



# Clinical features and epidemiology of severe fever with thrombocytopenia syndrome in dogs in the Republic of Korea: an observational study (2019–2020)

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## Abstract

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease with a high mortality rate for humans and cats. The clinical course and prognosis of SFTS in dogs remains unclear. In the present study, we investigated the clinical and epidemiological characteristics of SFTS virus (SFTSV) infection in dogs. All evaluated dogs exhibited an acute course and symptoms including fever (57.1%), anorexia (57.1%), depression (42.9%), and vomiting (35.7%). Thrombocytopenia was present in 45.5% of dogs, while jaundice was not observed. C-reactive protein, alanine transaminase, and alkaline phosphatase were elevated in some cases. Viral clearance occurred within 6 to 26 days. Phylogenetic analysis revealed that the SFTSV sequences were consistent with viruses circulating in the Republic of Korea. As dogs often live in close contact with humans, awareness of the clinical and epidemiological features of SFTS in dogs is crucial. Further large-scale studies are necessary to investigate SFTSV infection in dogs.

**Keywords** Dogs · Severe fever with thrombocytopenia syndrome (SFTS) · Republic of Korea · Viral clearance · Zoonotic disease · Phylogenetic analysis

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## Introduction

Severe fever with thrombocytopenia (SFTS) is a zoonotic disease, with reported cases of direct transmission from dogs to humans (Saijo and Shimojima 2018) and from cats to humans, including veterinary personnel (Kida et al. 2019; Yamanaka et al. 2020). Moreover, antibodies against the SFTS virus (SFTSV) have been identified in veterinary hospital workers in Japan (Kirino et al. 2021). Cases of presumed transmission of SFTSV from domestic dogs to humans have been reported in the Republic of Korea (ROK), while an *in vivo* study in dogs confirmed that intraspecies SFTSV transmission could occur by contact; these findings suggest that infection can occur in animals as well as humans (Chung et al. 2020; Park et al. 2021).

Many studies have assessed the presence of SFTSV in samples from dogs in China, Japan, and the ROK. For canine SFTS, the RNA positive rate is 0.23%–0.88%, while the antibody seroprevalence is 7.4%–68.18% (Ding et al. 2014a; Huang et al. 2019; Kang et al. 2019; Kimura et al. 2018; Lee et al. 2017, 2018; Li et al. 2014; Tian et al. 2017). Reported SFTSV prevalence rates in dogs are 5.3%

(19/359) (Niu et al. 2013) in China, 0.9% (1/114) (Matsui et al. 2021) in Japan, and 0.2% (1/426) in shelter dogs (Lee et al. 2017) and 2.9% (3/103) in military dogs (Kang et al. 2019) in the ROK. Meanwhile, reported SFTSV seroprevalence rates are 37.9% (136/359) (Niu et al. 2013) and 7.4% (23/311) (Li et al. 2014) in China, 9.1% (3/33) in outdoor dogs and 14.3% (2/14) in impounded dogs in Japan (Kimura et al. 2018), and 13.9% (59/426) in shelter dogs (Lee et al. 2018) and 21.4% (22/103) in military dogs (Kang et al. 2019) in the ROK.

To our knowledge, clinical infection has been reported only in two dogs with natural infection and 16 dogs with experimental infection (Han et al. 2020; Nam et al. 2020; Park et al. 2021). Dogs typically exhibit fever, anorexia, depression, vomiting, and pink eyes. Hematological features include thrombocytopenia; anemia; leukopenia; leukocytosis; and increased alanine transaminase (ALT), alkaline phosphatase (ALP), and C-reactive protein (CRP) levels. Fever and thrombocytopenia are major clinical features. Fever is the most common symptom and is associated with an increase in tumor necrosis factor alpha, which acts on the endothelium to increase vasodilation and vascular permeability (Seynhaeve et al. 2006). Thrombocytopenia is caused by macrophage phagocytosis in the spleen when the virus attaches to platelets (Jin et al. 2012). Although fever is not a prognostic factor for humans (Liu et al. 2020; Xu et al. 2018), the severity of thrombocytopenia is an important prognostic factor (Li et al. 2020). There is no treatment protocol for SFTS infection in humans and animals, and treatment is symptomatic. Because natural clinical infection in dogs with SFTS has been reported only in a limited number of cases, the clinical characteristics and survival rate are currently not well known.

The aim of this study was to investigate clinical (symptoms and results of blood examinations) and epidemiological characteristics, including the findings of phylogenetic analysis, of SFTSV infection in dogs in the ROK.

## Materials and methods

### Sample collection

Between April 2019 and December 2020, blood was collected from 448 dogs exposed to hard ticks or exhibiting clinical symptoms similar to those of SFTS at 166 animal hospitals in the ROK. Collected blood samples were centrifuged to harvest the sera, and all sera samples were stored at  $-80^{\circ}\text{C}$  until analysis. When the SFTSV RNA was confirmed, blood samples for complete blood count (CBC) and serum chemistry, urine samples, and swab samples (rectal, nose, eye, oral) were requested for follow-up.

## Detection of SFTSV RNA and sequencing

RNA was extracted from 200- $\mu\text{L}$  aliquots of serum using a Gene-spin Viral DNA/RNA Extraction Kit (iNtRON Biotechnology, Seongnam, ROK) according to the manufacturer's instructions. RNA was also extracted from urine samples and swab samples (rectal, nose, eye, oral) obtained for follow-up. The viral RNA was stored at  $-80^{\circ}\text{C}$  until use. Each RNA sample was tested using nested reverse transcription-polymerase chain reaction (RT-PCR) assays to detect the small (S) segment of SFTSV. Primary PCR was performed using one-step RT-PCR premix (Solgent, Daejeon, ROK) with previously designed primers: NP-2F (5'-CAT CAT TGT CTT TGC CCT GA-3') and NP-2R (5'-AGA AGA CAG AGT TCA CAG CA-3') (Yoshikawa et al. 2014). The primary reaction was performed with an initial step of 30 min at  $50^{\circ}\text{C}$  and 15 min at  $95^{\circ}\text{C}$  for denaturation, followed by 40 cycles of 20 s at  $95^{\circ}\text{C}$ , 40 s at  $52^{\circ}\text{C}$ , and 30 s at  $72^{\circ}\text{C}$ , with a final extension step of 5 min at  $72^{\circ}\text{C}$ . Nested PCR was conducted using 1  $\mu\text{L}$  of the primary PCR product as a template and PCR premix (BIOFACT, Daejeon, ROK) with previously described primers: N2-F (5'-AA Y AAG ATC GTC AAG GCA TCA-3') and N2-R (5'-TAG TCT TGG TGA AGG CAT CTT-3') (Oh et al. 2016). The reaction for the nested PCR was 25 cycles of 20 s at  $94^{\circ}\text{C}$ , 40 s at  $55^{\circ}\text{C}$ , and 30 s at  $72^{\circ}\text{C}$ . Secondary PCR products were separated by electrophoresis on 1.2% agarose gels, visualized after staining with EcoDye™ Nucleic Acid Staining Solution (BIOFACT, Daejeon, ROK), and purified using a DNA Gel Extraction Kit (Bionics, Seoul, ROK). In addition to nested RT-PCR, viral RNA was quantified using a PowerChek SFTSV Real-time PCR kit (Kogenebiotech, Seoul, ROK), according to the manufacturer's instructions, in the StepOnePlus Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA).

## Sequencing and phylogenetic analysis

To confirm the SFTSV PCR products, positive PCR amplicons were directly sequenced using an Applied Biosystems 3730 DNA Analyzer (PE Applied Biosystems, Foster City, CA, USA). Sequence homology with other deposited sequences were identified by searches using the Basic Local Alignment Search Tool network service ([https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE\\_TYPE=BlastSearch&LINK\\_LOC=blasthome](https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome)). The obtained sequences were aligned and analyzed using Molecular Evolutionary Genetics Analysis Version 7.0 (MEGA7) software. Phylogenetic trees were constructed using the maximum likelihood method. Sequences of

the SFTSV S segment previously identified in the ROK, China, and Japan were obtained from GenBank and used for a comparative analysis.

### Indirect immunofluorescence assay (IFA)

IFA slides were prepared using SFTSV-infected Vero E6 cells. Vero E6 cells were resuspended at  $5 \times 10^3$  cells/well in medium (2% fetal bovine serum in Dulbecco's modified Eagle medium), added to each well of a 24-well slide, and incubated in 5% CO<sub>2</sub> for 16 h. The slides were fixed with 100% acetone for 10 min at  $-20$  °C. After blocking with 5% goat serum for 2 h, serum samples were diluted to 1:50, 1:100, 1:200, 1:400, and 1:800 with phosphate-buffered saline (PBS) for attaching the diluted serum and incubated in 5% CO<sub>2</sub> for 90 min. After washing with PBS, fluorescein isothiocyanate -conjugated anti-dog immunoglobulin G (IgG) (Sigma-Aldrich, St. Louis, MO, USA) was added to each well of the antigen slide and incubated in 5% CO<sub>2</sub> for 1 h. The IFA slides were visualized using the EVOS™ M7000 Imaging System (Invitrogen, Frederick, MD, USA).

### Enzyme-linked immunosorbent assay (ELISA)

For the detection of SFTSV-specific antibodies in the canine sera, 96-well plates (Thermo Scientific, Waltham, MA, USA) were coated with 100 ng/well of purified recombinant nucleoprotein (NP) at 4 °C overnight. For preparation of the recombinant protein, the NP-encoding gene from a human SFTSV isolate was cloned into the pET28a(+) vector (Novagen, Gibbstown, NJ, USA) and the plasmid transfected into the *Escherichia coli* strain BL21. After induction with 0.1-mM isopropyl  $\beta$ -D-thiogalactoside, the recombinant protein was purified using HisTrap HP histidine-tagged protein columns (GE Healthcare, Chicago, IL, USA) according to the manufacturer's instructions. After coating with the purified recombinant NP, the 96-well plates were blocked with 5% skim milk in PBS containing 0.05% Tween 20 for 2 h at room temperature (RT); they were subsequently incubated for 1 h at RT with 1  $\mu$ L/well of canine serum in 5% skim milk. Binding antibody in the serum samples was detected using horseradish peroxidase-conjugated goat anti-dog IgG (Abcam, Cambridge, UK). Substrate solution containing 3,3',5,5'-tetramethylbenzidine was added to allow color development. The reaction was performed for 10 min at RT, and 1 M H<sub>3</sub>PO<sub>4</sub> solution was used to stop the reaction. The optical density was measured at 450 nm for each well using a microplate reader (BioTek Instruments, Winooski, VT, USA).

### Virus isolation

Collected canine serum samples were inoculated onto monolayers of Vero E6 cells for virus isolation, as previously described (Han et al. 2020). After adaptation and proliferation of SFTSV in Vero E6 cells, the virus was confirmed by RT-PCR and indirect IFA using supernatants of infected cells and infected cells, respectively. In the ROK, SFTSV is a biosafety level 3 (BSL 3) pathogen; therefore, all experiments were conducted in a BSL 3 laboratory.

### Full genome sequencing

For complete genetic sequencing of SFTSV, nucleotide sequence analyses of the full segments of S, M, and L were completed through rapid amplification of cDNA ends. All generated nucleotide sequences of Dog 1 and Dog 12 have been deposited in GenBank under accession numbers OL773687 and OK423754 for the S segment, OM179920 and OM179921 for the M segment, and OM179922 and OM179923 for the L segment.

### Statistical analysis

Statistical analyses were performed using a statistical software (Prism 9.3.1, Graphpad). The Shapiro–Wilk test was used to test normality. Because age, CBC, and serum chemistry values were not normally distributed, median values were calculated.  $P < 0.05$  was considered statistically significant.

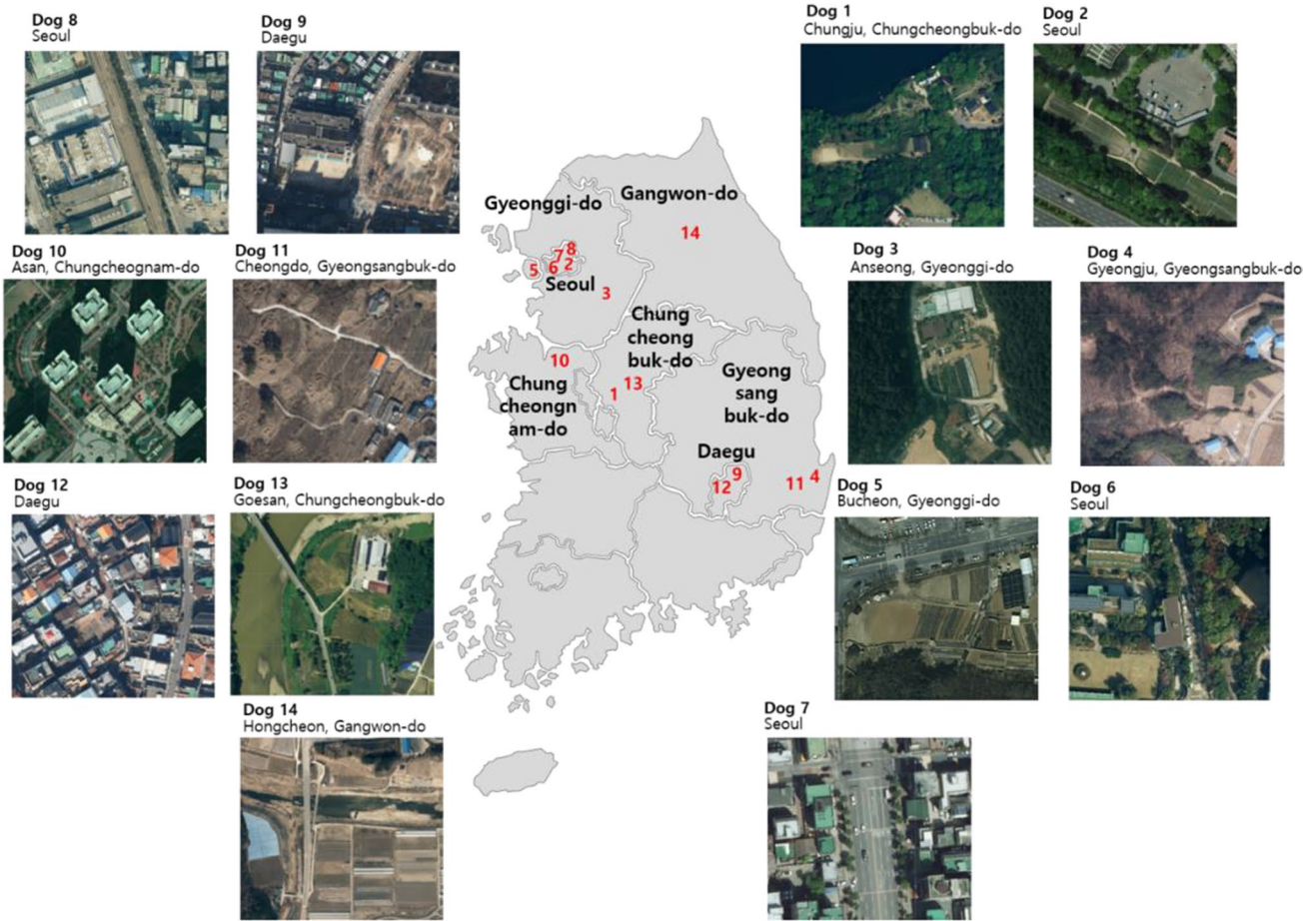
## Results

### Dogs with SFTS

In total, 14 companion dogs infected with SFTS were included in this study; breeds included Maltese (3), Poodle (4), Cocker spaniel (1), Mixed (1), Chihuahua (2), Cavalier King Charles spaniel (1), Pomeranian (1), and Bichon Friese (1). There were nine castrated males, two intact females, two spayed females, and one intact male. The median age was 3 years (1–10 years). The walking locations of these dogs varied and included Seoul (4), Gangwon-do (1) Gyeonggi-do (2), Chungcheongbuk-do (2), Chungcheongnam-do (1), Daegu (2), and Gyeongsangbuk-do (2) (Fig. 1). Nine of the 14 dogs (64.3%) had a history of exposure to ticks in urban parks or walking trails around residential areas.

### Clinical symptoms of SFTS in dogs

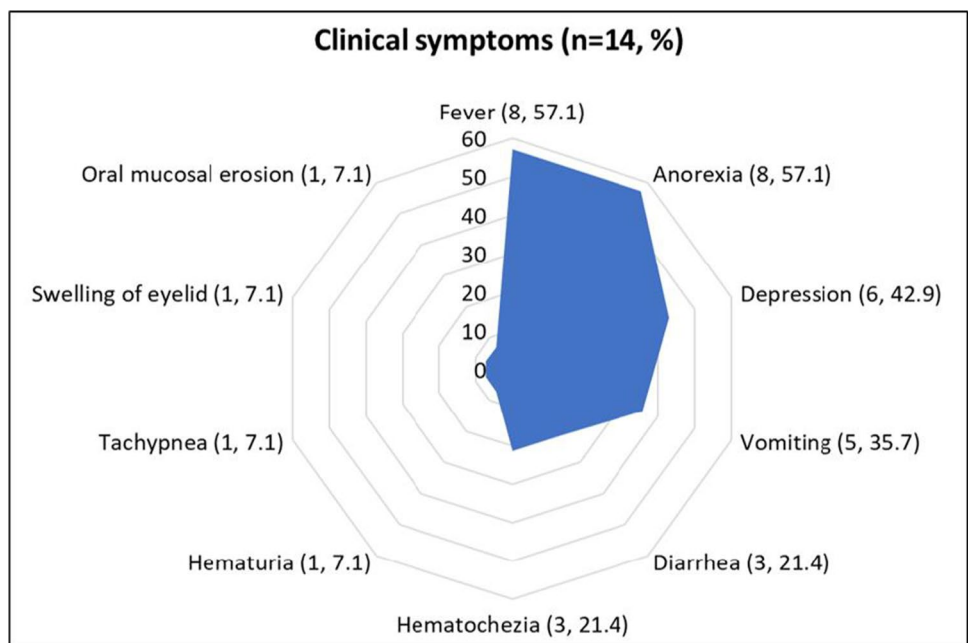
The infected dogs showed fever (57.1%, 8/14; reference, 38.0°C–39.2°C), anorexia (57.1%, 8/14), depression (42.9%,



**Fig. 1** Regional distribution and satellite images of 14 companion dogs with positivity for severe fever with thrombocytopenia syndrome virus (SFTSV) in the Republic of Korea (ROK). The image in the center is a geographic map of SFTSV RNA prevalence in canine

sera in the ROK. The red Arabic numerals indicate the dogs with detection of SFTSV RNA (for example, number 1 indicates Dog 1). Photographs of the walking locations of the dogs are also shown

**Fig. 2** Clinical symptoms of severe fever with thrombocytopenia syndrome (SFTS). Summary of clinical symptoms in 14 positive dogs



6/14), vomiting (35.7%, 5/14), diarrhea (21.4%, 3/14), hematochezia (21.4%, 3/14), hematuria (7.1%, 1/14), tachypnea (7.1%, 1/14), eyelid swelling (7.1%, 1/14), and oral mucosal erosion (7.1%, 1/14; Fig. 2). The median body temperature was 39.7 °C (range, 38.4 °C–40.2 °C) and exceeded 40 °C in only two dogs.

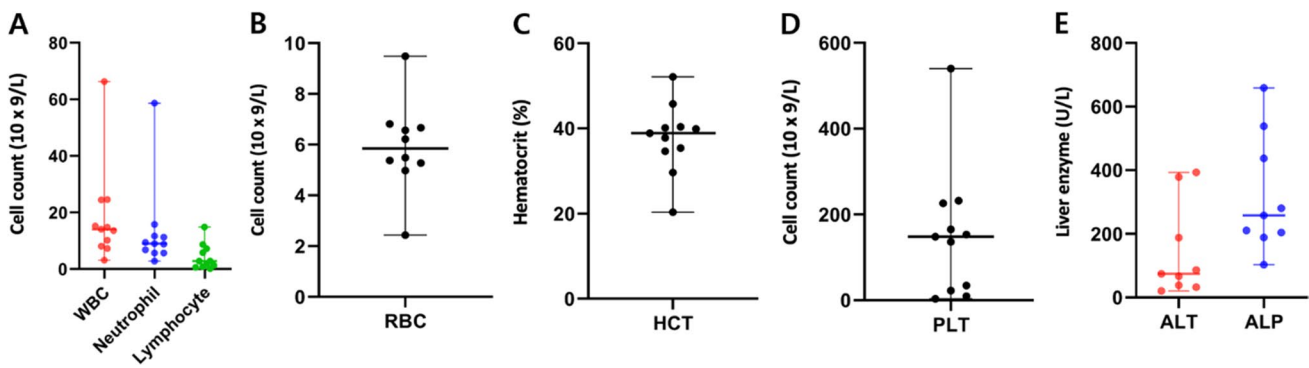
**Laboratory results**

Complete blood count was performed for 11 dogs (Fig. 3, Table 1). The platelet count decreased below the reference range in 45.5% (5/11) of dogs, while it decreased but remained within the reference range in 27.3% (3/11) of dogs. Leukogram analysis showed leukocytosis (27.3%, 3/11),

leukopenia (18.2%, 2/11), lymphocytosis (18.2%, 2/11), and lymphopenia (27.3%, 3/11). Erythrogram analysis showed decreased hematocrit and a red blood cell (RBC) count lower than the reference range in 27.3% (3/11) of dogs and a decrease in the RBC count and hemoglobin level within the reference range in 7.1% (1/11) of dogs. C-reactive protein was increased in all six tested dogs. Eight dogs were tested for ALT and ALP and increased levels were observed in two (25%) and six (75%) dogs, respectively.

**Other tick-borne diseases**

Blood samples were examined to a differential diagnosis of tick-borne diseases. Specifically, PCR was used to test for



**Fig. 3** Laboratory results for 11 companion dogs with severe fever with thrombocytopenia syndrome (SFTS). **A** Cell count in a leukogram, including total white blood cells ( $n = 11$ ), neutrophils ( $n = 11$ ),

and lymphocytes ( $n = 11$ ). **B** Red blood cell count ( $n = 11$ ). **C** Hematocrit ( $n = 11$ ). **D** Platelet count ( $n = 11$ ). **E** Liver enzymes ( $n = 8$ )

**Table 1** Results of blood analysis for 14 dogs with severe fever with thrombocytopenia syndrome

Parameters	No. of patients (%)	Results of parameters			Reference range (units)
		Minimum	Median	Maximum	
<b>Complete blood count</b>					
Leukocytosis	3/11 (27.3%)	24.7	13.6	66.3	6–17 ( $10^9/L$ )
Leukopenia	2/11 (18.2%)	4.0		3.1	
Lymphocytosis	2/11 (18.2%)	7.2	2.8	8.7	1–4.8 ( $10^9/L$ )
Lymphopenia	3/11 (27.3%)	0.2		0.6	
Eosinopenia	2/5 (40.0%)	0.01	0.02	0.03	2–10 ( $10^9/L$ )
Thrombocytopenia	5/11 (45.5%)	0.3	2.2	13.6	20–50 ( $10^{10}/L$ )
Decreased RBC count	4/10 (40.0%)	2.4	5.3	5.4	5.5–8.5 ( $10^{12}/L$ )
Decreased hemoglobin	2/11 (18.2%)	5.8	13.4	18.4	12–18 (g/dL)
Decreased HCT	3/11 (27.3%)	20.4	29.6	35.4	37–55 (%)
<b>Serum chemistry</b>					
Increased CRP	6/6 (100%)	1.6	18.4	161.1	0–1 (mg/L)
Increased ALT	2/8 (25.0%)	378	385.5	393	10–125 (U/L)
Increased AST	2/3 (66.7%)	134	215	296	0–50 (U/L)
Increased ALP	6/8 (75.0%)	204	352.5	659	23–212 (U/L)
Increased glucose	2/6 (33.3%)	118	133.5	148	74–120 (mg/dL)

\*RBC, red blood cell; HCT, hematocrit; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase

*Anaplasma phagocytophilum*, *A. bovis*, *Ehrlichia chaffensis*, *E. canis*, *Borrelia* spp., and *Babesia gibsoni* and SensPERT Ab test kits (VetAll Laboratories®, Goyang-si, ROK) were used to test for *Anaplasma* spp., *Borrelia burgdorferi*, *E. canis*, and *B. gibsoni*. Only one animal showed antibody positivity against *Borrelia burgdorferi*. All the remaining tick-borne disease antigen and antibody tests showed negative results.

### Detection of SFTSV RNA by RT-PCR

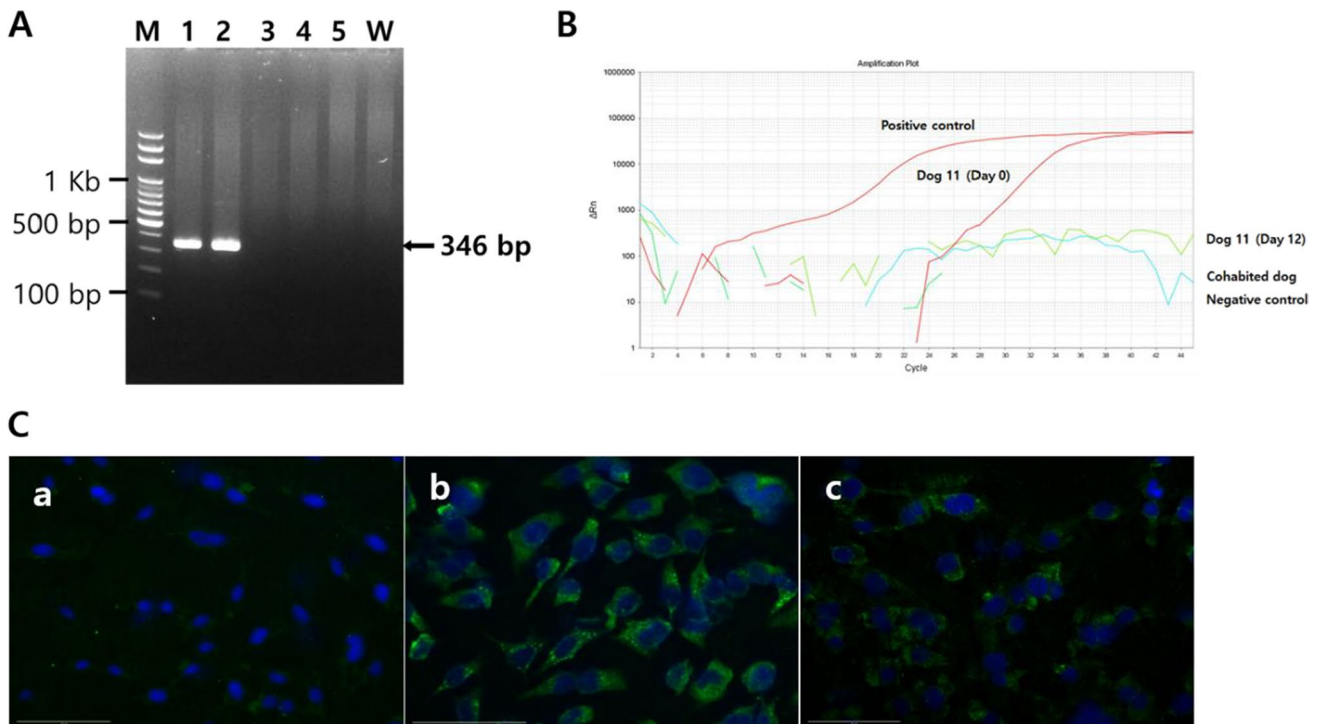
Using PCR, 14 out of 448 serum samples were positive for SFTSV; the positive rate was 3.1% (Fig. 4A). Specifically, virus clearance was confirmed through follow-up in 11 of the 14 dogs. Although daily blood samples were not collected, the duration of virus clearance was 6 to 26 days (Table 2). In addition, SFTSV was detected in the urine sample of Dog 12 (Table 3). Accordingly, a serum sample of the dog cohabiting with Dog 12 was obtained and tested for the SFTSV RNA, and the result was negative. In addition, all other cohabiting dogs showed negativity for the SFTSV RNA (Fig. 4B).

### Detection of SFTSV antibodies by IFA and ELISA

IFA was used to detect anti-SFTSV antibodies in the samples of 10 of the 14 dogs, and four showed positivity (Table 2; Fig. 4C). In the case of Dog 1, it was confirmed that the IgG titer was higher on day 12 ( $\leq 800$ ) than on day 5 ( $\leq 400$ ). Dog 3 was negative on day 0 and positive on day 15 ( $\leq 100$ ). Although blood tests were not conducted every day, the results suggested that it took 5 (Dog 1) to 15 days (Dog 3) for the formation of antibodies. ELISA was used to detect anti-SFTSV antibodies in three dogs, and seropositivity was confirmed for Dog 11 and Dog 12. In addition, continuous follow-up of Dog 1 confirmed that antibodies persisted for approximately 1 year.

### Sequencing and phylogenetic analysis

The nucleotide sequences obtained from our study have been deposited in GenBank under accession numbers MN398158, MW004841-MW004855, and MZ171135-MZ171136. The partial sequence (MW004854) of SFTSV detected in the urine of Dog 12 was confirmed to be the same as the sequence detected in the serum (MW004855). The thirteen sequences of



**Fig. 4** Detection of severe fever with thrombocytopenia syndrome virus (SFTSV) RNA by reverse transcription-polymerase chain reaction (RT-PCR) and results of the indirect immunofluorescence assay (IFA). **A** Gel electrophoresis of PCR results for detecting small segments (346 bp) of the SFTS viral RNA. M, 100-bp marker; 1–2, SFTSV RNA-positive companion dogs; 3–5, SFTSV RNA-negative companion dogs; W, water control. **B** Real-time PCR results for Dog

11. A positive control and Dog 11 (on Day 0) were positive for the SFTSV RNA. Dog 11 (on Day 12), a cohabiting dog, and a negative control showed RNA negativity. **C** Results of IFA for SFTS antibody detection in the sera of companion dogs. **a** Negative control, **b** 1:400 dilution ratio in serum, **c** 1:800 dilution ratio in serum. The blue color represents 4', 6-diamidino-2-phenylindole and the green color represents green fluorescent protein. Scale bar = 75  $\mu$ m

**Table 2** Detection of RNA and antibody of the severe fever with thrombocytopenia syndrome virus in companion dogs

Case numbers	Detection of RNA by RT-PCR				Detection of antibody by IFA or ELISA		
	1 <sup>st</sup> positive	2 <sup>nd</sup> positive	3 <sup>rd</sup> positive	Negative	Seronegative	1 <sup>st</sup> seropositive	2 <sup>nd</sup> seropositive
Dog 1	Day 0	Day 5	-	Day 12	Day 0	Day 5 (≤ 400) <sup>abc</sup>	Day 12 (≤ 800) <sup>abc</sup>
Dog 2	Day 0	-	-	Day 15	Day 0	-	-
Dog 3	Day 0	Day 8	-	Day 15	Day 0	Day 15 (≤ 100) <sup>a</sup>	-
Dog 4	Day 0	-	-	Day 10	-	Day 0 (≤ 50) <sup>a</sup>	Day 10 (≤ 50) <sup>a</sup>
Dog 5	Day 0	-	-	Day 6	Day 0	-	-
Dog 6	Day 0	-	-	Day 7	Day 0	-	-
Dog 7	Day 0	-	-	Day 15	Day 0	-	-
Dog 8	Day 0	-	-	Day 11	Day 0	-	-
Dog 9	Day 0	-	-	Day 12	Day 0	-	-
Dog 10	Day 0	-	-	Day 26	Day 0	-	-
Dog 11	Day 0	-	-	Day 12	Day 0	Day 12 <sup>b</sup>	-
Dog 12	Day 0	Day 8	Day 10	-	-	Day 0 <sup>b</sup>	Day 8 <sup>b</sup>
Dog 13	Day 0	-	-	-	-	ND	-
Dog 14	Day 0	-	-	-	Day 0	-	-

*RT-PCR*, reverse transcription-polymerase chain reaction; *IFA*, indirect immunofluorescence assay; *ELISA*, enzyme-linked immunosorbent assay; *ND*, not done; ( ), serum immunoglobulin G titer using IFA; <sup>a</sup>detection using IFA; <sup>b</sup>detection using ELISA; <sup>c</sup>detection of immunoglobulin M; -, unavailable

**Table 3** Detection of the severe fever with thrombocytopenia syndrome virus (SFTSV) RNA in serum, urine, and swab samples (oral, nose, eye, rectal) from companion dogs using polymerase chain reaction (PCR)

SFTS-positive dogs	Serum	Urine	Swab			
			Rectal	Nose	Eye	Oral
Dog 2	+	N	-	-	N	N
Dog 3	+	-	-	-	-	-
Dog 4	+	-	-	-	N	-
Dog 6	+	N	N	N	N	-
Dog 7	+	N	-	-	N	-
Dog 8	+	-	N	-	N	-
Dog 9	+	-	-	-	-	-
Dog 10	+	-	N	N	N	N
Dog 11	+	-	-	N	N	-
Dog 12	+	+	-	-	-	-
Total	10	1	0	0	0	0

*SFTS*, severe fever with thrombocytopenia syndrome; *N*, no sample; +, PCR positive for SFTSV; -, PCR negative for SFTSV

sera obtained in this study showed 94.2%–100.0% identity with each other. Phylogenetic analysis identified four, two, and two subgenotypes of B-3, B-2, and B-1, respectively, and five were identified as genotype D. It was confirmed that most of the samples belonged to genotype B (Fig. 5 and Fig. 6). The sequence of Dog 5 could not be obtained due to a lack of samples.

**Treatment and prognosis**

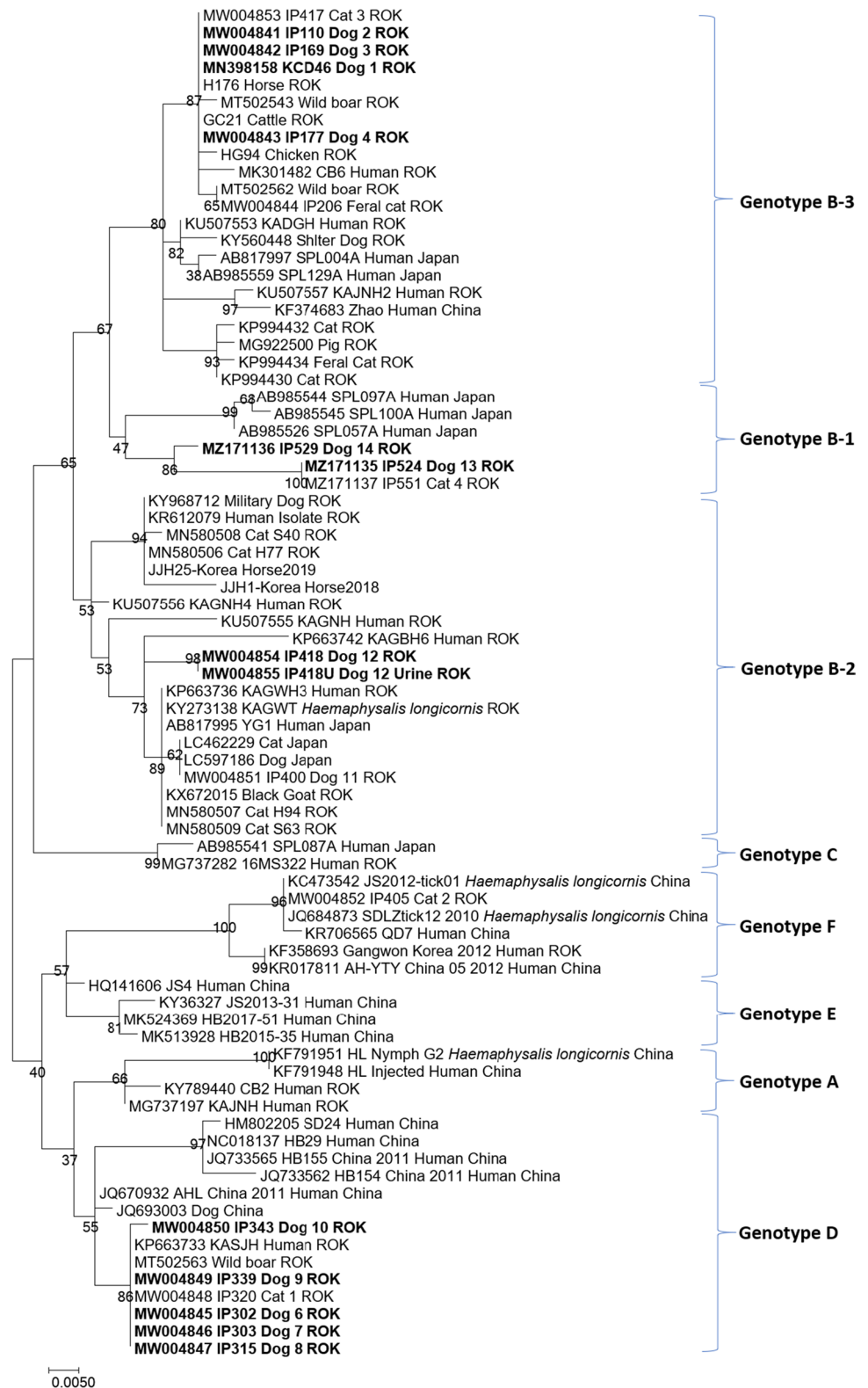
The dogs underwent antibiotic and symptomatic treatment. Antibiotics such as doxycycline, metronidazole, ciprofloxacin, cefaclor, and amoxicillin were used according to each

individual case, and famotidine, metoclopramide, maropitant, and sucralfate were used for symptomatic treatment. Two dogs were hospitalized for 1 day each, and both showed severe anemia and received a single blood transfusion. All dogs survived with complete resolution of symptoms.

**Discussion**

To date, natural clinical infection with SFTSV has been reported only in two dogs (Han et al. 2020; Nam et al. 2020). In the present observational study, we investigated

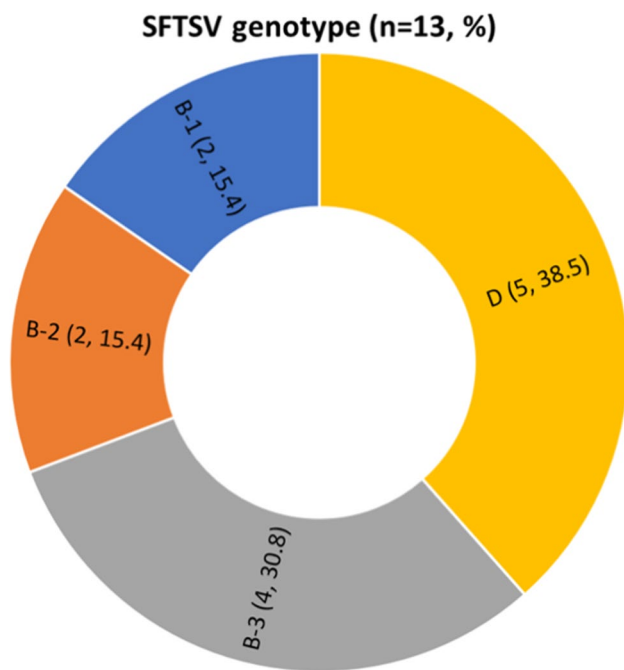
**Fig. 5** Phylogenetic tree and genotypes of the severe fever with thrombocytopenia syndrome (SFTS) virus (SFTSV), based on analysis of partial sequences of the small segments (346 bp) of the SFTS viral RNA. The sequences identified from SFTSV-positive companion dogs samples are indicated in boldface. Maximum-likelihood analysis has been used to construct the phylogenetic tree, based on the Kimura two-parameter model (1,000 bootstrap replicates). ROK, Republic of Korea



the clinical features of SFTS infection in 14 dogs in the ROK. The results suggested that dogs show a clinical course different from that observed in humans and cats. Moreover, all dogs recovered and survived.

According to the new classification method for the SFTSV genome, eight (8/13, 61.5%) of the sequences identified in this study were confirmed to be genotype B, which is the most prevalent in the ROK (Yun et al. 2020). The





**Fig. 6** Genotypes of the severe fever with thrombocytopenia syndrome (SFTS) virus (SFTSV), based on analysis of partial sequences of the small segments (346 bp) of the SFTS viral RNA. Comparison of genotypes of the SFTSV S segment in 13 dogs

remaining five (38.5%) were identified as genotype D, which has not been recently identified in the ROK and is a genotype mainly found in China. After virus isolation and full genome sequencing, all genotypes of Dog 1 and Dog 12 were identified as genotype B, and they were confirmed to correspond to subgenotypes B-3 and B-2, respectively. Subgenotype B-3, to which the sequences of Dogs 1, 2, 3, and 4 in the present study belonged, is not only a human isolate (MK301482, ROK); horse (MT989463, ROK), wild boar (MT502543, ROK), goat, chicken, and cat (MW004853, ROK) have been confirmed to be in the same cluster. This means that subgenotype B-3 is dominant in various animals in the ROK. In our follow-up study, Dog 12, with an SFTSV RNA positive urine sample, was identified as genotype B-2, with confirmation of 96.4% similarity to a human isolate (KP663742, ROK). Dogs 6, 7, 8, 9, and 10, identified as genotype D, showed 99.4%–100.0% similarity, and a human isolate sequence (KP663733, ROK) and a wild boar sequence (MT502563, ROK) were confirmed in the same cluster. When the sequence of a Chinese domestic dog (JQ693003, China) was compared with the sequences of Dogs 6, 7, 8, 9, and 10 in this study, the similarity was found to be consistent at 99.8%–99.1%.

Human and feline patients with SFTS present with symptoms such as fever, thrombocytopenia, encephalitis, multiple organ failure, and death (Kim et al. 2013; Takahashi et al. 2014; Yu et al. 2011). The dogs in the present study showed

some similar symptoms, although there was no case of encephalitis, multiple organ failure, or death. Clinical symptoms occurred as early as 1 day after exposure to ticks. Fever was observed in 57.1% dogs, with severe fever (over 40 °C) occurring only in two dogs. In a previous study in which dogs were experimentally infected with SFTSV, immunosuppressed dogs showed high fever (above 40 °C) while immunocompetent dogs showed slightly elevated fever (above 39.5 °C) (Park et al. 2021). Only one immunocompetent dog had high fever. It can be assumed that the host's immune status influences the severity of fever. In our study of dogs with natural infection, 42.9% did not have fever; however, SFTS was considered because of exposure to ticks. Thrombocytopenia was present in 45.5% dogs, with 27.3% showing a decrease in platelet numbers within the reference range. Only one dog showed hematuria and hematochezia. In feline SFTS, thrombocytopenia was observed in 91.7% (22/24) of cases (Matsuu et al. 2019). Similar to the results observed in the previous study of canine SFTS, in our study, even when thrombocytopenia occurred, severe anemia occurred in only one dog, and most of the dogs did not show anemia (Han et al. 2020; Nam et al. 2020; Park et al. 2021). These findings are comparable to those reported for feline SFTS (Matsuu et al. 2019). In human SFTS, a link between the platelet count and clinical outcome has been suggested; this may be related to the activation of the cytokine network, the vascular endothelium, and the coagulation/fibrinolysis system, rather than virus attachment to platelets (Li et al. 2020).

No deaths from SFTS infection have been reported in canine studies, including the present study (Han et al. 2020; Nam et al. 2020). In the present study, only symptomatic treatment with drugs such as doxycycline and metronidazole was administered, and only one dog with severe anemia required blood transfusion while two dogs were hospitalized for 1 day. All other dogs were managed as outpatients, and most clinical symptoms resolved within 2 weeks. Cats are highly sensitive to SFTSV, with a mortality rate of 62.5% (Matsuno et al. 2018; Matsuu et al. 2019; Park et al. 2019; Sakai et al. 2021; Seto et al. 2020). Moreover, the mortality rate for humans is approximately 20% (Seo et al. 2021). Reported factors associated with poor survival in feline SFTS infection included fever (> 39.5 °C;  $P=0.020$ ) and elevated creatine phosphokinase (CPK) levels ( $P=0.002$ ), SFTSV copy numbers ( $P=0.027$ ), and IgG levels ( $P=0.004$ ) (Matsuu et al. 2019). All cats also developed jaundice, although it was not related to survival ( $P=0.179$ ). In our study, severe fever was observed in only two dogs, and quantitative IgG using ELISA and the CPK levels were not measured; therefore, comparisons cannot be made with cats. IgG was confirmed using IFA, and two dogs showed positivity. Because all dogs survived, it was difficult to determine risk factors for mortality. The severity of fever and disease in viral infections, including SFTS, are cytokine-related, and

cytokine storm is associated with patient prognosis (Deng et al. 2012; Ding et al. 2014b; Hu et al. 2018; Sun et al. 2012, 2014). In human SFTS, an increase in several cytokines such as interferon (IFN)- $\alpha$  (IFN- $\alpha$ ), IFN- $\gamma$ , granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1 $\alpha$ , interleukin-6, and IFN-inducible protein-10 was associated with disease severity. However, there are limited studies involving animals and further research involving a larger number of dogs is required to determine whether dogs exhibit disease characteristics consistent with our findings.

There were no evidence of SFTSV transmission from dogs to other dogs or owners in this study. In the ROK and Japan, cases of SFTSV transmission from companion animals such as dogs (Chung et al. 2020; Kim et al. 2021; Park et al. 2021) and cats (Kida et al. 2019; Tsuru et al. 2021; Yamanaka et al. 2020) to other animals or close human contacts, such as owners or veterinarians, have been reported. The seropositivity rate for veterinarians and nurses working in veterinary hospitals has been reported as 2.2%–4.2%, with positivity despite the absence of clinical symptoms, and this was significantly higher than that reported for healthy blood donors (Ando et al. 2021; Kirino et al. 2021). Human-to-human transmission occurs through close contact with infected body fluids (Kim et al. 2015; Liu et al. 2012; Yoo et al. 2016, 2018), and it can be assumed that transmission between animals occurs in a similar manner (Park et al. 2021). In our study, viral RNA testing was performed for various samples, namely serum and urine samples and oral, eye, nose, and rectal swab samples. For one dog, the viral RNA was detected in the urine. In a previous study of dogs, SFTS viral shedding in the urine and rectal swabs persisted until 16 days after infection (Park et al. 2021). SFTSV invades multiple organs (Huang et al. 2019; Park et al. 2019, 2020). Dogs can function as a reservoir host for SFTSV (Wang et al. 2021), and even if animals and humans are not directly bitten by ticks, infection can occur through various indirect routes. Despite these risks, no treatment strategy has been established for humans and animals. Depending on the patient's symptoms, symptomatic treatments such as fluids, antibiotics, transfusion, antipyretics, G-CSF, intravenous immunoglobulin, plasma exchange, and monoclonal antibodies are available. In humans, the effectiveness of antiviral agents such as ribavirin and favipiravir was reported to be insufficient (Seo et al. 2021). Cytokine storm is an important pathological process in SFTS; however, there is no established treatment protocol for the use of steroids in SFTS and these should be used with caution as the incidence of complications may increase (Jung et al. 2021; Kim et al. 2016; Nakamura et al. 2018). It is necessary to establish a treatment protocol for SFTS and develop effective antiviral agents and vaccines.

In our study, all dogs infected with SFTSV were exposed to ticks in urban parks and trails. This was confirmed by checking the aerial photos obtained by tracking their locations. Therefore, even in urban areas, an area with bushes is likely to be inhabited by ticks because of the entry of abandoned animals and wild animals. Accordingly, even an urban area is not safe in terms of SFTS infection, and parental education, including advice to avoid areas with bushes or instructions on the use of tick repellents during outdoor activities, is necessary to reduce exposure to ticks. When handling tick-exposed animals, personal protective equipment and infection control should be prioritized, and awareness among veterinary personnel should be increased.

This study has some limitations. First, the sample size was small. The clinical characteristics of SFTS may change if a larger scale study is performed. Second, this was not a controlled study in terms of time of diagnosis, examination items, and treatment methods; it was an observational study of patient samples and data from several different veterinary hospitals. It is necessary to study the clinical characteristics and risk factors for survival while testing and treating a larger number of patients in the same environment.

## Conclusions

In the present study of clinical infection with SFTSV in dogs, all dogs received only symptomatic treatment and survived. The clinical course of the dogs was different to that observed in humans and cats. Further studies should identify the reasons for differences in the clinical course of SFTS among species. Even if the severity of SFTSV infection in dogs is mild to moderate, interspecies transmission is possible, so guidelines for the prevention and diagnosis of SFTS in dogs are warranted.

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**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Han SW, and Oh YI. Conceptualization: Han SW, Chae JS; Methodology and Data curation: Han SW; Formal analysis: Han SW, Oh, YI; Funding acquisition: Chae JS; Investigation: Han SW; Project administration: Chae JS; Resources: Rim JM, Cho YK, Kim DH, Kang JG; Supervision: Choi KS, Chae JS; Validation: Han SW, Oh YI, Chae JS; Writing—original draft: Han SW, Oh YI; Writing—review and editing: Han SW, Oh YI.

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**Data availability** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval** This study was approved by the Seoul National University Institutional Animal Care and Use Committee (IACUC No. SNU-190617–6) and conducted in strict accordance with the recommendations in the National Guideline.

**Consent to participate** The owners of the dogs provided informed consent.

**Consent for publication** Not applicable.

**Competing interests** The authors have no conflict of interest.

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