International Journal of Infectious Diseases 171 (2026) 109020

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Long-term kinetics of IgG, IgM, and neutralizing antibodies in patients with severe fever with thrombocytopenia syndrome: A 5-year follow-up study

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ARTICLE INFO

Article history:
Received 10 April 2026
Revised 24 July 2026
Accepted 28 July 2026

Keywords:
Severe fever with thrombocytopenia syndrome
Serological response
Indirect immunofluorescence assay
Enzyme-linked immunosorbent assay
Neutralizing antibody

ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is a life-threatening tick-borne disease endemic to East Asia. Despite its high fatality rate and increasing incidence, the long-term kinetics of humoral immune responses in patients with SFTS remain poorly understood.

Methods: We analyzed serum from 109 patients hospitalized with SFTS between 2015 and 2023. Antibody responses were assessed using indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and plaque reduction neutralization test (PRNT). Antibody kinetics were described by outcome, but time-to-seroconversion was not compared because follow-up differed before death.

Results: The SFTSV viral load peaked within 1-9 days after symptom onset, before declining. SFTSV-specific IgG antibodies were detected by IFA from days 5-9 and by ELISA from days 10-14, peaking on days 20-24. IgM responses appeared later, peaking on days 20-24 (IFA) and 25-29 (ELISA). Neutralizing antibodies ($PRNT_{50} \geq 1:10$) emerged from day 10 and peaked on days 20-24. SFTSV-specific IgG and neutralizing antibodies remained detectable for up to 5 years, with all patients evaluated at the 5-year follow-up remaining seropositive (3/3). Seroconversion of IgG and neutralizing antibodies occurred only in survivors and was absent in fatal cases. IgM responses were completely undetectable in fatal patients.

Conclusion: SFTSV-specific binding and neutralizing antibodies developed strongly in survivors and persisted for up to 5 years. Seroconversion was not detected in fatal cases, although this may reflect limited follow-up. These findings indicate a link between early humoral responses and clinical outcomes, but do not establish protective immunity.

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https://doi.org/10.1016/j.ijid.2026.109020
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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging zoonotic disease caused by SFTS virus (SFTSV), which belongs to the genus *Bandavirus*, family *Phenuiviridae*, and order *Bunyanirales*. The disease is primarily transmitted by ticks, particularly *Haemaphysalis longicornis* [1]. Since it was first reported in China in 2011 [1], SFTS has been identified in South Korea and Japan in 2013 [2,3]. It is now endemic in China, South Korea, and Japan, with a fatality rate of approximately 20%-30% [4,5]. SFTS remains a life-threatening infectious disease with no specific antiviral treatment, posing a significant public health concern in East Asia [6,7]. Additionally, climate change and the expansion of tick habitats, particularly of *H. longicornis*, have increased the risk of SFTSV transmission [8,9].

The immune response plays a critical role in the pathogenesis of SFTS [10]. A better understanding of host immune responses to SFTSV is essential for improving diagnostic accuracy, guiding clinical management, and developing effective preventive strategies [11,12]. Although previous studies have focused primarily on viral kinetics during the acute phase of SFTS, data on long-term antibody responses remain limited [13]. To address this knowledge gap, we conducted a comprehensive 5-year follow-up study of antibody responses in SFTS survivors, aiming to characterize the long-term persistence of humoral antibody responses. Furthermore, by comparing antibody responses between survivors and fatal cases [14]. We sought to highlight the prognostic potential of serological markers in disease outcomes.

Despite the critical role of neutralizing antibodies in viral clearance, longitudinal studies evaluating the kinetics of binding and neutralizing antibodies after SFTSV infection remain limited. Therefore, we conducted a 5-year follow-up study to characterize the kinetics of SFTSV-specific IgG, IgM, and neutralizing antibodies from acute infection through long-term convalescence and compared humoral responses between survivors and fatal cases to explore their prognostic significance. This study offers a comprehensive temporal profile of immune responses in SFTS, spanning from acute infection to long-term convalescence.

Methods

Sample collection

We collected blood samples from 109 patients hospitalized with SFTS from June 2015 to October 2023 in South Korea. Long-term follow-up samples were collected opportunistically during routine outpatient visits rather than at predetermined intervals. Consequently, participants contributing samples at each follow-up time point were not necessarily the same, and the long-term data did not constitute a complete paired longitudinal cohort. Three survivors had serum samples available at the 5-year follow-up. SFTS was confirmed by detecting SFTSV RNA in plasma using real-time reverse transcription polymerase chain reaction (RT-PCR). The study protocol was approved by the Institutional Review Board of Chosun University (Permit Nos. 2013-10-001 and 2021-10-001). All participants provided written informed consent to participate in the study. All experiments were performed in accordance with the relevant guidelines and regulations.

Quantification of SFTSV RNA

SFTSV RNA in plasma specimens was confirmed using the Bioneer Exicycler 96 Real-time PCR kit (Bioneer Inc., Korea) by real-time RT-PCR. The nucleocapsid protein (NP) gene of the S segment was amplified from the RNA template using the following primers: SQ-F (5′-ACCTCTTTGACCCTGAGTTWGACA-3′), SQ-R (5′-CTGAAGGAGACAGGTGGAGATGA-3′) and probe (5′-[FAM] TGC-CTTGACGATCTTA [BHQ1]-3′). A standard curve was generated by determining the copy number from serial dilutions (10^1-10^8 copies) of the target gene-cloned plasmid. cDNA was synthesized as follows: 50°C for 30 minutes, 95°C for 10 minutes; PCR amplification was performed as follows: 45 cycles at 95°C for 15 seconds and 60°C for 45 seconds. Viral RNA concentrations were expressed as log10 copies/ml based on the standard curve generated from serial plasmid dilutions.

Enzyme-linked immunosorbent assay (ELISA)

The IgG and IgM levels of the patients with SFTS were measured using indirect ELISA with NP recombinant protein of SFTSV as the antigen. After adding 0.2 μg NP recombinant protein to each well of the ELISA plate overnight at 4°C, the wells were washed with phosphate-buffered saline with 0.05% Tween 20 (PBS-T) solution followed by the addition of 5% skimmed milk in PBS-T for blocking. The patient's serum (1:100 dilution) was added in triplicate for reaction with the antigen protein at 37°C for 2 hours. After washing, the diluted horseradish peroxidase-conjugated goat anti-human IgG (Cat No. 628420, Thermo Fisher Scientific, Waltham, MA, USA) and goat anti-human IgM (Cat No. bs-0345G-HRP, Bioss, Woburn, MA, USA), as secondary antibodies, were incubated at 37°C for 1 hour. After washing, 50 μl of 3,3′-, 5,5′-tetramethylbenzidine substrate solution was added to each well and incubated at 20-25°C for 30 minutes. Then, 25 μl of 1 N H_2SO_4 was added to stop the reaction. Subsequently, the absorbance at 450 nm (A_{450}) was measured. An A_{450} value of mean + 3 standard deviations or more was established as the positive cutoff value using ELISA on clinical samples from 25 individuals who underwent health screening.

Indirect immunofluorescence assay (IFA)

To perform the IFA, the SFTSV strain KADGH/2013/Korea obtained from the Korea Disease Control and Prevention Agency was used to infect Vero E6 cells (Korean Cell Line Bank, KCLB No. 21587). To prepare the SFTSV antigen slide, cells infected for 3 days were cultured overnight on Teflon-coated well slides at 37°C in a 5% CO_2 environment and fixed with 80% acetone the next day. The patient's serum was diluted using a two-fold serial dilution from 1:32 and then reacted with SFTSV antigens in a moist chamber for 30 minutes at 37°C. After washing, the slides were further incubated with secondary antibodies at 1:400 dilution (fluorescein isothiocyanate-conjugated anti-human IgG and IgM; MP Biomedicals, OH, USA). The slides were examined using a fluorescence microscope (Olympus IX73, magnification: 400×) after dispensing the mounting solution (Vector Laboratories). An IgG and IgM antibody titer of ≥1:32 was established as the cutoff value using IFA on clinical samples from 25 individuals who underwent health screening.

Plaque reduction neutralization test

For detection of SFTSV neutralizing antibodies, 100 μl of four-fold serially diluted test serum was mixed with 100 μl of 100 plaque-forming units of the SFTSV strain KADGH/2013/Korea and incubated at 37°C for 1 hour. The virus:serum mixture (100 μl) was added to Vero E6 cells, and adsorption was performed at 37°C in an incubator with 5% CO_2 for 1 hour, after which a 1% methylcellulose overlay prepared in cell culture maintenance medium (Dulbecco's modified Eagle's medium, 2.5% heat-inactivated fetal bovine serum) was applied. At 14 days postinfection, the inverse of the highest dilution of serum providing 50% ($PRNT_{50}$) viral plaque reduction relative to the virus-only infection was reported as the

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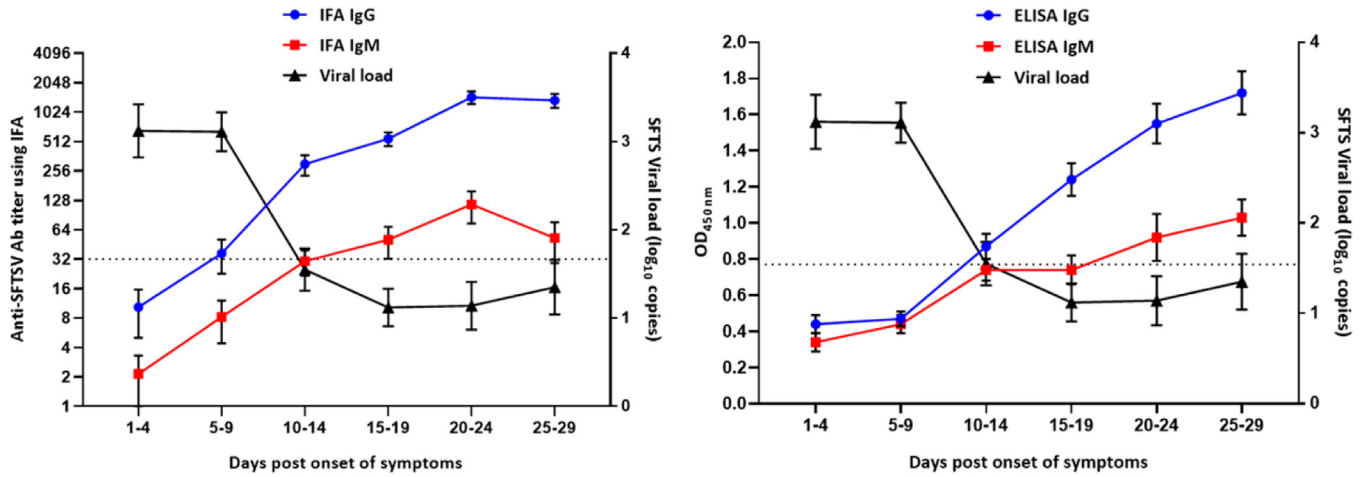


Figure 1. Kinetics of viremia and antibody response of SFTSV-IgG and IgM in IFA (left) and ELISA (right) according to the days postonset of symptoms. Data are denoted as the mean with standard error of mean (SEM). ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; SEM, standard error of the mean; SFTSV, severe fever with thrombocytopenia syndrome virus.

titer. A 1:10 dilution was considered the lowest possible significant titer. All cell culture infection experiments were performed in a biosafety level 3 laboratory at the Health and Environment Research Institute of Gwangju City.

Data analysis

Statistical analyses were performed using GraphPad Prism 8.0.1 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). Data on 50% viral plaque reduction relative to virus-only infection ($PRNT_{50}$) were analyzed by nonlinear regression analysis at 50% inhibition concentration (IC_{50}) using GraphPad Prism 8.0.1. Comparisons among multiple groups were performed using the Kruskal–Wallis test with Dunn's multiple comparisons test. Comparisons between two groups were performed using the Mann–Whitney *U* test. Statistical significance was defined as $P < 0.05$. The Kaplan–Meier method was used to estimate time to seroconversion among survivors using SPSS Statistics 26. Patients who did not undergo seroconversion during available follow-up were censored at the time of their last serum sample. Formal comparisons of time to seroconversion between survivors and fatal cases were not performed because all fatal cases had their final observation before day 14, leaving no fatal participants at risk at the proposed 14-day landmark. Death before seroconversion therefore represented an informative competing event, and reliable landmark or competing-risk estimates could not be obtained.

Results

Viremia and antibody responses in patients with SFTS

A total of 109 patients with laboratory-confirmed SFTS were analyzed. The SFTSV viral load ranged from 3.07 to 3.20 log10 copies/ml on days 1-9 after symptom onset and declined thereafter over the course of the disease. SFTSV-specific IgG antibodies, as detected by IFA (cutoff $\geq$ 1:32), became detectable on days 5-9, while IgG positivity by ELISA (cutoff $A_{450} \geq 0.75$) was observed from days 10-14. IgM antibodies, as assessed by IFA (cutoff $\geq$ 1:32), were detected on days 15-19, and IgM by ELISA (cutoff $A_{450} \geq 0.77$) was detected on days 20-24. The titers of SFTSV-specific IgG and IgM measured by IFA peaked on days 20-24 (mean $\pm$ SEM; IgG titer: 1:1416 $\pm$ 189.6; IgM titer: 1:132.8 $\pm$ 40.23), while the ELISA readings peaked on days 25-29 (IgG A_{450}: 1.57 $\pm$ 0.17; IgM A_{450}: 0.92 $\pm$ 0.13). Detailed kinetic data for viral load and antibody responses using IFA and ELISA are shown in Figure 1.

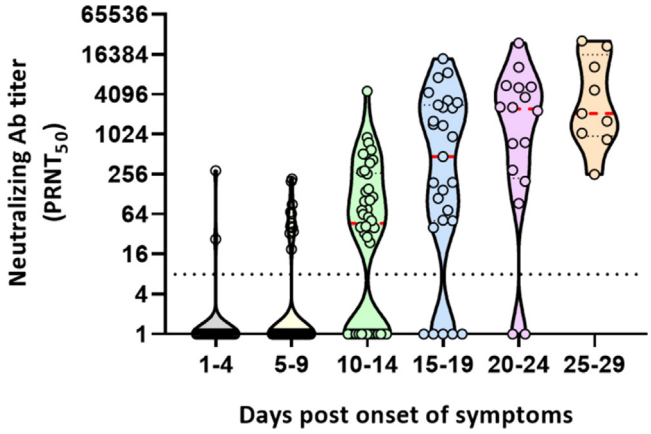


Figure 2. Neutralizing antibody response in patients according to the days postonset of symptoms. The dotted lines indicate the detection limit of 1:10. The red line in the plot denotes the median. SFTSV, severe fever with thrombocytopenia syndrome virus.

Neutralizing antibody responses in patients with SFTS

Serum samples from 109 patients were evaluated using plaque reduction neutralization test (PRNT). The highest serum dilution that reduced plaque numbers by 50% ($PRNT_{50}$) was determined, with seropositivity defined at a titer of $\geq$1:10 (Figure 2). The median neutralizing antibody titer was <1:10 (positivity rate: 7.4%, 2/27) on days 1-4 after symptom onset, increasing to 1:46.5 (95% confidence interval [CI]: 0-264; positivity rate: 64.3%, 27/42) on days 10-14. Peak neutralization occurred on days 20-24 after symptom onset (median $PRNT_{50}$ titer: 1:2469; 95% CI: 225-5312), with 87.5% (14/16) of serum samples testing positive (Figure 2, Supplementary Tables 1 and 2).

Time-dependent seropositivity rates

Seropositivity for SFTSV-specific antibodies increased progressively after symptom onset. By IFA (cutoff $\geq$ 1:32), the IgG seropositivity rates were 72.4% (42/58), 86.8% (33/38), 90.0% (18/20), and 100% (13/13) on days 10-14, 15-19, 20-24, and 25-29, respectively.

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Table 1
Seropositivity rates of SFTSV-specific IgG, IgM, and neutralizing antibodies according to days after symptom onset.

	Seropositivity (%)						
	Days postonset of symptoms	1-4	5-9	10-14	15-19	20-24	25-29
IFA	**IgG (≥1:32)**	7/35 (20%)	32/69 (46.4%)	42/58 (72.4%)	33/38 (86.8%)	18/20 (90%)	13/13 (100%)
	IgM (≥1:32)	1/35 (2.9%)	5/69 (7.2%)	16/58 (27.6%)	16/38 (42.1%)	15/20 (75%)	8/13 (61.5%)
	IgG or IgM	7/35 (20%)	34/69 (49.3%)	42/58 (72.4%)	33/38 (86.8%)	18/20 (90%)	13/13 (100%)
ELISA	**IgG (A_{450} ≥ 0.75)**	4/32 (12.5%)	9/67 (13.4%)	29/56 (51.8%)	27/36 (75%)	17/18 (94.4%)	11/12 (91.7%)
	IgM (A_{450} ≥ 0.77)	3/32 (9.4%)	11/67 (16.4%)	17/56 (30.4%)	14/36 (38.9%)	10/18 (55.6%)	8/12 (66.7%)
	IgG or IgM	7/32 (21.9%)	19/67 (28.4%)	33/56 (58.9%)	29/36 (80.6%)	17/18 (94.4%)	11/12 (91.7%)
$PRNT_{50}$	**$PRNT_{50}$ (≥1:10)**	2/27 (7.4%)	11/54 (20.4%)	27/42 (64.3%)	22/27 (81.5%)	14/16 (87.5%)	9/9 (100%)

Values are presented as the number of positive samples/numbers of tested samples (%). The number of tested samples varied among time points because serum samples were collected at different stages of illness.
A_{450}, optical density at 450 nm; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; $PRNT_{50}$, 50% inhibition of plaque reduction neutralizing test.

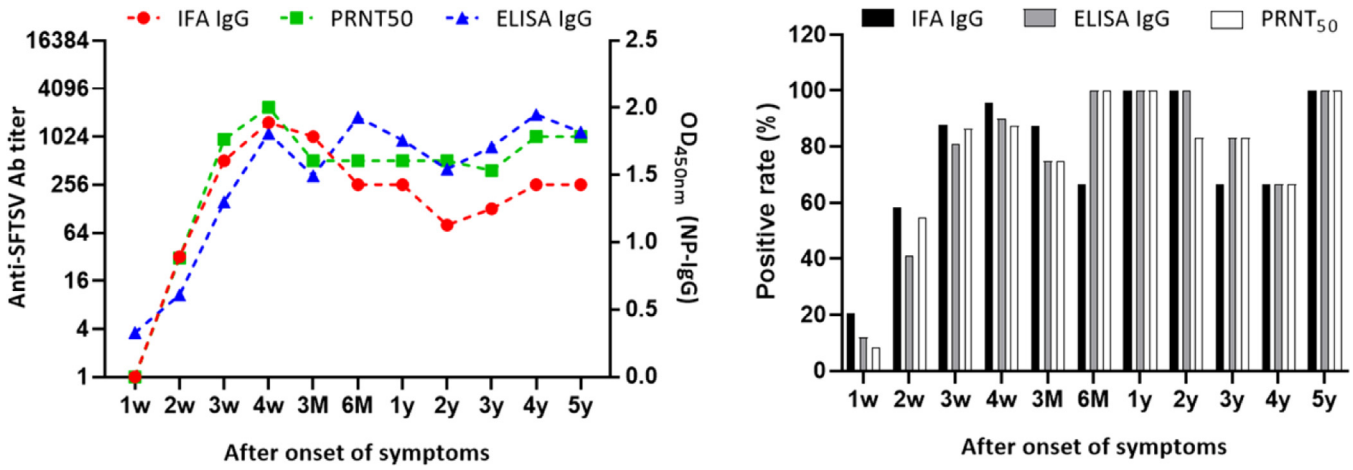


Figure 3. Long-term kinetics and seropositivity rates of SFTSV-specific IgG and neutralizing antibodies up to 5 years after symptom onset. IgG, immunoglobulin G; $PRNT_{50}$, 50% inhibition of plaque reduction neutralizing test; SFTSV, severe fever with thrombocytopenia syndrome virus.

The IgM seropositivity increased more gradually, with rates of 27.6% (16/58), 42.1% (16/38), 75.0% (15/20), and 61.5% (8/13) over the same intervals. The proportion of patients who were positive for either IgG or IgM by IFA reached 100% (13/13) on days 25-29.

For ELISA (cutoffs: IgG A_{450} ≥ 0.75 and IgM A_{450} ≥ 0.77), IgG seropositivity rates were 51.8% (29/56), 75.0% (27/36), 94.4% (17/18), and 91.7% (11/12) on days 10-14, 15-19, 20-24, and 25-29, respectively. The corresponding IgM seropositivity rates were 30.4% (17/56), 38.9% (14/36), 55.6% (10/18), and 66.7% (8/12). The seropositivity for either IgG or IgM by ELISA reached 91.7% (11/12) on days 25-29. Neutralizing antibody responses, assessed by $PRNT_{50}$ (cutoff ≥ 1:10), followed similar trends, with positivity rates of 64.3% (27/42), 81.5% (22/27), 87.5% (14/16), and 100% (9/9) on days 10-14, 15-19, 20-24, and 25-29, respectively (Table 1).

Kinetics of antibody responses in patients with SFTS up to 5 years after symptom onset

SFTSV-specific IgG titers by IFA peaked at 4 weeks postonset (median: 1:1536; 95% CI: 1024-2048), with a positivity rate of 95.8% (23/24). Although the titers declined thereafter, detectable IgG responses were observed up to 5 years after symptom onset (median: 1:256; 95% CI: 128-512), with all available patients remaining seropositive (3/3). Similarly, ELISA-based IgG responses remained detectable at the 5-year follow-up in all available patients (3/3) (Figure 3, Supplementary Table 3). The neutralizing antibody titers assessed by $PRNT_{50}$ also peaked at 4 weeks (median: 1:2383; 95% CI: 745-12751; 87.5% positivity, 14/16), declined after 3 months (median: 312), but remained detectable for up to 5 years. The positivity rates were 75% (6/8) at 3 months, 100% (3/3) at both 6 months and 1 year, 83.3% (5/6) at 2 and 3 years, 66.7% (2/3) at 4 years, and 100% (3/3) at 5 years (Figure 3, Supplementary Table 3). However, these long-term findings should be interpreted cautiously because only three participants were available for evaluation at the 5-year follow-up, resulting in imprecise estimates of seropositivity and antibody titers. Furthermore, the $PRNT_{50}$ positivity rates at years 4 and 5 were based on very small and not necessarily identical groups of participants; therefore, the apparent fluctuation should not be interpreted as a true temporal increase in neutralizing antibody persistence.

Antibody responses and seroconversion in survivor and fatal cases

The SFTSV-specific antibody responses were markedly low or absent in fatal cases throughout the disease course. IgM was undetectable in fatal cases across all time points by both IFA and ELISA. In contrast, survivors showed clear seroconversion. SFTSV-specific IgG was detectable by 2 weeks postonset in survivors (median: 1:64; 95% CI: 1-256), increasing to 2048 (95% CI: 1024-2048) at 4 weeks (Figure 4a, b, Supplementary Table 4). The neutralizing antibody titers increased from 33 (95% CI: 1-128.5) at 2 weeks to 2383 (95% CI: 773-12,236) at 4 weeks in survivors but remained undetectable in fatal cases (Figure 4c, Supplementary Table 4).

Seroconversion of SFTSV-specific IgG and neutralizing antibodies was assessed among survivors using serum samples collected within 35 days after symptom onset (Figure 5). Among survivors, the median time to IgG seroconversion was 16 days by IFA (95% CI, 13.9-18.0), and the median time to $PRNT_{50}$ seroconversion was

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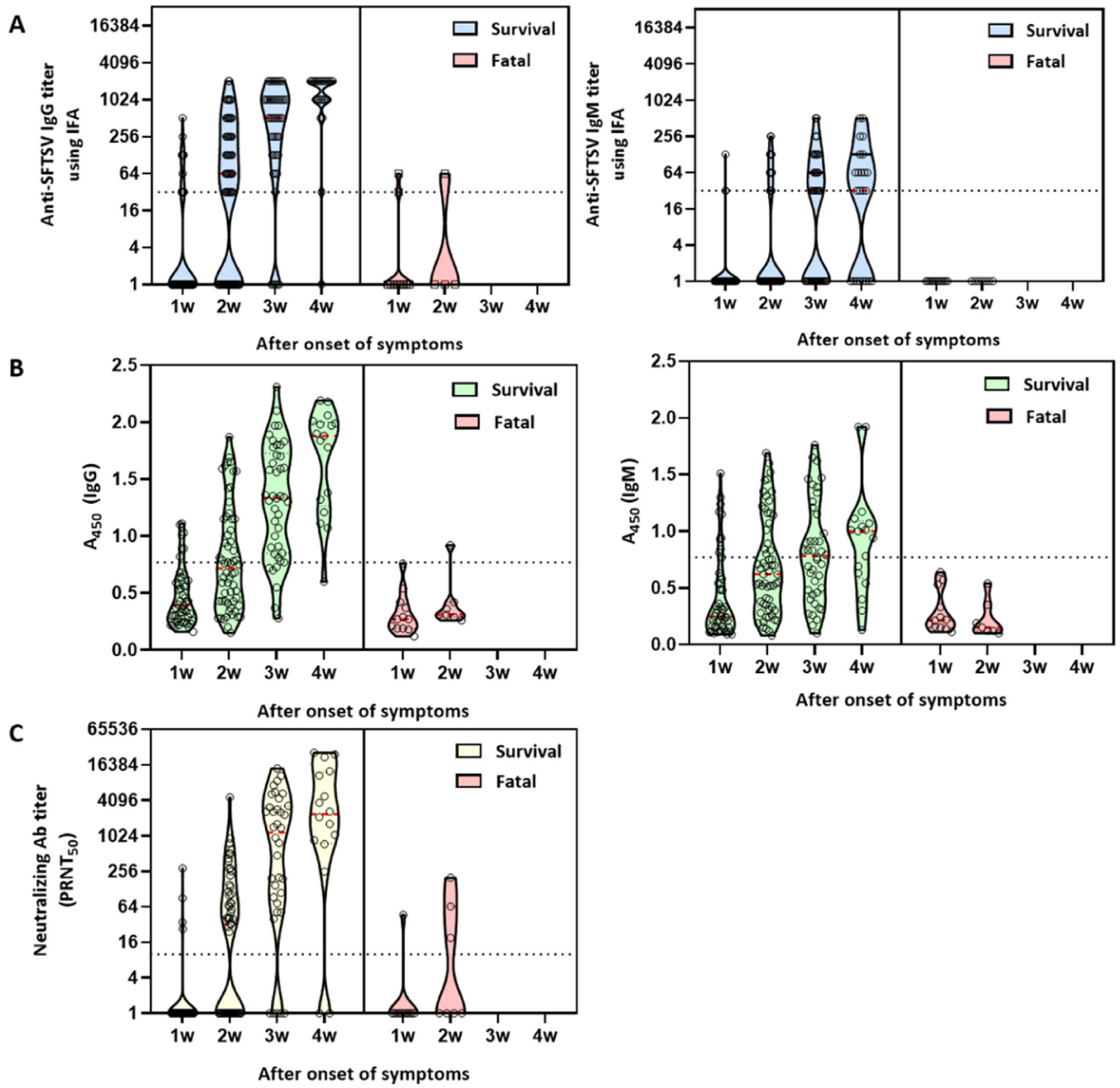


Figure 4. Antibody responses of SFTSV-specific IgG, IgM, and $PRNT_{50}$ after symptom onset in survivors and fatal cases. (a) Antibody response of SFTSV-IgG and IgM using IFA. The dotted lines indicate the detection limit of 1:32. (b) Antibody response of SFTSV-IgG and IgM using ELISA. The dotted lines indicate that the detection limit is A_{450} 0.75 and 0.77 for IgG and IgM, respectively. (c) Neutralizing antibody response. The dotted lines indicate the detection limit of 1:10. The red line in the plot denotes the median. ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; $PRNT_{50}$, 50% inhibition of plaque reduction neutralizing test; SFTSV, severe fever with thrombocytopenia syndrome virus.

18 days (95% CI, 16.4-19.6). Formal comparisons of time to seroconversion between survivors and fatal cases were not performed because all fatal cases had their final observation before day 14, leaving no fatal participants at risk at the proposed 14-day landmark. Death before seroconversion therefore represented an informative competing event, and reliable landmark or competing-risk estimates could not be obtained.

Discussion

This study provides a comprehensive longitudinal analysis of SFTSV-specific antibody responses—including IgG, IgM, and neutralizing antibodies—tracking their kinetics from the acute phase through long-term recovery over 5 years in patients with SFTS. Our findings demonstrate that SFTSV–specific IgG responses measured by IFA emerge from days 5-9 after symptom onset, while IgM appears from days 15-19, with both reaching peak levels at around 3 weeks (Figure 1). These findings align with those of prior studies and highlight the importance of considering the delayed IgM response to SFTSV in the disease course [15,16].

Neutralizing antibodies became detectable on days 10-14 after symptom onset, peaked at days 20-24, and persisted for up to 5 years in survivors, suggesting sustained humoral immune responses (Figures 2 and 3). Although antibody titers gradually

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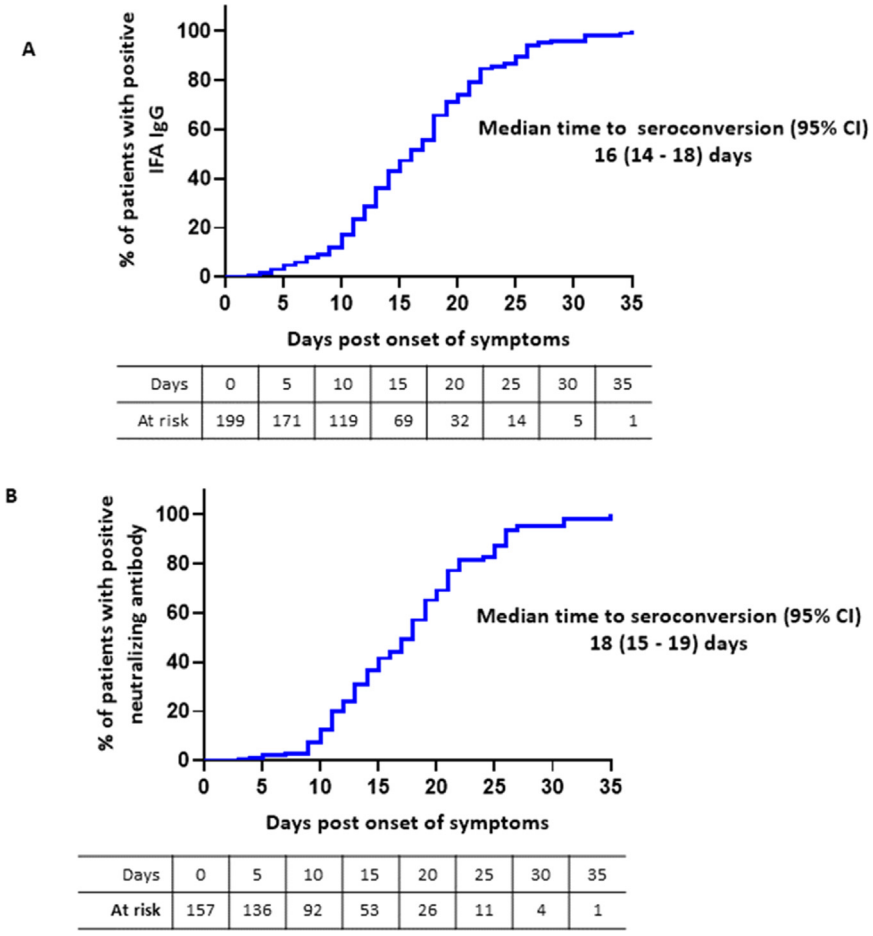


Figure 5. Time to SFTSV-specific antibody seroconversion among survivors. Kaplan–Meier curves show the cumulative probability of seroconversion for SFTSV-specific IgG, measured by indirect immunofluorescence assay (IFA) (a), and neutralizing antibodies, measured by the 50% plaque reduction neutralization test ($PRNT_{50}$) (b), among survivors within 35 days after symptom onset. Seroconversion was defined as an IFA IgG titer of ≥1:32 or a $PRNT_{50}$ titer of ≥1:10. Numbers at risk are shown below each panel, and median seroconversion times are presented with 95% confidence intervals. Formal comparisons with fatal cases were not performed because many fatal cases died before the expected seroconversion window, precluding a reliable time-to-event comparison.

declined over time, detectable IgG and neutralizing antibody responses were observed for up to 5 years among the available participants, suggesting durable immune responses. However, because cellular immune responses, cross-strain neutralization, and immune correlates of protection were not evaluated, the persistence of these antibodies should not be interpreted as evidence of protection against reinfection. A prior study reported that neutralizing antibody was initially detected at 15 days after symptom onset in surviving patients with SFTS, peaked at 2 months, and then gradually declined, persisting for up to 10 years [13,17]. The long-term persistence of neutralizing antibodies observed in our study is consistent with durable humoral immune responses that may be maintained in survivors [14,17,18]. However, because cellular immune responses and immune correlates of protection were not evaluated, these findings should not be interpreted as evidence of protective immunity against reinfection.

A key finding of our study was the distinct pattern of antibody responses observed between survivors and fatal cases. Although early-phase statistically significant differences were not consistently observed during the first week after symptom onset due to the few fatal cases and limited follow-up, survivors showed progressive increases in SFTSV-specific IgG and neutralizing antibody responses, whereas seroconversion was not observed in the available samples from fatal cases. However, many fatal cases died before or near the expected seroconversion window observed in survivors (Figures 4 and 5, Supplementary Table 4). Therefore, the absence of observed seroconversion in fatal cases cannot be directly interpreted as definitive evidence of failed humoral immunity. Differential survival and follow-up precluded a reliable comparison of time to seroconversion between the two groups. The observed pattern may reflect both impaired virus-specific humoral responses and insufficient observation time before death [13,15,17,18]. Larger prospective studies with standardized serial sampling and an adequate number of patients surviving beyond the seroconversion window are required to determine the prognostic significance of early antibody responses.

Notably, neutralizing antibodies persisted in some survivors for up to 5 years, indicating durable humoral responses after natural infection. However, whether these antibody responses confer long-term protection remains unknown because cellular immunity and immune correlates of protection were not assessed. This should be considered when interpreting seroconversion-based comparisons between groups. The distinct antibody kinetics between survivors and fatal cases may reflect fundamental differences in host immune responses, viral replication dynamics, or disease severity [14,15,19].

Among the available samples from fatal cases, SFTSV-specific IgG, IgM, and neutralizing antibodies were largely undetectable (Figure 4). This pattern may be consistent with impaired B cell-mediated humoral responses; however, the short observation period before death precludes a definitive conclusion. Previous studies have proposed that failure of IgG seroconversion in fatal cases

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may be due to defective class-switch recombination [16,20,21]. The absence of detectable IgM in the available fatal-case samples may suggest abnormalities not only in class-switch recombination but also in the initial activation or expansion of virus-specific B cells, although this interpretation requires confirmation in prospectively sampled cohorts. The serological profile in fatal cases was characterized by absent or low SFTSV-specific IgG responses measured using NP ELISA and whole-virus IFA, together with undetectable neutralizing activity in the available samples. Recent studies have also shown that class-switched IgG^+ B cells are more susceptible to SFTSV infection than class-unswitched IgM^+ B cells. This may contribute to the disruption of effective plasmablast responses and the emergence of dysfunctional B-cell subsets in fatal SFTS [22].

The study has implications for vaccine development. Given the lack of an approved SFTS vaccine, understanding long-term immune responses is essential for designing effective immunization strategies [23,24]. Our findings suggest that an ideal vaccine should elicit durable neutralizing antibody responses, although the contribution of cellular immunity and the immune correlates required for protection remain to be defined. Future studies should investigate the persistence and effectiveness of vaccine-induced immunity in comparison to natural infection.

Despite these important findings, our study has certain limitations. First, although follow-up was performed for up to 5 years, only three participants were available for evaluation at the final follow-up time point, resulting in imprecise estimates and limiting the generalizability of the long-term findings. In addition, follow-up samples were collected opportunistically, and participants differed across follow-up time points; therefore, the data do not represent a complete paired longitudinal cohort. Consequently, the estimates of long-term antibody persistence are based on a limited sample size with wide confidence intervals and should be interpreted cautiously. The apparent fluctuation in $PRNT_{50}$ positivity between years 4 and 5 likely reflects random variation resulting from the very small and partially nonoverlapping samples at the late follow-up time points, rather than a biologically meaningful rebound in neutralizing antibody responses. Larger prospective longitudinal studies with standardized serial sampling are needed to confirm the durability of antibody responses beyond 5 years. Second, cellular immune responses, including SFTSV-specific T-cell responses, were not assessed in this study. Therefore, although durable antibody responses were observed, the immune correlates of protection against SFTSV remain unknown, and protective immunity cannot be inferred from antibody measurements alone. A comprehensive analysis of both humoral and cellular immunity would provide a more complete understanding of immune protection against SFTSV. Future studies with larger sample sizes and cellular immunity profiling may provide further insights into protective correlates against SFTSV.

In conclusion, this study provides a comprehensive analysis of SFTSV-specific antibody responses, tracking the kinetics of IgG, IgM, and neutralizing antibodies from the acute phase to long-term recovery. SFTSV-specific binding and neutralizing antibodies remained detectable for up to 5 years among the limited number of participants available for long-term evaluation, with neutralizing titers peaking at 4 weeks postonset and remaining detectable thereafter. These findings suggest the potential for durable humoral immune responses following natural infection. However, further studies incorporating cellular immune responses are required to determine whether these sustained antibody responses translate into long-term protective immunity. In contrast, seroconversion was not observed in the available samples from fatal cases; however, many fatal cases died before the expected seroconversion window, preventing a reliable comparison of seroconversion timing or rates between survivors and fatal cases. Therefore, early humoral responses may be associated with clinical outcome, but their independent prognostic significance cannot be established from the present data and requires confirmation in larger prospective studies. These findings have significant implications for SFTS diagnosis, prognosis, and vaccine development and underscore the need for further research into long-term immune protection and correlates of survival.

Key points

SFTS survivors developed sustained IgG and neutralizing antibody responses that persisted for up to 5 years. In contrast, seroconversion was not observed in fatal cases, although interpretation is limited by their shorter follow-up before death. These findings suggest that early humoral responses may be associated with favorable clinical outcomes.

Funding

This study was supported by a research fund from Chosun University Hospital 2025.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2026.109020.

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