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Acute kidney injury as a prognostic marker in severe fever with thrombocytopenia syndrome

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Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne illness with a notable morality risk that is becoming increasingly prevalent in East Asia (14–36%). Increasing evidence indicates a more direct role of the SFTS virus in renal impairment. However, few studies have explored the risk factors for and clinical outcomes of AKI in patients with SFTS. Therefore, in this study, we aimed to investigate risk factors and outcomes associated with AKI in patients with SFTS. In this retrospective cohort study, we included the data of 53 patients who were diagnosed with SFTS virus infection at Kangwon National University Hospital between 2016 and 2020. We incorporated laboratory data and medical information including comorbidities, complications, and mortality. Baseline characteristics, clinical features, laboratory parameters, and mortality rates of the non-AKI and AKI groups were compared. Patient survival of non-AKI and AKI groups were compared using the Kaplan–Meier method. To identify the population with poor prognosis, Cox regression analysis was used to identify the independent risk factors for in-hospital mortality in patients with SFTS. Of the 53 individuals, 29 (54.7%) were male, with an average age of 66.5 years. Nine patients (15.1%) died of SFTS. Twenty-seven (50.9%) patients exhibited AKI; the average time interval from fever onset to AKI occurrence was 3.6 days. Notably, 24 (88.9%) patients developed AKI within the first week of fever onset. Patients in the AKI group exhibited a significantly higher prevalence of diabetes and were older than those in the non-AKI group. The mortality rate was notably higher (29.6%) in the AKI group than in the non-AKI group (3.8%). Within the AKI cohort, advanced stages (stages 2 and 3) showed a 50% mortality rate, which was significantly higher than the 17.6% mortality rate in patients with stage 1 AKI. Additionally, Kaplan–Meier curves revealed lower survival rates among patients with AKI than among those without AKI ($P = 0.017$). Cox regression analysis identified leukopenia and elevated serum creatinine levels as significant risk factors for mortality. AKI is a common complication associated with SFTS. Moreover, the mortality rate was significantly higher in the patients who developed AKI than in those who did not. Our findings underscore the pivotal role of AKI as a prognostic marker of disease severity in patients with SFTS.

Keywords Acute kidney injury, Severe fever with thrombocytopenia syndrome, Risk factors, Mortality

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging febrile illness caused by the Dabie bandavirus, a segmented negative stranded RNA virus. Formerly known as the SFTS virus (SFTSV), it belongs to the genus Bandavirus, within the family Phenuiviridae, and order Bunyavirales. The disease first emerged in China in 2009[1], and subsequently, cases have been reported in South Korea[2], Japan[3], Vietnam[4], and Taiwan[5]. SFTSV is a zoonotic disease primarily transmitted by ticks such as *Haemaphysalis longicornis*. Clinical manifestations of SFTS include high fever, lymphadenopathy, thrombocytopenia, elevated hepatic enzyme levels, gastrointestinal disturbances, and hemorrhagic tendencies. In advanced and severe scenarios, patients can progress to multi-organ failure, culminating in a daunting fatality rate that exceeds 30%[6]. Although various risk factors associated

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with mortality have been identified, Jo et al. reported that SFTS viral RNA loads in the plasma can serve as valuable markers for predicting mortality[7].

Acute kidney injury (AKI), a clinical sequela, has been observed in 14–36% of patients with SFTS[8–15]. Initial evidence indicated that AKI was a byproduct of the systemic deterioration observed in SFTS, which was predominantly attributed to multiorgan failure. However, emerging evidence suggests a more direct role for the SFTS virus in renal compromise. Autopsy-based evaluations of renal tissues from patients who died of SFTS detected SFTS viral antigens and nucleic acids using immunohistochemistry and reverse transcriptase-polymerase chain reaction (RT-PCR)[16]. Furthermore, a recent study reported that the viral load excreted through urine via the kidney serves as a reliable predictor of mortality[14]. Therefore, AKI is a common complication that serves as a pivotal clinical marker associated with the pathogenesis of SFTS.

We designed our study to offer an in-depth exploration of AKI's prevalence and implications of AKI in patients with SFTS. Our objectives included a thorough analysis of AKI incidence, a detailed examination of mortality rates stratified by AKI stage, and an overarching investigation into how AKI affects overall mortality in patients with SFTS.

Methods

Ethics statement

This study followed the ethical guidelines outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the Kangwon National University Hospital (KNUH-A-2020–03-016–002). The requirement for informed consent was waived owing to the retrospective nature of the study.

Patients

In accordance with the SFTS screening criteria of Kangwon National University Hospital, we included patients who participated in recent outdoor activities such as farming, hiking, or exposure to ticks or animals, and exhibited clinical symptoms of SFTS, including fever, chills, myalgia, and diarrhea, along with thrombocytopenia. Patients younger than 18 years of age were excluded from the study.

Between January 2016 and December 2020, a total of 381 patients were screened for SFTSV at Kangwon National University Hospital. After excluding 3 patients below 18 years of age, 53 patients were confirmed to have SFTS. Diagnosis was confirmed through detection of the viral nucleic acids in plasma using RT-PCR. We retrospectively reviewed medical records, including demographics, comorbidities, clinical manifestations, laboratory data, and mortality.

In accordance with the prevailing national guidelines, a diagnosis of SFTS is established when patients exhibit distinct clinical symptoms of SFTS alongside one or more of the following laboratory findings: (1) isolation of SFTSV from the patient's blood, (2) detection of virus-specific IgM antibodies in the patient's blood, (3) identification of SFTSV RNA in the blood, and (4) a significant increase in virus-specific antibodies of at least four-fold between acute and convalescent serum samples. The presence of viral nucleic acids in SFTSV was confirmed by RT-PCR, which targeted the glycoprotein and nucleoprotein genes of SFTSV RNA. The test was conducted at the National Institute of Health and Environment according to the guidelines of the Korean Centers for Disease Control and Prevention.

Definition of AKI

We determined the presence and stage of AKI in all patients enrolled in our study.

AKI was defined using serial creatinine values in accordance with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines[17]. AKI stage 1 was defined as 1.5–1.9 times the reference value or an increase of ≥ 0.3 mg/dL. Stage 2 was defined as 2.0 to 2.9 times the reference value. Stage 3 was defined as ≥ 3 times the reference value, an increase of ≥ 4.0 mg/dL, or the initiation of renal replacement therapy. In cases where patients presented to the hospital for the first time or after a long interval and where baseline creatinine values were unavailable, we adhered to the proposed criteria for retrospective diagnosis and staging of AKI suggested by Duff et al.[18]. According to this, AKI stage 1 is defined by a decrease to 0.66–0.49 times from the reference serum creatinine value in the following 7 days, Stage 2 by a decrease to 0.5–0.32 times, and Stage 3 by a decrease to ≤ 0.33 times the reference value or a reduction ≥ 4.0 mg/dL.

Statistical analysis

Clinical manifestations, comorbidities, and laboratory data were analyzed. Baseline characteristics were analyzed using descriptive statistics and were reported as n (proportions, %) or mean ± SD as appropriate. χ^2-test or Fisher's test was used to analyze categorical variables. Analysis of variance (ANOVA) and t-tests were used to analyze continuous variables. Cumulative survival rates were assessed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using Cox regression to identify risk factors for mortality. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS ver9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Seasonal trends and AKI incidence

Between January 2016 and December 2020, 381 patients were screened for SFTSV. Among them, 53 adult patients were diagnosed with SFTS using RT-PCR and were included in the analysis (Fig. 1). Of the 53 patients diagnosed with SFTS, the peak incidence was observed in September and October, which aligned with the patients' hospital visits between May and October (Supplementary Fig. 1).

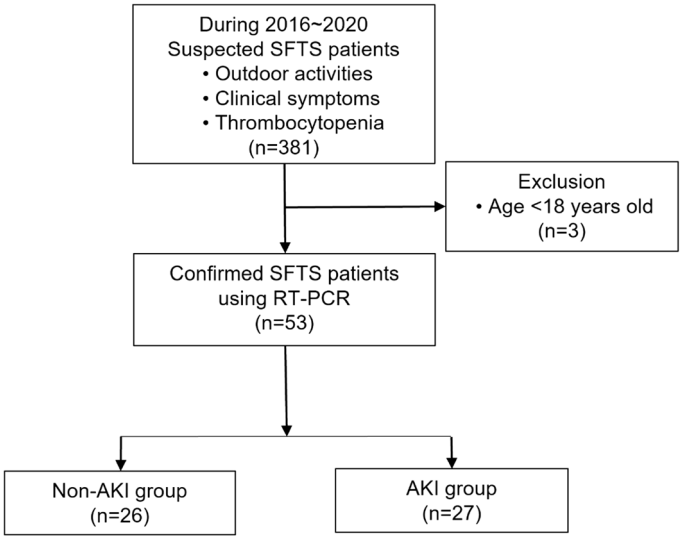

Fig. 1. Flowchart of participant selection. SFTS, severe fever with thrombocytopenia syndrome; RT-PCR, reverse-transcription polymerase chain reaction; AKI, acute kidney injury.

AKI occurred in 27 (50.9%) patients. The distribution of AKI stages revealed that 17 (32.1%) patients were at stage 1 and 10 (18.9%) were at stage 2 or 3. Notably, 5 (9.3%) patients required renal replacement therapy, all of whom required continuous renal replacement therapy (CRRT). The average duration of CRRT was 10 days (range, 2 36 days). Of these five patients, 3 (60%) had hypertension and 3 (60%) had diabetes as underlying conditions.

Of the 27 patients categorized as having AKI, 23 had already developed AKI upon their initial presentation to the hospital. When determining the onset of AKI relative to the fever onset, the data indicated an average duration of 3.9 ± 3.6 days. Additionally, 24 (88.9%) of the 27 patients manifested AKI within one week of fever onset.

Baseline characteristics according to AKI stage

Detailed baseline characteristics categorized according to the AKI stage are presented in Table 1. Among the patients, 54.7% were male, with an average age of 66.5 years. An apparent trend suggested that the severity of AKI was correlated with advancing age ($P = 0.041$). Regarding comorbidities, 45.3% had hypertension, and 20.8% had diabetes mellitus. Patients with advanced AKI had a higher prevalence of diabetes mellitus ($P = 0.019$). Tick-bite lesions were observed in 49.1% of patients.

Fever was the most commonly recorded systemic sign—detected in 90.6% of patients—followed by myalgia and general weakness. General weakness was predominant in the AKI cohort ($P = 0.047$). Gastrointestinal symptoms were also frequently observed; diarrhea was the most common symptom (50.9%), followed by anorexia (45.3%) and nausea (30.2%). Among the neurological symptoms, altered mental status was confirmed in 37.7% of the patients. It was more frequently observed in patients with AKI, and even more so in patients with higher AKI stages ($P = 0.012$).

In laboratory assessments, patients with SFTS exhibit leukopenia, thrombocytopenia, and elevated serum levels of liver enzyme and lactate dehydrogenase (LDH). When stratified by the presence of AKI and its stage, we observed increased levels of blood urea nitrogen (BUN) and serum creatinine in the AKI group ($P = 0.015$ and $P = 0.011$, respectively) (Table 2). Serum sodium levels were similar in both groups; however, serum potassium levels were significantly higher in the AKI stages 2 and 3 groups than in the non-AKI and AKI stage 1 groups ($P = 0.007$). Additionally, serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein were significantly higher in advanced AKI stages. Proteinuria of 1 + or more was found to be significantly higher in the AKI group compared to the non-AKI group ($P = 0.013$).

Complications of SFTS

The spectrum of severe medical complications is shown in Table 3. Hypotension, defined as a systolic blood pressure < 90 mmHg, was prominently observed, accounting for 26.4% of cases. Encephalopathy occurred in 20.8% of patients, whereas pneumonia, mechanical ventilation, and rhabdomyolysis were present in 13.2%. Specifically, complications such as hypotension, mechanical ventilation, and disseminated intravascular coagulation (DIC) were significantly prevalent in the AKI group, with the frequency increasing with higher AKI stages.

The overall mortality rate was 15.1%. The mortality rate significantly increased with AKI severity: 3.8% in the non-AKI group, 17.6% in AKI stage 1, and 50% in AKI stages 2 and 3 ($P = 0.004$) (Supplementary Fig. 2).

A notable observation in this study was the variation in mortality rates depending on the initial point of admission. Of the 53 patients, two were diagnosed and treated at outpatient clinics, 35 were admitted to the infectious disease department, and 16 were admitted across different departments, including nephrology (n = 4) and hepatology (n = 3). We compared the baseline characteristics and initial laboratory values of patients admitted to the infectious disease department and other departments and found that fever was more prevalent in patients

	Total (n = 53)	Non-AKI (n = 26)	AKI stage 1 (n = 17)	AKI stage 2 + 3 (n = 10)	*P*-value
Sex, male (%)	29(54.7%)	15(57.7%)	7(41.2%)	7(70.0%)	0.318
Age, years	66.5 ± 15.5	61.4 ± 17.4	69.5 ± 13.5	74.7 ± 7.7	0.041
Current smoking (%)	41(77.4%)	17(65.4%)	15(88.2%)	9(90.0%)	0.123
Comorbidity					
Hypertension	24(45.3%)	9(34.6%)	9(52.9%)	6(60.0%)	0.291
Diabetes mellitus	11(20.8%)	2(7.7%)	4(23.5%)	5(50.0%)	0.019
Chronic liver disease	5(9.4%)	2(7.7%)	2(11.8%)	1(10.0%)	0.903
Cerebrovascular disease	2(3.8%)	1(3.8%)	1(5.9%)	0(0.0%)	0.741
Heart disease	3(5.7%)	0(0.0%)	3(17.6%)	0(0.0%)	0.034
Solid tumor	4(7.5%)	2(7.7%)	2(11.8%)	0(0.0%)	0.535
Physical findings					
Conjunctival injection	3(5.7%)	1(3.8%)	2(11.8%)	0(0.0%)	0.378
Lymphadenopathy	6(11.3%)	4(15.4%)	2(11.8%)	0(0.0%)	0.426
Tick-bite lesions	26(49.1%)	13(50.0%)	10(58.8%)	3(30.0%)	0.348
Systemic signs and symptoms					
Fever	48(90.6%)	24(92.3%)	16(94.1%)	8(80.0%)	0.438
Myalgia	30(56.6%)	17(65.4%)	8(47.1%)	5(50.0%)	0.444
Back pain	2(3.8%)	1(3.8%)	1(5.9%)	0(0.0%)	0.741
Sore throat	5(9.4%)	3(11.5%)	0(0.0%)	2(20.0%)	0.201
General weakness	26(49.1%)	9(34.6%)	9(52.9%)	8(80.0%)	0.047
Skin rash	7(13.2%)	4(15.4%)	3(17.6%)	0(0.0%)	0.383
Respiratory and cardiovascular signs and symptoms					
Cough	4(7.5%)	1(3.8%)	1(5.9%)	2(20.0%)	0.247
Sputum	6(11.3%)	3(11.5%)	2(11.8%)	1(10.0%)	0.989
Dyspnea	2(3.8%)	0(0.0%)	2(11.8%)	0(0.0%)	0.111
Chest pain	1(1.9%)	1(3.8%)	0(0.0%)	0(0.0%)	0.589
Gastrointestinal signs and symptoms					
Anorexia	24(45.3%)	14(53.8%)	7(41.2%)	3(30.0%)	0.401
Nausea	16(30.2%)	7(26.9%)	7(41.2%)	2(20.0%)	0.450
Vomiting	9(17.0%)	4(15.4%)	3(17.6%)	2(20.0%)	0.943
Diarrhea	27(50.9%)	13(50.0%)	9(52.9%)	5(50.0%)	0.980
Abdominal pain	15(28.3%)	6(23.1%)	6(35.3%)	3(30.0%)	0.679
Hemorrhagic signs and symptoms					
Oral bleeding	2(3.8%)	1(3.8%)	1(5.9%)	0(0.0%)	0.741
Gastrointestinal bleeding	1(1.9%)	0(0.0%)	0(0.0%)	1(10.0%)	0.112
Petechiae	2(3.8%)	0(0.0%)	1(5.9%)	1(10.0%)	0.317
Neurologic signs and symptoms					
Headache	13(24.5%)	8(30.8%)	3(17.6%)	2(20.0%)	0.579
Dizziness	12(22.6%)	6(23.1%)	4(23.5%)	2(20.0%)	0.975
Altered mentality	20(37.7%)	5(19.2%)	8(47.1%)	7(70.0%)	0.012

Table 1. Baseline characteristics of SFTS patients according to AKI stage. **P*-values correspond to comparisons between the non-AKI, AKI stage 1, and AKI stage 2 + 3 groups.

admitted to the infectious disease department, whereas abdominal pain was more common in patients admitted to other departments (Supplementary Table 1). Initial laboratory values, such as white blood cell (WBC) count, blood urea nitrogen (BUN) levels, and serum creatinine levels, were significantly higher in patients hospitalized in other departments (Supplementary Table 2). Patients admitted to the Infectious Disease Department had a lower mortality rate than those admitted to other departments (5.7% vs. 43.8%).

When 27 patients of the AKI group were followed up for one year after discharge, there were 8 deaths, 11 patients were lost to follow-up, and only 1 of the 8 tracked patients was confirmed to have developed chronic kidney disease, with an estimated glomerular filtration rate below 60.

Survival analysis of AKI and non-AKI patients

Kaplan–Meier curves revealed that survival rates were lower in the AKI group than in the non-AKI group (Fig. 2A). Stratification into non-AKI, AKI stage 1, and AKI stages 2 and 3 groups revealed significant differences in survival (log rank $P = 0.002$) (Fig. 2B).

	Total (n = 53)	NonAKI (n = 26)	AKI stage 1 (n = 17)	AKI stage 2 + 3 (n = 10)	*P*-value
WBC ($\times 10^3$/ul)	2.6 ± 2.0	2.3 ± 1	2.7 ± 2.5	3.3 ± 2.5	0.373
Platelet ($\times 10^3$/ul)	79.6 ± 53.2	92.1 ± 67.5	64.9 ± 35.4	71.9 ± 24.0	0.235
BUN (mg/dL)	26.8 ± 19.2	20.0 ± 14.5	29.6 ± 19.5	39.7 ± 23.4	0.015
Creatinine (mg/dL)	1.1 ± 0.6	0.9 ± 0.5	1.2 ± 0.5	1.6 ± 0.7	0.011
Sodium (mEq/L)	136.1 ± 3.7	137.0 ± 2.6	136.1 ± 5.3	134.0 ± 1.9	0.098
Potassium (mEq/L)	4.1 ± 0.6	4.0 ± 0.4	4.0 ± 0.5	4.6 ± 0.7	0.007
Albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.4	3.7 ± 0.4	3.9 ± 0.5	0.409
AST (U/L)	406.6 ± 766.4	202.9 ± 250.1	352.3 ± 469.9	1028.8 ± 1507.2	0.011
ALT (U/L)	130.5 ± 149.8	88.6 ± 88.8	128.8 ± 132.9	242.4 ± 239.5	0.019
ALP (U/L)	101.7 ± 88.3	90.9 ± 67.5	97.8 ± 112.0	136.5 ± 91.7	0.380
TB (mg/dL)	0.5 ± 0.2	0.4 ± 0.1	0.5 ± 0.2	0.6 ± 0.4	0.114
CK (U/L)	923.6 ± 1064.3	988.8 ± 1232.9	711.0 ± 712.2	1107.3 ± 1143.8	0.608
LDH (U/L)	1274.0 ± 1134.6	1110.1 ± 897.2	1130.3 ± 580.4	2035.4 ± 2083.8	0.113
PT (INR)	1.0 ± 0.2	1.0 ± 0.2	1. ± 0.1	1.0 ± 0.1	0.850
PT (sec)	12.8 ± 1.2	12.5 ± 1.0	12.9 ± 1.5	13.2 ± 0.9	0.237
aPTT (sec)	48.6 ± 19.8	45.8 ± 10.8	51.4 ± 28.4	50.9 ± 22.0	0.634
CRP (mg/dL)	0.9 ± 1.3	0.6 ± 0.9	0.8 ± 0.8	2.0 ± 2.1	0.012
Urinalysis, n(%)					
RBC (≥ 5/HPF)	11(22.5)	3(13.6)	7(41.2)	1(10.0)	0.036
WBC (≥ 5/HPF)	10(20.4)	1(4.6)	6(35.3)	3(30.0)	0.095
Protein (≥ 1 +)	40(81.6)	14(63.6)	16(94.1)	10(100.0)	0.013

Table 2. Baseline laboratory values. *AKI* acute kidney injury, *WBC* white blood cell, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *TB* total bilirubin, *CK* creatinine kinase, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastin clotting time, *CRP* C-reactive protein, *RBC* red blood cell, *HPF* high-power field. *Urinalysis was performed on 49 patients. **P*-values correspond to comparisons between the non-AKI, AKI stage 1, and AKI stage 2 + 3 groups.

	Total (n = 53(100.0%))	Non-AKI (n = 26(49.1%))	Stage 1 (n = 17(32.1%))	Stage 2 + 3 (n = 10(18.9%))	*P*-value
Hypotension	14(26.4%)	3(11.5%)	5(29.4%)	6(60.0%)	0.012
Encephalopathy	11(20.8%)	4(15.4%)	5(29.4%)	2(20.0%)	0.540
Pneumonia	7(13.2%)	2(7.7%)	2(11.8%)	3(30.0%)	0.204
Mechanical ventilation	7(13.2%)	0(0.0%)	2(11.8%)	5(50.0%)	< 0.001
Rhabdomyolysis	7(13.2%)	3(11.5%)	3(17.6%)	1(10.0%)	0.800
Arrhythmia	6(11.3%)	2(7.7%)	3(17.6%)	1(10.0%)	0.596
Pulmonary congestion	4(7.5%)	1(3.8%)	3(17.6%)	0(0.0%)	0.149
DIC	2(3.8%)	0(0.0%)	0(0.0%)	2(20.0%)	0.011
Cerebral infarction	2(3.8%)	1(3.8%)	1(5.9%)	0(0.0%)	0.741
SCMP	2(3.8%)	1(3.8%)	1(5.9%)	0(0.0%)	0.741
Death	9(15.1%)	1(3.8%)	3(17.6)	5(50.0)	0.004

Table 3. Complications in SFTS patients. *SFTS* severe fever with thrombocytopenia syndrome, *AKI* acute kidney injury, *DIC* disseminated intravascular coagulation, *SCMP* stress-induced cardiomyopathy. **P*-values correspond to comparisons between the non-AKI, AKI stage 1, and AKI stage 2 + 3 groups.

Risk factors for mortality

Using Cox regression analysis, we identified risk factors associated with mortality (Table 4). In univariate analysis, WBC count, BUN, creatinine, AST, ALT, and alkaline phosphatase (ALP) emerged as significant risk factors for mortality. Stage 3 AKI was identified as a significant risk factor compared to the group without AKI. In the multivariate analysis, only WBC and serum creatinine levels showed significant results.

Discussion

In this study, we investigated the clinical implications of AKI in patients with SFTS. Half of the patients with SFTS in our cohort developed AKI with varying degrees of severity. The association between AKI severity and adverse outcomes, particularly the significant increase in mortality rates in patients with advanced AKI, highlights the importance of understanding and addressing renal compromise in patients with SFTS. Moreover, the average

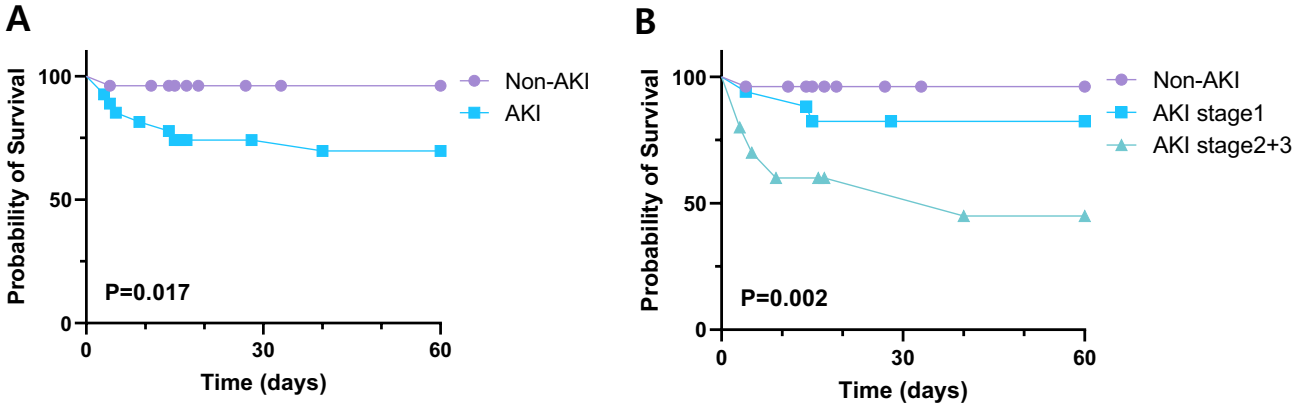

Fig. 2. Kaplan–Meier curves of patient survival: (**A**) Comparison between non-AKI and AKI Groups, (**B**) Comparison according to AKI Stage.

Characteristics	Univariate HR (95% CI)	Model1* HR (95% CI)	Model2** HR (95% CI)
Sex (female)	0.659(0.176–2.470)		0.309(0.028–3.385)
Age, years	1.043(0.978–1.112)		1.110(0.998–1.236)
AKI			
AKI stage 1 vs non-AKI	5.357(0.508–56.502)		
AKI stage 2 vs non-AKI	6.520(0.322–121.334)		
AKI stage 3 vs non-AKI	**99.998(5.151–999.999)**		
Comorbidity			
Hypertension	1.645(0.388–6.968)		
Diabetes mellitus	4.229(0.904–19.787)		
Chronic liver disease	1.250(0.123–12.708)		
Cerebrovascular disease	5.357(0.304–95.062)		
Heart disease	2.625(0.212–32.518)		
WBC (< 3.8 × 10^3/ul)	**25.936(3.723–180.666)**	**31.250(2.232–5000.000)**	**833.333(2.008–33,333.333)**
Hemoglobin (< 12.6)	2.643(0.531–13.145)		
Platelet (< 50 × 10^3/ul)	0.552(0.102–2.995)		
BUN (> 22.0 mg/dL)	**7.500(1.377–40.837)**		
Creatinine (> 1.20 mg/dL)	**8.998(1.847–43.838)**	**8.175(1.276–52.357)**	**7.569(1.453–28.144)**
Albumin (< 3.8 g/dL)	3.176(0.700–14.421)		
AST (> 400 U/L)	**6.607(1.421–30.916)**		
ALT (> 200 U/L)	**7.917(1.644–38.144)**		
ALP (> 120 U/L)	**12.500(2.356–66.326)**		
TB (> 0.5 mg/dL)	2.270(0.612–12.092)		
CK (> 165 U/L)	2.000(0.370–10.809)		
LDH (> 1000 U/L)	0.286(0.053–1.531)		
PT (> 1.16 INR)	5.375(0.304–95.062)		
aPTT (> 35.0 s)	0.900(0.159–5.096)		
CRP (> 0.3 mg/dL)	**8.762(1.009–76.075)**		

Table 4. Risk factor of mortality. *AKI* acute kidney injury, *WBC* white blood cell, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *TB* total bilirubin, *CK* creatinine kinase, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastin clotting time. *Model 1: stepwise analysis based on univariate model results. **Model 2: Adjusted for age, sex, white blood cell count, and creatinine. Significance values are bold.

interval from the onset of fever to the occurrence of AKI was 3.9 days, suggesting the possibility of AKI as an early marker that can predict the severity of SFTS.

The clinical course of SFTS is categorized into febrile, multi-organ dysfunction, and convalescent stages. It was hypothesized that in severe cases, a one-week febrile stage would occur, followed by the development of multiorgan dysfunction, such as AKI, as a consequence of a cytokine storm. However, recent evidence indicates that SFTSV directly invades the renal tissue of patients with SFTS, and the increased viral load in the urine is

associated with adverse outcomes[14]. Furthermore, within the AKI group of our study, AKI occurred in 88.9% of patients within the first week of fever onset. This suggests that the kidney is involved early in the course of SFTS and may be involved in its pathogenesis.

AKI is a major complication of SFTS. A previous Korean study conducted between 2013 and 2015 reported an acute renal failure occurrence rate of 14.2%[9]. Another study documented kidney dysfunction at baseline in 36% of 11 patients with SFTS[15]. In Chinese studies, renal insufficiency was observed in 27.8% of 115 patients with SFTS and in 36% of 25 patients with SFTS[8,10]. These reports, although valuable, did not focus on AKI and thus lacked a clear definition of kidney dysfunction. Recently, studies using the term AKI have been published[11,12], and two studies investigated the incidence of AKI in patients with SFTS according to the KDIGO guidelines[13,14]. We reviewed the literature on the incidence of AKI and fatality among patients with SFTS and summarized the representative findings in a table (Table 5). Four studies reported that the incidence of AKI in patients with SFTS ranges from 21.6 to 27.5%. Our study revealed that AKI was documented in 50.9% of the patients with SFTS. Our study represents the highest reported AKI incidence, which we attribute to an older patient population with concurrent comorbidities (i.e., diabetes and hypertension) that likely manifest as preexisting chronic kidney disease. Additionally, this may be due to our comprehensive definition of AKI, following not only the KDIGO guidelines but also including patients for whom baseline creatinine values were unavailable, in alignment with the definition proposed by Duff et al.[18]. This allowed the inclusion of many patients who had already experienced AKI from their initial hospital admission to the AKI group. Furthermore, using a broader AKI definition to predict the severity of SFTS early is unlikely to pose a clinical concern.

When examining the characteristics of the AKI group, old age and the presence of diabetes mellitus emerged as factors that contributed to the occurrence of AKI in the SFTS group, which is consistent with the results of a previous study[13]. Among the signs and symptoms, general weakness and mental changes occurred more frequently as AKI severity increased. Additionally, high initial serum creatinine, AST, ALT, CRP were significantly associated with AKI. These findings are consistent with those of a previous study, which reported a higher incidence of encephalopathy in the AKI group, along with significantly elevated levels of serum creatinine, AST, ALT, CRP, and other laboratory parameters[13]. In another study by Zhang et al., similar to our study, the AKI group had significantly higher serum creatinine and AST levels and increased mortality[14].

The detection of viral nucleic acids in the kidney in SFTS has already been well established through both animal experiments and autopsies[16,19]. In a study using a pathogenic C57/BL6 mouse model of SFTS, the viral load in the kidney was found to be the second highest after the spleen at 1 d post-infection, which was accompanied by pathological glomerular changes in the kidney, with no overt tubular injury or inflammatory infiltrates at 14 days post-infection[19]. Furthermore, the presence of viral antigens and nucleic acids was observed by immunohistochemistry and RT-PCR in the renal tissue of a single SFTS victim during autopsy evaluations[16]. Although the kidney is directly invaded by the virus, and AKI is a common and significant complication, there is limited research on the role and significance of AKI in SFTS. Zhang et al.[14] measured urine SFTS virus levels, which were significantly higher in the AKI group and closely related to patient mortality. In our study and in a previous study, the AKI group exhibited significantly higher mortality than the non-AKI group[13]. AKI can be easily detected using serial blood tests and is a remarkable prognostic tool. Given its ease of identification, it is imperative that its role in patient prognostication garner further attention in clinical practice. In this study, the rapid onset of AKI post-fever, averaging 3.9 days—in patients with SFTS accentuated AKI's pivotal role of AKI as an early and critical marker for gauging patient severity.

The mortality rate in the present study was 15.1%. Based on recent research findings, the SFTS mortality rate in South Korea from 2018 to 2022 is 18.7%[20], the mortality rate in China from 2011 to 2021 is 5.1%[21], and that in Japan from 2013 to 2017 is 27%[22]. After the SFTS was first introduced to the academic community in 2009, early studies reported a mortality rate as high as 30%[23]. However, recent studies reported decreased mortality rates. Despite the absence of a disease-specific therapeutic agent, the improvement in the mortality rate of SFTS can be attributed to a heightened understanding of disease progression as SFTS becomes more widely recognized. This enhanced knowledge will enable rapid diagnosis and more aggressive treatment of SFTS with meticulous attention. At our center, we adhere to a standardized protocol for managing SFTS. However, patients admitted to the infectious disease department are often suspected of having SFTS during the early course of the disease, whereas those in other departments are primarily diagnosed with hepatitis or pre-renal AKI. This difference may have led to a delayed diagnosis of SFTS and the application of our protocol. Our findings indicate that patients initially admitted to the infectious disease department had a higher likelihood of survival than those admitted to other departments. Although patients admitted to the infectious disease department may have milder disease,

Publication	Incidence of AKI	Fatal cases	
		Non-AKI group	AKI group
Zhang et al.[14]	28/102 (27.5%)	1/74 (1.4%)	14/28 (50.0%)
Ra et al.[12]	12/45 (26.7%)	3/33 (9.1%)	4/12 (33.3%)
Zhang et al.[13]	55/208 (26.4%)	10/153 (6.5%)	27/55 (49.1%)
Nie et al.[11]	25/116 (21.6%)	32/91 (35.2%)	18/25 (72.0%)

Table 5. Literature review on incidence of acute kidney injury and fatality among patients with severe fever with thrombocytopenia syndrome.

the difference in outcomes could be attributed to early suspicion and aggressive supportive treatments, such as early plasma exchange, providing valuable lessons for clinicians.

In terms of factors influencing mortality, AKI stage 3 was significant in the univariate analysis; however, its significance disappeared in the multivariate analysis, possibly because of a confounding effect. However, the initial serum creatinine level remained a significant factor in multivariate analysis. Kaplan–Meier analysis confirmed lower survival rates among AKI patients, especially those in advanced stages, compared to the non-AKI group. Increased vigilance is warranted in cases in which patients have high initial creatinine levels at admission or develop AKI during hospitalization.

This study has several limitations. First, this was a single-center study with a small number of patients. Therefore, further studies involving larger cohorts are required to confirm the significance of AKI. Second, some patients did not have baseline creatinine values, which limited our ability to confirm AKI using the KDIGO criteria. However, we attempted to identify all AKI cases using an alternative definition proposed by Duff et al.. Third, RT-PCR was exclusively employed as a confirmatory test for SFTS, potentially leading to the exclusion of patients with SFTS who tested negative on RT-PCR. Fourth, because of the retrospective nature of the study, urine RT-PCR data were not available. This limits our ability to correlate urine viral loads with AKI scores. Future prospective studies should include urine RT-PCR to provide a more comprehensive understanding of the relationship between the viral load and AKI in patients with SFTS.

Conclusions

In the present study, AKI was identified as a common complication in patients with SFTS. On average, it took 3.9 days from fever onset to AKI development. We found that old age and diabetes mellitus were risk factors for AKI, and initial serum creatinine level was an independent risk factor for fatality in patients with SFTS. Kaplan–Meier curves revealed lower survival rates among patients with AKI than among those without AKI, especially as the AKI stage advanced. Taken together, our findings highlight the high incidence of AKI in patients with SFTS and underscore its pivotal role as an early prognostic indicator of AKI severity.

Data availability

The data are not available for public access owing to patient privacy concerns; however, data are available from the corresponding author upon reasonable request.

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Author contributions

J.M.L. and J.I.P. conceived of and designed the study. J.M.L., H.L.K. and J.I.P. wrote the manuscript. W.S.O., S.S., S.L., H.B., and J.I.P. collected the data, and C.K., Y.J.L., and Y.D.J. verified the data. M.L. and D.D.H. performed statistical analyses. All authors have reviewed and revised the manuscript prior to submission.

Competing interests

The authors declare no competing interests.

Additional information

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