	406 (68.7)	122 (33.4)	<.001[b]	0.676
Nausea	427 (72.3)	185 (50.7)	<.001[b]	0.608
Vomiting	213 (36.0)	112 (30.7)	.089[b]	0.527
Abdominal pain	158 (26.7)	84 (23.0)	.199[b]	0.519
Diarrhea	224 (37.9)	59 (16.2)	<.001[b]	0.609
Blush (n = 634)	28 (10.0)	158 (44.6)	<.001[b]	0.673
Neck red (n = 634)	19 (6.8)	114 (32.2)	<.001[b]	0.627
Chest red (n = 634)	10 (3.6)	88 (24.9)	<.001[b]	0.606
Hemoptysis	7 (1.2)	3 (0.8)	.750[d]	0.502
Conjunctival congestion	42 (7.1)	107 (29.3)	<.001[b]	0.611
Eyelids swelling (n = 634)	12 (4.3)	48 (13.6)	<.001[b]	0.546
Jaundice	3 (0.5)	2 (0.6)	1.000[d]	0.500
Enlarged lymph nodes	241 (40.8)	4 (1.1)	<.001[d]	0.698
Hepatosplenomegaly (n = 634)	3 (1.1)	3 (0.9)	1.000[d]	0.501
Oliguria (n = 634)	24 (8.6)	71 (20.1)	<.001[b]	0.557
Mucosal hemorrhage	86 (14.6)	61 (16.7)	.368[b]	0.511
Rash	7 (1.2)	2 (0.6)	.495[d]	0.569
Petechial or bruise	72 (12.2)	30 (8.2)	.054[b]	0.503
Outcome			<.001[b]	0.500
Cure	484 (81.9)	351 (96.2)		
Deterioration	96 (16.2)	11 (3.0)		
Fatal when discharged from hospital	11 (1.9)	3 (0.8)		
Laboratory Parameters on Admission				
White blood cells, $\times 10^9$/L, median (IQR)	2.3 (1.6-3.4)	8.7 (5.6-14.9)	<.001[c]	0.930
<4	474 (80.2)	37 (10.1)	<.001[b]	0.871
4-10	105 (17.8)	220 (60.3)		
≥10	12 (2.0)	108 (29.6)		
Platelet counts, $\times 10^9$/L, median (IQR)	58 (40-81)	53 (34-86)	.269[c]	0.468
<50	212 (35.9)	112 (30.7)	.247[b]	0.528
50-100	312 (52.8)	206 (56.4)		
≥100	67 (11.3)	47 (12.9)		
Positive urine protein (n = 694)	261 (58.1)	203 (82.9)	<.001[b]	0.624
Prolonged coagulation time (n = 433)	140 (43.1)	27 (25.0)	.001[b]	0.590

Abbreviations: AUC, area under the curve; HFRS, hemorrhagic fever with renal syndrome; IQR, interquartile range; SD, standard deviation; SFTS, severe fever with thrombocytopenia syndrome.

NOTE: The variables with AUC>0.600 were further entered for multivariate analysis.

[a] *t* test.

[b] $\chi 2$ test.

[c] Non-parametric test.

[d] Fisher exact test.

characteristics of HFRS, was also observed in SFTSV-infected patients. Likewise, thrombocytopenia, as one of the hallmarks of SFTS, was also frequently and comparably recorded in HFRS patients. Despite these atypical features, other indicators, including frequency of previous tick/mouse contact, enlarged lymph nodes, and WBC $\leq 3.4 \times 10^9$/L, remained to be significantly different between 2 types of infections. Moreover, after taking into account these atypical cases, a model that made use of enlarged lymph nodes and WBC counts, together with the classic manifestations such as blush and low back pain, enabled adequate differential diagnosis between HFRS and SFTS in both endemic areas. Still, the effectiveness of the model needs to be evaluated by further clinical studies in other endemic regions.

CONCLUSIONS

This study had limitations that were inherent to retrospective study. Because SFTS viremia is known to wane quickly from 7 days postadmission [13], some of the SFTSV infection might be missed by both loss of viremia and inadequate timing to develop IgM responses. We made no effort to determine the etiological agents of the remaining negative patients, because SFTS and HFRS were among the top list of endemic diseases with high case fatality. In particular, for SFTS disease, more attention and fear were caused because of its high case fatality and person-to-person transmission via human blood [1, 14]. In case of confirmed SFTSV infection at early illness, strict person protection measures should be adopted. Although there is currently no effective therapy for SFTS patients, several experimental therapies such as plasma exchange therapy [15, 16], intravenous Ig plus steroid [17], and convalescent serum therapy [18] might be beneficial if adopted at early stage of the disease. Therefore, the current findings might provide information to guide prevention measures and clinical practice in endemic regions where both diseases exist.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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