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ORIGINAL RESEARCH

Prognostic Value of Serum Ferritin for Patients with Severe Fever with Thrombocytopenia Syndrome: A Single-Center Retrospective Cohort Study

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ABSTRACT

Introduction: This article aims to evaluate the prognostic value of ferritin in patients with severe fever with thrombocytopenia syndrome (SFTS).

Methods: Patients with SFTS diagnosed at the Infection Department of Wuhan Union Medical College Hospital from July 2018 to November 2021 were included. The best cutoff value was determined by receiver-operating characteristic (ROC) curve. The survival curve was analyzed by Kaplan-Meier method and compared among different serum ferritin subgroups by log-rank test. Cox regression model was used to evaluate the effect of prognosis on overall survival (OS).

Results: A total of 229 patients with febrile thrombocytopenia syndrome were enrolled. There were 42 fatal cases, with a fatality rate of 18.3%. The best critical value of serum ferritin was 16.775 mg/l. With increasing serum ferritin level, the cumulative mortality increased significantly (log-rank, $P < 0.001$). Cox univariate regression analysis and adjusted confounding factors such as age, viral load, liver and kidney function and blood coagulation function showed that, compared with the low ferritin group, the high ferritin group demonstrated poorer OS.

Conclusions: The serum ferritin level before treatment can be considered a valuable index for predicting the prognosis of patients with SFTS.

Keywords: Severe fever with thrombocytopenia syndrome; Ferritin; Prognostic; Adverse outcome; Risk factors

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Key Summary Points
SFTS disease has a high fatality rate.
Serum ferritin level may be a predictor of poor prognosis in patients with SFTS.
What was learned from the study?
Serum ferritin is a potential biomarker of adverse clinical outcome in patients with SFTS.
The study of iron metabolism in patients with SFTS may provide new help for their treatment.

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease with high mortality, caused by severe fever with thrombocytopenia syndrome virus (SFTSV) [1], currently also known as Dabie bandavirus [2]. SFTS can be transmitted through tick bites and contact with patients' blood or blood-carrying secretions [3–5]. The clinical manifestation of SFTS lacks specificity. Most patients have fever, gastrointestinal manifestations (anorexia, abdominal pain, diarrhea, etc.), systemic poisoning symptoms, disturbance of consciousness and multiple organ damage, accompanied by thrombocytopenia and/or leukocytopenia [4, 6]. At present, there are no vaccines or specific antiviral drugs for prevention and treatment [7], and the clinical treatment is still based on symptomatic support. In 2017, the World Health Organization (WHO) listed SFTS as an infectious disease requiring urgent research and development because of its high case fatality rate and the possibility of transmission [8]. For seriously ill patients, the disease can quickly develop into multiple organ failure and eventually lead to adverse clinical outcomes [9]. Therefore, it is very important for SFTS patients to identify the high risk of adverse clinical outcome in time.

Serum ferritin (FER) is a kind of iron storage protein, which is widely measured as an index of iron status. Detecting FER is easy and straightforward, so it can often be done in the clinic. In addition to long-term use as an alternative indicator of iron storage in the body, FER also represents an acute phase protein, which is upregulated and elevated in infectious and non-infectious inflammation [10], including chronic kidney disease [11], diabetes [12], malignant tumors [13] and inflammation [14, 15]. Furthermore, there is growing evidence that circulating ferritin may play a pathogenic role in inflammatory diseases through its signal transduction as part of innate immune response and regulation of lymphocyte function [16, 17]. Consequently, FER may be a useful biomarker due to its accessibility and correlation with significant inflammatory response secondary to infection. Therefore, our study evaluated the clinical value of serum ferritin in patients with SFTS by analyzing the correlation between the level of serum ferritin and prognosis of patients with SFTS to provide some guidance for judging the condition and prognosis of SFTS patients in clinical work.

METHODS

Patients

From July 2018 to November 2021, a total of 229 patients with SFTS were enrolled in the Department of Infectious Diseases, Union Hospital of Tongji Medical College. Patients with SFTS were diagnosed according to one or more of the following criteria: (1) SFTSV was isolated from the patient's serum; (2) real-time reverse transcription polymerase chain reaction was positive for SFTSV RNA; (3) seroconversion or a four-fold increase in antibody titer was detected between acute and convalescent sera. The exclusion criteria were: (1) lack of clinical data for research; (2) complicated with kidney disease, malignant tumor or autoimmune disease; (3) combined with other active or acute viral infections. The research protocol was approved by the Ethics committee of the Tongji Medical College of Huazhong University of

Science and Technology and completed in accordance with the Declaration of Helsinki. The need to obtain informed consent from individual patients was waived, given the retrospective nature of the study.

Data Collection

Retrospective collection of demographic data, laboratory tests (first blood examination during hospitalization) and disease outcomes was carried out at patient discharge as the end point of observation. The laboratory department of our hospital used an Abbott chemiluminescence immunoanalyzer to detect the level of serum ferritin. The kit and calibrator were purchased from Abbott in the USA.

Statistical Analysis

Statistical analysis and statistical graphs were carried using SPSS (version 23.0) and GraphPad Prism (version 8.0). Continuous variables and classified variables were expressed as median, interquartile range (IQR) and *n* (%). The cutoff value of the FER was determined using receiver-operating characteristic (ROC) curve analyses. Categorical variables were compared using the Fisher exact or χ^2 test. Continuous variables were compared using the Mann-Whitney *U* or Student's *t* test, as appropriate. Kaplan-Meier method was used to analyze the survival curves among different serum ferritin subgroups and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regressions were conducted to evaluate the prognostic significance of each variable with respect to overall survival (OS). The significant risk factors identified by univariate analysis were then entered into the multivariate analysis. Correlations between FER and other clinical parameters were assessed using the Spearman correlation coefficient. A two-tailed *P* value < 0.05 was considered statistically significant.

Table 1 Baseline characteristics of patients with SFTS

	Total (*N* = 229)
Age, years	62 (54–69)
Sex, male	107 (46.7)
Ferritin, mg/l	8.44 (3.75–19.97)
Viral load (lg10 copies/ml)	3.41 (2.66–4.28)
WBC, g/l	2.17 (1.485–3.30)
NEU, g/l	1.26 (0.77–2.11)
LYM, g/l	0.58 (0.40–0.92)
PLT, g/l	42.00 (31.50–58.00)
ALT, U/l	84.00 (50.50–160.50)
AST, U/l	229.00 (118.50–416.50)
ALP, U/l	66.00 (53.00–96.50)
ALB, g/l	30.50 (27.80–33.70)
BUN, mmol/l	4.79 (3.37–6.59)
Cr, μmol/l	71.00 (59.60–88.20)
CK, U/l	30.50 (27.80–33.70)
LDH, U/l	828.50 (535.50–1381.50)
D-D, mg/l	3.29 (1.75–5.93)
PT, S	12.80 (12.20–13.60)
APTT, S	53.80 (46.32–62.52)
INR	0.98 (0.92–1.07)

Data are *n* (%) or median (interquartile range, IQR)
WBC white blood cell, *NEU* neutrophil, *LYM* lymphocyte, *PLT* platelet count, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *ALB* albumin, *BUN* blood urea nitrogen, *Cr* creatinine, *CK* creatine kinase *LDH* lactate dehydrogenase, *D-D* D-dimer, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

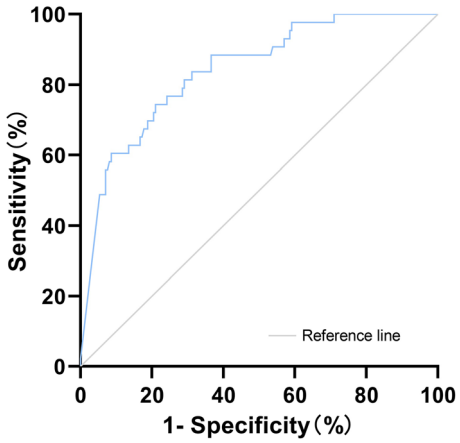

Fig. 1 ROC for serum ferritin based on OS. ROC, receiver-operating characteristic; OS, overall survival

RESULTS

Baseline Characteristics of Patients with SFTS

A total of 229 eligible SFTS patients were enrolled, including 187 non-fatal (81.7%) and 42 fatal (18.3%) cases. There were 107 (46.7%) males and 122 (53.3%) females, with a median age of 62 years. The basic characteristics and laboratory indicators are showed in Table 1.

Characteristics of Patients with Different Ferritin Levels

According to the ROC curve (Fig. 1), the cutoff value of serum ferritin was 16.775 mg/, and the AUC value was 0.84 (95% CI 0.777–0.904, sensitivity: 76.2%, specificity: 80.1%). According to the above best cutoff point, the patients were divided into low ferritin and high ferritin groups. The patient characteristics are showed in Table 2. The age in the high ferritin group was significantly higher than that in the low ferritin group. In laboratory tests, compared with the low ferritin group, the high ferritin group had higher levels of viral load, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (Cr), creatine kinase (CK), lactate dehydrogenase (LDH), D-dimer (D-D) and activated partial thromboplastin time (APTT) and lower platelet (PLT) and albumin (ALB) counts; there were significant differences between the two groups ($P < 0.05$).

Kaplan-Meier Method and Log-Rank Test

Kaplan-Meier method was used to analyze survival curves based on serum ferritin levels, and log-rank test was used to compare them. The results of survival analysis showed that compared with the low ferritin group, the high ferritin group demonstrated poorer OS ($P < 0.001$, Fig. 2).

Univariate and Multivariate Analysis for Adverse Outcomes

We further evaluated the role of serum ferritin levels as an independent risk factor for adverse outcomes in patients with SFTS. In model I–IV, we gradually controlled other risk factors, such as age, viral load, laboratory parameters (PLT, ALT, AST, ALP, ALB, BUN, CR, CK, LDH, APTT, D-dimer) and disturbance of consciousness. The results showed that the serum ferritin level was an independent prognostic factor for adverse outcomes in model I–IV (Table 3).

Correlation Between Ferritin and Clinical Parameters

In our research, we found the ferritin level showed positive correlation with viral load ($r = 0.466$, $P < 0.0001$), ALT ($r = 0.502$, $P < 0.0001$), AST ($r = 0.627$, $P < 0.0001$), ALP ($r = 0.302$, $P < 0.0001$), CK ($r = 0.446$, $P < 0.0001$), LDH ($r = 0.446$, $P < 0.0001$), BUN ($r = 0.245$, $P = 0.0002$), Cr ($r = 0.150$, $P = 0.0238$), D-dimer ($r = 0.524$, $P < 0.0001$) and APTT ($r = 0.464$, $P < 0.0001$) and was inversely associated with PLT ($r = -0.407$, $P < 0.0001$) and ALB ($r = -0.313$, $P = < 0.0001$) (Fig. 3).

DISCUSSION

In view of the fast progress of SFTS disease and high case fatality rate, it is important to identify

Table 2 Characteristics of patients with different ferritin levels

	Low ferritin group (N = 158)	High ferritin group (N = 71)	P value
Age, years	61 (53–69)	63 (58–70)	0.048
Sex, male	70 (44.3%)	37 (52.1%)	0.341
Viral load (lg10 copies/ml)	3.04 (2.54–3.73)	4.37 (3.64–4.99)	< 0.001
WBC, g/l	2.17 (1.41–3.18)	2.25 (1.58–3.65)	0.279
NEU, g/l	1.22 (0.70–1.92)	1.38 (0.95–2.33)	0.127
LYM, g/l	0.57 (0.39–0.85)	0.59 (0.40–1.00)	0.736
PLT, g/l	47.00 (35.00–63.00)	34.5 (21.25–50.25)	< 0.001
ALT, U/l	62.00 (42.00–141.00)	133.00 (87.25–234.00)	< 0.001
AST, U/l	157.00(91.00–305.00)	420.00 (273.75–761.50)	< 0.001
ALP, U/l	62.00 (52.00–81.00)	92.00 (55.50–123.75)	< 0.001
ALB, g/l	31.30 (28.20–34.50)	28.95 (26.65–31.52)	0.001
BUN, mmol/l	4.43 (3.11–5.81)	5.43 (4.21–7.65)	< 0.001
Cr, μmol/l	69.10 (59.20–82.50)	78.85 (62.80–95.25)	0.008
CK, U/l	431.00 (236.00–966.00)	1090.00 (462.00–2266.00)	< 0.001
LDH, U/l	677.00 (463.00–907.00)	1485.00 (976.25–2088.00)	< 0.001
D-D, mg/l	2.35 (1.43–4.68)	5.53 (3.64–7.98)	< 0.001
PT, S	12.80 (12.20–13.60)	12.80 (12.30–13.60)	0.316
APTT, S	50.70 (45.10–57.80)	61.40 (53.00–74.17)	< 0.001
INR	0.98 (0.92–1.07)	0.99 (0.93–1.08)	0.236

Data are n (%) or median (interquartile range, IQR)

WBC white blood cell, *NEU* neutrophil, *LYM* lymphocyte, *PLT* platelet count, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *ALB* albumin, *BUN* blood urea nitrogen, *Cr* creatinine, *CK* creatine kinase, *LDH* lactate dehydrogenase, *D-D* D-dimer, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

critically ill patients early. Our study revealed the value of ferritin levels in assessing the risk of death in patients with SFTS.

The dynamic regulation of ferritin in normal iron metabolism is an important host regulatory mechanism. Further studies on primary inflammatory diseases have shown that apart from this homeostasis, ferritin is also a key marker of inflammatory pathology and a pathogenic participant, and its signal transduction is part of innate immune response and regulation of lymphocyte function. This effect is supported in clinical practice because it can be used not only as a biomarker of disease progression and prognosis, but also as a target for therapeutic intervention [10]. The predictive value of ferritin as a potential marker of critical clinical outcome was described by Lachmann et al. [18]; they found that the increase of ferritin was linked to the deterioration of clinical status. In addition, previous studies also showed that elevated serum ferritin levels can predict the severity and adverse outcome of patients

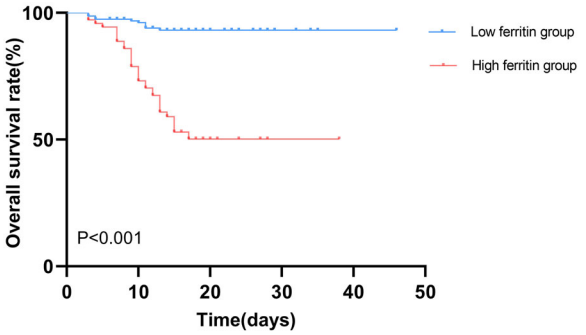

Fig. 2 Kaplan-Meier survival curves of OS between low and high ferritin groups. Log-rank test, $P < 0.05$ was considered statistically significant. *OS* overall survival

with influenza, dengue fever and COVID-19 [15, 19–21].

Studying the ROC curve, we found that the level of ferritin can predict the prognosis of patients with SFTS. In term of the results of the ROC curve, the patients were divided into a low and high ferritin group for further comparison. The K-M survival analysis showed that patients with higher levels of ferritin had a poorer prognosis ($P < 0.001$), as expected. To verify whether ferritin is an independent risk factor for the prognosis of patients with SFTS, we established Cox regression model I–IV according to the baseline results. Model II–IV adjusted the confounding factors such as age, viral load, liver and kidney function and blood coagulation function and showed that ferritin level was still an independent factor for adverse clinical outcomes in patients with SFTS (HR = 4.312, 95% CI 1.67–11.13, $P = 0.003$). In addition, the level of serum ferritin was positively correlated with viral load, ALT, AST, ALP, CK, LDH, BUN, Cr, D-D and APTT and negatively correlated with PLT and ALB, suggesting that with increasing ferritin level, damage to liver, kidney and coagulation function was aggravated to varying degrees.

Kupffer cells [22], macrophages [23–25] and proximal tubular renal cells [26] have been demonstrated to secrete ferritin in a variety of in vivo and in vitro conditions. Although macrophages are not the only source of serum ferritin, there is sufficient evidence to prove their role in its production. The main source of extreme methemoglobinemia in hemophagocytic histiocytosis (HLH) is activated macrophages in bone marrow or spleen [24, 27]. HLH reports were also available for patient with SFTS [28, 29]. Hemophagy was also observed in bone marrow of SFTS patients without HLH [30] because of the lack of bone marrow aspiration data. This study failed to make a further comparative analysis of patients with secondary HLH secondary to SFTSV infection. Animal studies of SFTS have also shown that activated macrophages in the spleen may show hemophagocytic activity, which may lead to methemoglobinemia [31]. Additionally, previous studies also showed that intracellular infection can induce ferritin secretion by activating secretory autophagy of human

Table 3 Univariate and multivariate Cox regression analysis of adverse outcomes

	Model I HR (95%CI)	Model II HR (95%CI)	Model III HR (95%CI)	Model IV HR (95%CI)
Low ferritin group ($N = 158$)	Reference	Reference	Reference	Reference
High ferritin group ($N = 71$)	7.951 (3.91–16.18)	7.288 (3.58–14.85)	3.694 (1.68–8.12)	4.312 (1.67–11.14)
P value	< 0.001	< 0.0001	0.001	0.003

Model I, unadjusted
Model II, adjusted for age
Model III, adjusted for model II plus viral load
Model IV, adjusted for model III plus laboratory variables (PLT, ALT, AST, ALP, ALB, BUN, Cr, CK, LDH, APTT, D-dimer)
HR Hazard ratio, *CI* confidence interval

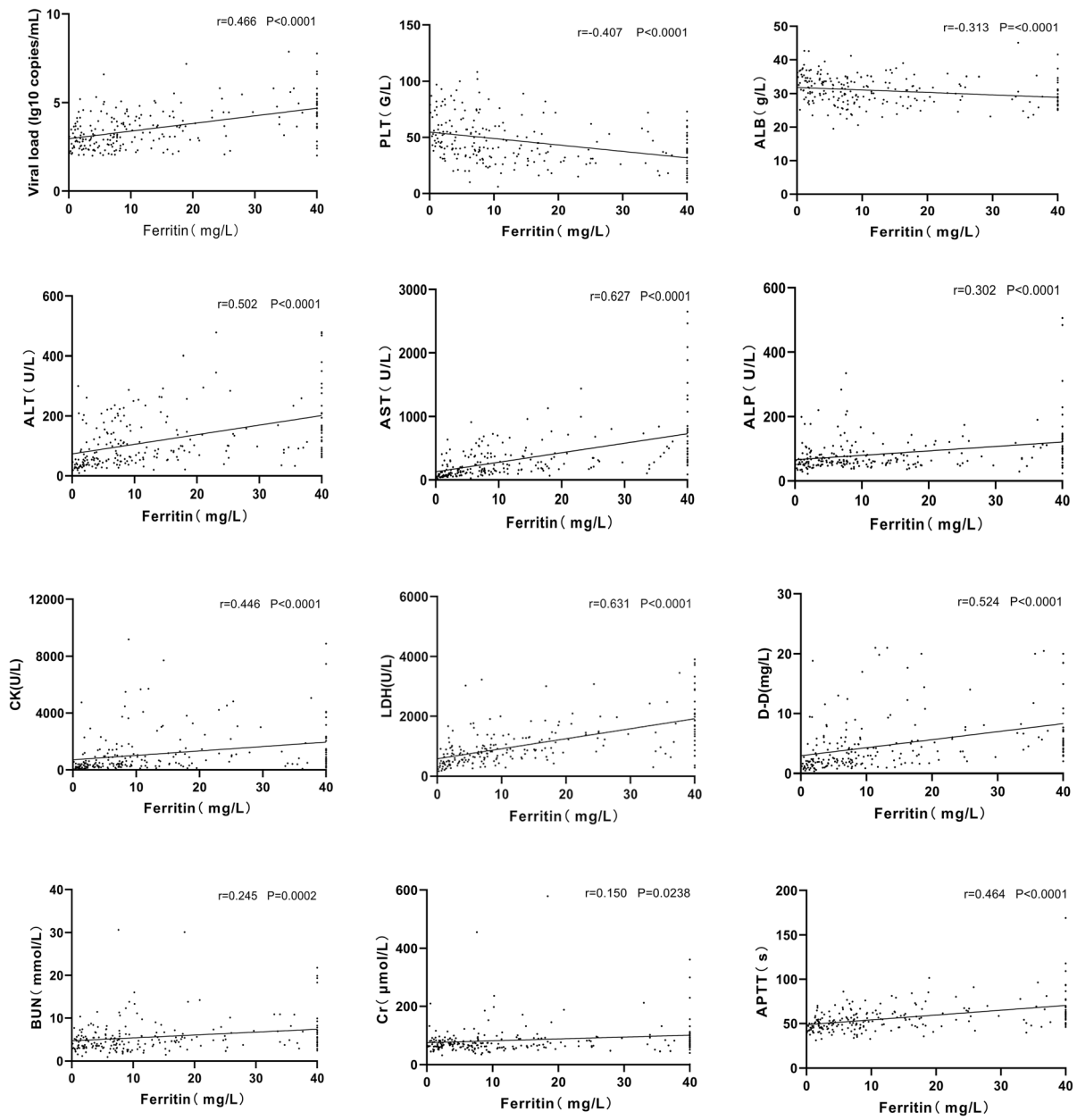

Fig. 3 Correlation between the ferritin and clinical parameters. *PLT* platelet count, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *CK* creatine kinase, *LDH* lactate dehydrogenase, *D-D* D-dimer, *BUN* blood urea nitrogen, *Cr* creatinine, *APTT* activated partial thromboplastin time

monocytes, resulting in a raise in serum ferritin [32]. Further studies are needed to explore the mechanism of elevated serum ferritin in patients with SFTS.

However, our research also has some limitations. First, this was a single-center retrospective study, which may bias our results. Second, we did not evaluate the dynamic level of the indicators. Therefore, further multicenter, large-sample, prospective randomized controlled trials are required to substantiate the effect of ferritin on the prognosis of patients with SFTS.

CONCLUSION

The serum ferritin level is a convenient early warning biomarker of adverse clinical outcomes. In clinical practice, this helps doctors pay more attention to patients with a high risk of fatal outcome.

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Author Contributions. Lei Zhao designed the work and revised the manuscript. Jiao Xie and Meng-Zhao Su contributed to the collection of data, participated in the statistical analysis of the data and drafted the manuscript. Yiping Dang contributed to the partial revision of the article. All authors read and approved the final manuscript.

Disclosures. Jiao Xie, Mengzhao Su, Yiping Dang and Lei Zhao declare that they have no conflict of interest in this research.

Compliance with Ethics Guidelines. The research protocol was approved by the Ethics committee of the Tongji Medical College of Huazhong University of Science and Technology and completed in accordance with the Declaration of Helsinki. The need to obtain informed consent from individual patients was waived, given the retrospective nature of the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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