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Adenosine Deaminase as a Potential Diagnostic and Prognostic Biomarker for Severe Fever with Thrombocytopenia Syndrome

Hongling Ye, Xiawen Lin, Zheng Zhang, Zhiye Xu, Taihong Huang, Shijie Cai, Yinyin Fan,* and Sen Wang*

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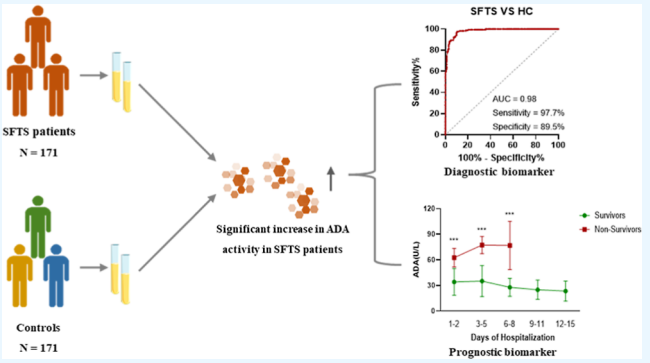
ABSTRACT: Background: Severe fever with thrombocytopenia syndrome (SFTS) is a serious infectious disease caused by the Dabie bandavirus, with a high mortality rate. Currently, there are no effective vaccines or specific treatments for SFTS. Early diagnosis and accurate severity assessment are crucial. Methods: This study included 171 cases of SFTS, COVID-19, and hepatitis B virus (HBV) patients and healthy controls. We compared the serum adenosine deaminase (ADA) activity across these groups. The diagnostic and prognostic efficiency of serum ADA for SFTS was evaluated by using receiver operating characteristic (ROC) curve analysis. We also examined the correlation between serum ADA in SFTS patients and clinical lab parameters as well as serum cytokines. Results: SFTS patients had significantly higher serum ADA activity than those of COVID-19, HBV patients, and healthy controls. Nonsurvivor SFTS patients had notably higher ADA than survivors. ROC analysis indicated ADA as an effective SFTS diagnostic and prognostic biomarker. ADA correlated with prognosis, viral load, APTT, PT, AST, ferritin, negatively with HDL-c and LDL-c, and positively with cytokines like IL-6, TNF-α, and IL-1β. Multiorgan failure patients showed significant ADA increase. Conclusion: Elevated serum ADA activity in SFTS patients is linked with disease severity and prognosis, showing potential as a diagnostic and prognostic biomarker for SFTS.



1. INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is a severe infectious disease caused by the SFTS virus (SFTSV), renamed Dabie bandavirus in 2019 by the International Committee on Taxonomy of Viruses.[1] First isolated in China in 2010, the Dabie bandavirus is a single-stranded negative-sense RNA virus.[1,2] It is widely distributed in East and Southeast Asian countries. Ticks act as the primary reservoir host and transmission vector for this virus, and domesticated animals, such as cattle, sheep, and dogs, may also be reservoir hosts. The general population, particularly those in hilly, mountainous, and forested regions, is susceptible to infection.[3] SFTS symptoms include fever, myalgia, gastrointestinal issues, lymphadenopathy, and hematological abnormalities like thrombocytopenia and leukopenia.[4,5] Dabie bandavirus can trigger a cytokine storm, severe inflammatory response syndrome, and coagulation abnormalities, which may lead to multiorgan failure and high mortality in severe cases.[6] The pathogenic mechanism of SFTS is not fully understood, and there are no effective vaccines or specific treatments available, making early identification and accurate severity assessment vital.

ADA, an essential enzyme in purine nucleoside metabolism, converts adenosine to inosine.[7] Adenosine, a significant immunoregulatory factor, binds to its receptors to regulate monocytes, lymphocytes, and neutrophils, providing anti-inflammatory and immunosuppressive effects.[8,9] ADA's role in immune regulation involves degrading adenosine. Current research shows that ADA activity increases under conditions such as tumors and autoimmune diseases. Elevated ADA levels and activity are observed in various tumors, including gastric, bladder, and breast cancers.[10] Similarly, increased ADA activity is associated with disease activity in autoimmune conditions such as systemic lupus erythematosus (SLE), adult-onset Still's disease (AOSD), and Sjögren's syndrome (SS).[11−13] Additionally, high ADA activity in pleural fluid is a key diagnostic criterion for tuberculosis.[14,15]

In SFTS patients, immune dysregulation, including a cytokine storm from excessive immune activation, may contribute to mortality. ADA, implicated in immune regulation, has been associated with disease progression

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under various conditions. However, ADA activity levels in SFTS patients are not well defined. This study aims to systematically explore changes in ADA activity in SFTS patients and their clinical implications.

2. METHODS

2.1. Patients and Control Participants. This study investigated SFTS patients admitted to the Nanjing Drum Tower Hospital from January 2021 to June 2023. These patients underwent a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm SFTSV infection. The study received approval from the Institutional Review Board (IRB) of the Nanjing Drum Tower Hospital (approval no. 2022-238-02). This study cohort was composed of 79 males and 92 females with an average age of 62.1 ± 11.9 years. Based on the prognosis of SFTS patients, they were categorized into two groups: survivors and nonsurvivors. Additionally, this study included 171 cases of COVID-19 patients, 171 cases of HBV patients, and 171 healthy controls for comparison. There were no statistically significant differences in gender and age between the control group and the patient groups. Clinical data, including demographic information, laboratory results, and clinical symptoms, were collected from the electronic medical record system.

2.2. Detection and Collection of Clinical Parameters. This study utilized Beckman biochemical analyzers to measure serum ADA activity, transaminases, C-reactive protein (CRP), complement proteins C3 and C4, alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and other biochemical parameters. The measurement of serum ferritin was performed using a fully automatic chemiluminescence immunoassay analyzer (Siemens, Atellica IM1600). Additionally, blood cell counts, platelet counts, and hemoglobin tests were conducted by using a blood analyzer (Sysmex Corporation). Coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer, were measured by an automated coagulation analyzer (Sysmex CS-5100).

To analyze viral load, a fully automated nucleic acid extraction purification system and purification reagent kit were employed to extract total viral RNA from patients' serum. Following the manufacturer's instructions, we used the SFTSV quantitative assay kit to measure the SFTSV RNA load in serum samples, and quantitative PCR detection was performed on the Applied Biosystems ABI 7500 system. Cytokines in the serum, including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, IFN-γ, IFN-α, and TNF-α, were detected using flow cytometry, following the standard procedures provided by the manufacturer (EasyCell, Hangzhou Biogroup Technology Co). All these data were obtained from the hospital's laboratory information system and medical record system.

2.3. Receiver Operating Characteristic Curve Analysis. Receiver operating characteristic (ROC) curve analysis was used to differentiate the SFTS patient group from other control groups based on ADA activity. To determine the optimal cutoff value for the best differentiation between SFTS patients and the control group, we employed the Youden Index. The Youden Index is defined as the sum of sensitivity and specificity minus one. The diagnostic performance of serum ADA activity was assessed based on the area under the curve (AUC) of the ROC curve, along with sensitivity and specificity.

2.4. Statistical Analysis. Comparison between SFTS patients and other control groups was conducted using an unpaired *t*-test. Paired *t*-tests were employed to compare ADA activity between admission and follow-up for SFTS patients. A difference was considered statistically significant if the *p*-value was less than 0.05 ($p < 0.05$). All measured values were expressed as mean ± standard deviation. Pearson correlation analysis was utilized to explore relationships between clinical parameters, with significance considered if the *r*-value was greater than 0.2 and the *p*-value was less than 0.05 ($r > 0.2$, $p < 0.05$). Statistical analysis and data visualization were performed using GraphPad Prism 8.3 software.

3. RESULTS

3.1. Clinical Characteristics and Laboratory Parameters of Patients and Controls. This study included a total of 171 SFTS patients, comprising 147 survivors and 24 nonsurvivors. Additionally, the study involved 171 COVID-19 patients, 171 HBV patients, and 171 healthy controls. Clinical characteristics of surviving and nonsurviving SFTS patients are presented in Table 1. Nonsurvivors exhibited significantly higher proportions of shock, sepsis, encephalitis, and multiple organ failure (MOF) compared to survivors. Furthermore, there were significant statistical differences in platelet count, AST, LDH, ALB, and CRP between nonsurviving and surviving patients.

Table 1. Baseline Characteristics for Patients with SFTS

parameters	survival	nonsurvival	*P*
no	147	24	
male/female (n)	66/81	13/11	
age (years)	61.37 ± 12.07	66.58 ± 8.43	0.04
days of hospital stay	10.81 ± 7.31	7.42 ± 7.40	0.03
history n (%)			
hypertension	39 (27%)	11 (46%)	0.06
heart disease	3 (2%)	1 (4%)	0.53
diabetes	20 (14%)	5 (21%)	0.36
shock	5 (3%)	8 (33%)	<0.0001
sepsis	8 (5%)	6 (25%)	0.001
CNS symptoms	37 (25%)	8 (33%)	0.41
encephalitis	20 (14%)	9 (38%)	0.004
MOF	19 (13%)	9 (38%)	0.003
laboratory parameters			
neutrophils ($\times 10^9$/L)	4.09 ± 2.54	3.93 ± 3.90	0.85
lymphocytes ($\times 10^9$/L)	0.94 ± 0.63	1.23 ± 1.05	0.19
hemoglobin (g/L)	121.8 ± 22.28	120.2 ± 23.19	0.76
platelet ($\times 10^9$/L)	50.24 ± 46.22	102.3 ± 84.54	0.004
alanine aminotransferase (U/L)	114.5 ± 88.08	115.7 ± 178.5	0.97
aspartate aminotransferase (U/L)	517.3 ± 390.5	183.0 ± 199.7	<0.0001
LDH (U/L)	2412 ± 2092	754.1 ± 612.8	<0.0001
albumin (g/L)	29.68 ± 2.95	33.90 ± 4.28	<0.0001
globulin (g/L)	27.69 ± 6.05	29.28 ± 7.99	0.35
C-reactive protein (mg/L)	34.93 ± 45.08	15.26 ± 30.84	0.008

3.2. Significant Increase in ADA Activity in SFTS Patients. To investigate the levels and clinical significance of serum ADA activity in SFTS patients, we analyzed ADA activity among SFTS patients, COVID-19 patients, HBV patients, and healthy controls. The results indicated that ADA

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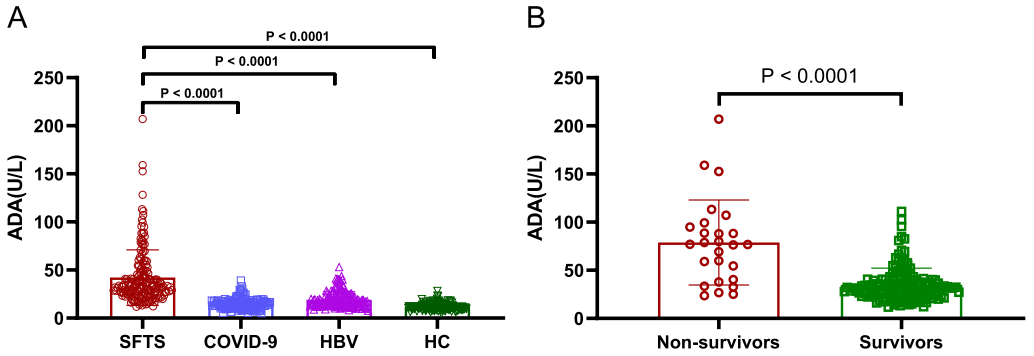

Figure 1. Comparison of serum ADA activity between SFTS patients and control group patients. Comparison of serum ADA activity among SFTS patients, COVID-19 patients, HBV-infected patients, and healthy controls (A), and between nonsurvivor and survivor patients with SFTS (B). Data are presented as mean ± standard deviation.

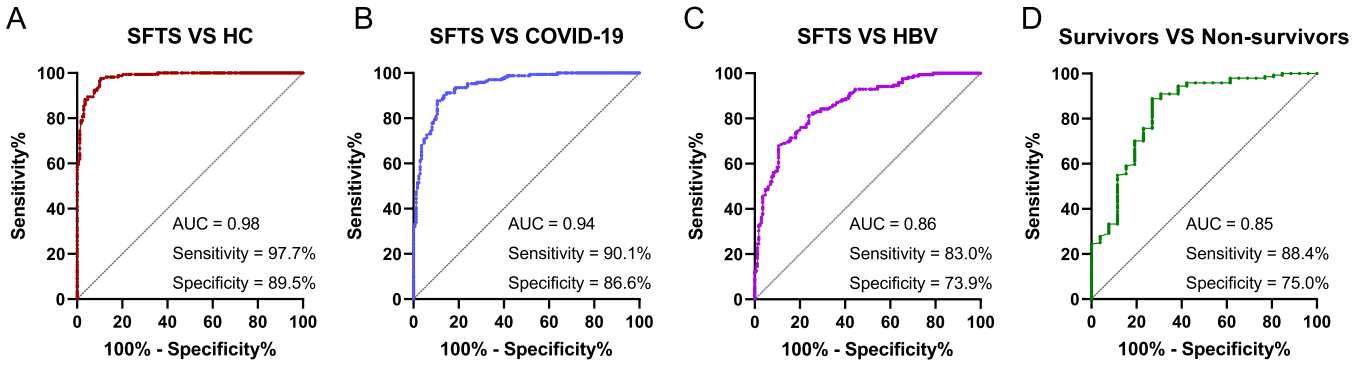

Figure 2. Using ROC curve analysis to evaluate the efficacy of ADA activity as a diagnostic and prognostic biomarker. ADA as a diagnostic marker to differentiate SFTS patients from healthy controls (A), ADA as a diagnostic marker to differentiate SFTS patients from COVID-19 patients (B), ADA as a diagnostic marker to differentiate SFTS patients from HBV-infected patients (C), and ADA as a prognostic marker to differentiate nonsurvivors from survivors (D).

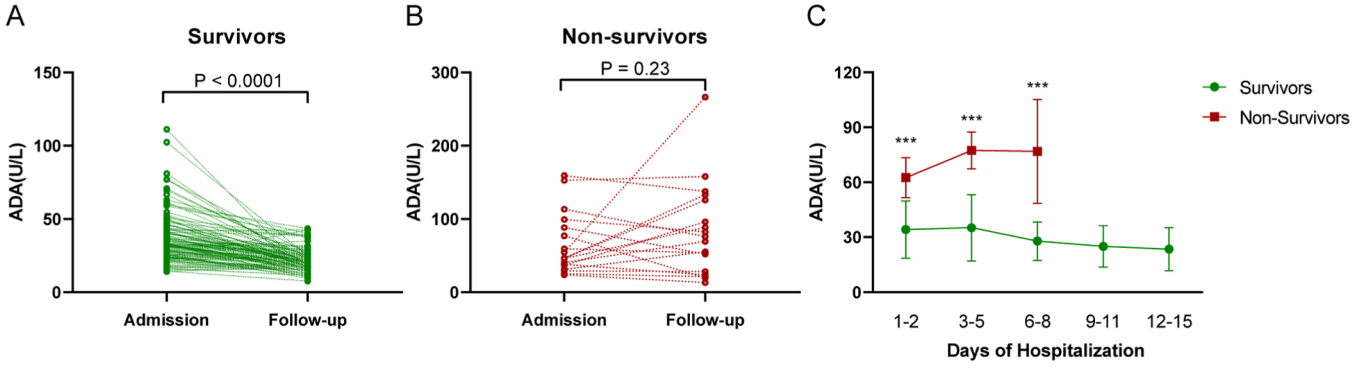

Figure 3. Dynamic changes in serum ADA activity. Changes in ADA activity at admission and during follow-up in survivors (n = 125). Statistical analysis using paired t-test (A). Changes in ADA activity at admission and during follow-up in nonsurvivors (n = 18). Statistical analysis using paired t-test (B). Changes in ADA activity in both survivors and nonsurvivors with increasing hospitalization duration (C).

activity in SFTS patients was significantly higher than that in healthy controls and also significantly higher than that in COVID-19 and HBV patients (Figure 1A). We also compared ADA activity between survivors and nonsurvivors among SFTS patients, and we found that ADA activity in nonsurvivors was significantly higher than in survivors (Figure 1B). This suggests that ADA activity significantly increases in patients infected with the Dabie bandavirus, surpassing levels seen in patients with SARS and HBV infections. Moreover, the increase in the ADA activity is more pronounced in patients with severe conditions.

3.3. ROC Curve Analysis of ADA Activity as a Biomarker for the Diagnosis and Prognosis Assessment of SFTS Patients. Due to the significant elevation of ADA activity in SFTS patients, we further employed ROC curve analysis to assess the efficacy of ADA activity as a diagnostic and prognostic biomarker. The ROC curve analysis demonstrated that ADA activity is a robust diagnostic biomarker, effectively distinguishing SFTS patients from healthy controls (AUC = 0.98, sensitivity = 97.7%, specificity = 89.5%) (Figure 2A). Additionally, ADA activity was effective in discriminating SFTS patients from individuals with other viral infections, such as COVID-19 patients (AUC = 0.94, sensitivity = 90.1%,

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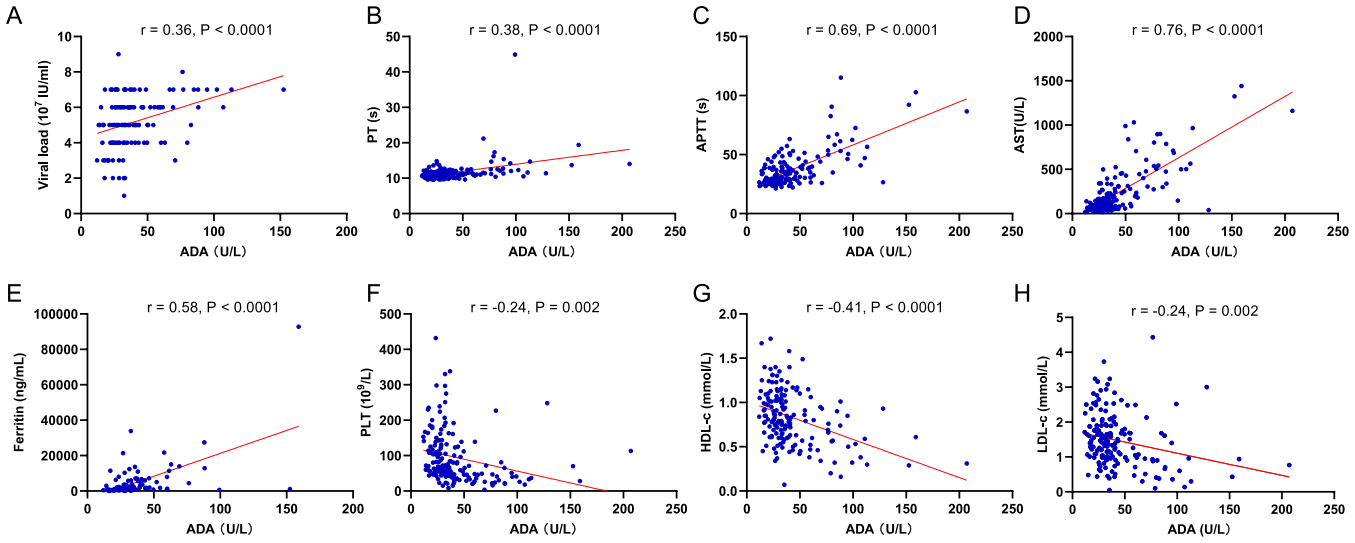

Figure 4. Correlation of ADA activity with clinical laboratory parameters. Analysis of the correlation of ADA activity with viral load, PT, APTT, AST, ferritin, PLT, HDL-c, and LDL-c (n = 171) (A–H).

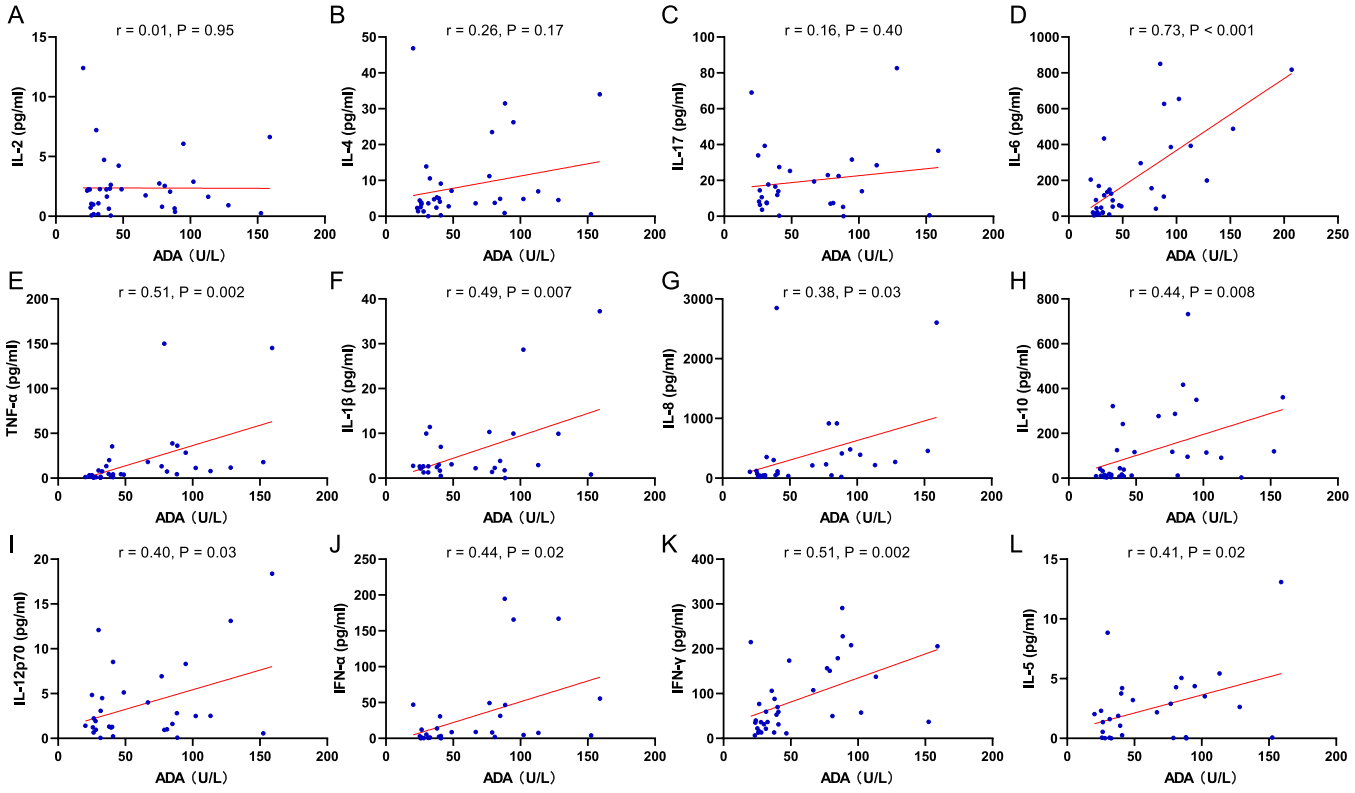

Figure 5. Correlation of ADA activity with serum cytokines. Analysis of the correlation between ADA activity and IL-6, TNF-α, IL-1β, IL-8, IL-10, IL-12 p70, IFN-α, and IFN-γ (n = 35) (A–H).

specificity = 86.6%) (Figure 2B) and HBV-infected patients (AUC = 0.86, sensitivity = 83.0%, specificity = 73.9%) (Figure 2C). Moreover, ADA activity served as a promising prognostic biomarker for SFTS patients, demonstrating good efficacy in distinguishing survivors from nonsurvivors (AUC = 0.85, sensitivity = 88.4%, specificity = 75.0%) (Figure 2D).

3.4. Dynamic Changes in Serum ADA Activity in Survivor and Nonsurvivor SFTS Patients. To further investigate the relationship between serum ADA activity and the prognosis of SFTS patients, we examined the dynamic changes in ADA activity during the course of the disease. We collected serum ADA concentrations upon patient admission, and for survivors, we collected ADA concentrations at discharge as follow-up data. For nonsurvivors, we collected the last serum ADA concentration before death. The study revealed that ADA activity in the follow-up of surviving patients significantly decreased (Figure 3A), while there was no statistical difference in ADA activity between follow-up and admission for nonsurvivors, and there was a trend of increase (Figure 3B). Additionally, we conducted a dynamic analysis of ADA activity over time for both surviving and nonsurviving patients based on the time after admission. The results showed

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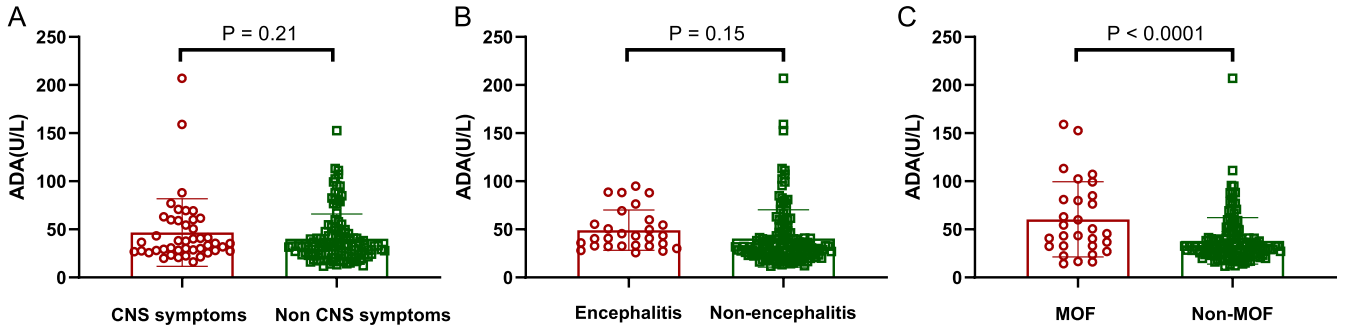

Figure 6. Comparison of ADA activity among SFTS patients with different clinical symptoms. Comparison of ADA activity between patients with CNS symptoms and those without CNS symptoms (A). Comparison of ADA activity between SFTS patients with and without encephalitis (B). Comparison of ADA activity between patients with MOF and those without MOF (C).

that ADA activity gradually decreased with the prolongation of hospitalization in survivors, whereas nonsurvivors, due to the severity of the illness, mostly succumbed within the first 8 days of admission, and we did not collect sufficient data for the period of 8−15 days. However, the results indicated that ADA activity in nonsurvivors remained significantly higher than in surviving patients. Furthermore, ADA activity in nonsurvivors did not decrease with prolonged hospitalization time (Figure 3C).

3.5. Correlation between ADA Activity and Clinical Parameters in SFTS Patients. During the course of the SFTSV infection, some clinical laboratory parameters undergo significant changes that may be associated with the severity of the disease. Therefore, we analyzed the correlation between serum ADA activity and clinical laboratory parameters. Viral load can reflect the severity of the disease to some extent, and the study found a significant positive correlation between serum ADA activity and viral load (Figure 4A). SFTS patients exhibit notable abnormalities in coagulation function, and our research indicates a significant positive correlation between serum ADA activity and both PT and APTT (Figure 4B,C). Additionally, ADA activity is also significantly positively correlated with AST and ferritin levels (Figure 4D,E). Thrombocytopenia is a typical symptom in SFTS patients, and this study found a significant negative correlation between serum ADA activity and PLT count (Figure 4F). Our previous research indicated a significant decrease in blood lipid levels in SFTS patients, and serum ADA activity showed significant negative correlations with both HDL-c and LDL-c (Figure 4G,H).

3.6. Correlation between ADA Activity and Serum Cytokines in SFTS Patients. Excessive inflammatory responses can lead to a cytokine storm, causing severe symptoms in SFTS patients. Various cytokines in the serum of SFTS patients show abnormal elevations. This study analyzed the correlation between serum ADA activity and 12 cytokines in the serum. The results revealed no significant correlation between serum ADA activity and IL-2, IL-4, and IL-17 (Figure 5A−C) while showing significant positive correlations with IL-6, TNF-α, IL-1β, IL-8, IL-10, IL-12 p70, IFN-α, IFN-γ, and IL-5 (Figure 5D−L). This further indicates that the elevated serum ADA activity is correlated to the severity of the disease in SFTS patients.

3.7. Relationship between ADA Activity and Clinical Symptoms in SFTS Patients. Severe SFTS patients may experience neurological involvement, and some may develop viral encephalitis or even MOF. Patients exhibiting these clinical symptoms often have a higher mortality rate. Therefore, we further analyzed the differences in the serum ADA activity among patients with different clinical manifestations. The study found no significant statistical difference in serum ADA activity between patients with and without neurological symptoms or between patients with and without encephalitis (Figure 6A,B). However, in patients with MOF, serum ADA activity was significantly higher than that in those without MOF (Figure 6C).

4. DISCUSSION

SFTS is a severe infectious disease with a high mortality rate and currently lacks a vaccine or specific treatment. Early diagnosis and accurate assessment of disease progression are thus crucial. Our study found a significant increase in ADA levels in SFTS patients, indicating its potential as a diagnostic and prognostic marker. ADA, an enzyme involved in adenosine metabolism, converts adenosine into inosine. Adenosine is a key immunoregulatory molecule that suppresses excessive inflammation.[16] Therefore, abnormal increases in ADA could reduce adenosine levels, affecting the adenosine−adenosine receptor pathway and potentially leading to an exaggerated inflammatory response. ADA consists of two isoenzymes: ADA1 and ADA2.[17] This study detected the total ADA activity. ADA1 is an intracellular protein that is widely expressed. A deficiency in ADA1 in humans can lead to severe combined immunodeficiency, characterized by a significant reduction in lymphocytes and impaired differentiation and function of other immune cells.[18] ADA2 is mainly a plasma protein secreted by monocytes and macrophages, and it is also the primary form of ADA present in the plasma.[19] ADA is also found in hepatocytes and can indicate liver function.[20] This study observed a significant positive correlation between serum ADA levels and AST as well as LDH levels, suggesting liver cell damage in SFTS patients as a possible cause for elevated ADA. However, we also found increased ADA levels in SFTS patients with normal transaminase levels (Figure S1), and since monocytes/macrophages and lymphocytes may be activated during SFTSV infection, the increase in serum ADA is likely primarily derived from monocytes/macrophages and lymphocytes.

In autoimmune diseases like SLE and SS, serum ADA activity is elevated and associated with disease activity.[11,13] Patients with AOSD also show increased ADA activity, suggesting its role as a potential biomarker for AOSD diagnosis.[12] These findings imply that under pathological conditions, abnormal ADA activity correlates with immune

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dysregulation. Research indicates that ADA activity may also increase abnormally in certain viral infections. For example, in HIV-infected patients, increased ADA activity is negatively correlated with CD4 counts and is a useful diagnostic tool.[21] Additionally, ADA activity has been proposed as a novel diagnostic method to differentiate between HIV monoinfection and coinfection with HBV or HCV.[22] In COVID-19 patients, ADA mRNA levels in nasopharyngeal swabs significantly increase. With a sensitivity of 81.8% and specificity of 83.4%, standardized ADA mRNA levels can help distinguish between infected and uninfected individuals, marking ADA as a potential biomarker.[23] This study identified a significant increase in ADA activity in SFTS patients, suggesting its potential as a diagnostic and prognostic marker. The positive correlation between ADA activity and viral load underscores a strong association with the disease severity and progression. In most SFTS patients, there is a notable decrease in the platelet count, more so in severe cases.[24,25] Our findings reveal a significant negative correlation between serum ADA activity and the platelet count, indicating that ADA activity reflects disease severity. Previous studies have shown abnormal lipid metabolism in SFTS patients, with decreased HDL levels correlating with poor prognosis.[26] HDL is known for its anti-inflammatory effects.[27,28] In our study, a negative correlation was found between ADA activity and HDL levels, suggesting a link between elevated levels of ADA and excessive inflammation in SFTS patients.

SFTSV and SARS-CoV-2 infections share similarities, including the involvement of cytokine storms, which are closely associated with the severity of viral infections.[29,30] Studies indicate significantly higher levels of various cytokines (IL-6, TNF-α, IFN-α, and IL-10) in SFTS patients compared to healthy controls. These cytokine concentrations correlate with SFTS severity.[31] Notably, excessive IL-6 and IL-10 production is linked to cytokine-storm-induced deaths in these patients. Our study found a significant positive correlation between serum ADA concentration and IL-6 and IL-10 levels, suggesting that ADA activity is a potential prognostic marker.[29,32] We also observed a positive correlation between ADA activity and various inflammatory cytokines, including TNF-α, IL-1β, and IL-8. Elevated ADA activity may lead to extensive adenosine degradation, which typically has anti-inflammatory and immunosuppressive effects. Therefore, increased ADA activity might trigger excessive immune cell activation, leading to cytokine storms. This study also analyzed the ADA activity differences in SFTS patients with various clinical symptoms. Due to the limited number of patients with comorbidities like hypertension, heart disease, and diabetes, we did not conduct a separate analysis for this subgroup. In patients with neurological symptoms or encephalitis, the ADA activity did not significantly differ from those without these symptoms. However, ADA activity was significantly elevated in patients with MOF, a severe complication. This marked increase in ADA activity in MOF patients further underscores its correlation with the severity and prognosis of SFTS. Significant numbers of natural and synthetic ADA inhibitors have already been discovered, some of which have been applied in clinical treatment. However, these inhibitors were primarily targeted at treating tumors and autoimmune diseases.[33] In early research, ADA inhibitors were also thought to be capable of inhibiting viral replication.[34] This study indicated that ADA might be involved in the pathogenesis of SFTSV, therefore developing ADA inhibitors for controlling viral infections emerged as a promising research direction.

5. CONCLUSIONS

This study found that ADA activity in the serum of SFTS patients is significantly increased and is significantly correlated with a variety of important clinical laboratory parameters and cytokines. ADA activity can serve as a potential diagnostic and prognostic biomarker for SFTS patients. Additionally, ADA and the adenosine pathway represent potential therapeutic targets for treating SFTS patients.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c00281.

Figure S1. Comparison of ADA activity between SFTS patients with normal transaminases and healthy controls (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yinyin Fan − *Department of Pancreatic and Metabolic Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*; Email: fyy1104@163.com

Sen Wang − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*; orcid.org/0009-0004-5249-8434; Email: njwangsen@163.com

Authors

Hongling Ye − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Xiawen Lin − *Department of Nuclear Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Zheng Zhang − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Zhiye Xu − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Taihong Huang − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Shijie Cai − *Department of Clinical Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c00281

Author Contributions

H.Y., X.L., and Z.Z. contributed equally to this work. S.W. and Y.Y.F. contributed to the design of the study and supervised the scientific work. H.L.Y., X.W.L., and Z.Z. contributed to the analysis and interpretation of the data. Z.Y.X., T.H.H., and S.J.C. contributed to the interpretation of the data. H.L.Y. drafted the manuscript. S.W. and Y.Y.F. revised the manuscript.

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All authors have read and approved the submission of this manuscript.

Notes

The authors declare no competing financial interest.

Ethical approval statement: This study was approved by the IRB of the Nanjing Drum Tower Hospital (2022-238-02), Nanjing, China.

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