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Evaluation of thrombospondin 1 as a novel biomarker in pediatric-onset systemic lupus erythematosus

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Abstract

Objective This study aimed to assess the potential of thrombospondin 1 (TBS-1) as a biomarker for pediatric-onset systemic lupus erythematosus (pSLE) and investigated its association with clinical characteristics and other laboratory tests in pSLE.

Methods A total of 112 pSLE and 50 age-matched and gender-matched healthy controls (HCs) were recruited in this study from January 2022 to June 2023 at West China Second University Hospital, Sichuan university. Plasma TBS-1 levels were measured, and clinical and laboratory findings were collected from the medical database.

Results The plasma TBS-1 level was significantly lower in pSLE patients (26778 ng/mL, IQR: 9875–59011) compared to HCs (100583 ng/mL, IQR: 58327–189547) ($P < 0.0001$). ROC analysis demonstrated that TBS-1 could effectively differentiate pSLE patients and HCs (AUC: 0.845, 95%CI: 0.785–0.905, $P < 0.0001$) with an optimal cut-off was 49,937 ng/mL, yielding a sensitivity of 84% and specificity of 70.5% based on the Youden index. Compared to TBS-1 positive patients, TBS-1 negative patients exhibited significant reductions in hemoglobin, IgM, and fibrinogen levels.

Conclusion In light of the current data, the efficacy of TBS-1 as a biomarker in pSLE diverged from its performance in adult SLE. In summary, TBS-1 shows potential as a biomarker for pSLE, particularly in hematological manifestations. Further investigations are essential to delve into the immunomodulatory roles of TBS-1 in the autoimmune pathways of pSLE.

Keywords Pediatric-onset systemic lupus erythematosus, Thrombospondin 1, Biomarker, Correlation

Introduction

Pediatric-onset systemic lupus erythematosus (pSLE) is a heterogeneous multisystem autoimmune/inflammatory disease characterized by disease-onset before 18 years of age and accounts for 15-20% of all systemic lupus erythematosus (SLE) cases [1]. It can affect every organ system and lead to significant damage, disability and even mortality. When compared to adult-onset SLE patients, pSLE patients exhibit higher disease activity, earlier development of damage and require more aggressive treatments [2]. Managing pSLE poses unique challenges due to patients' developmental stage and the potential

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long-term impact on their growth and development. The importance of laboratory testing in diagnosing pSLE cannot be overstated. Laboratory tests for pSLE are crucial in confirming the diagnosis, assessing disease activity, monitoring organ involvement, and guiding treatment decisions [3, 4].

Thrombospondin-1(TBS-1) is a 450-kDa glycoprotein mainly secreted by activated platelets [5]. In response to inflammatory environments or stress, it is also released by other normal cell types, such as fibroblasts, endothelial cells, smooth muscle cells, monocytes and macrophages [6–8]. TBS-1 has various physiological and pathophysiological functions in inflammation, angiogenesis, cell death, migration and immune regulation [9–14]. Its multifaceted functions make it an intriguing molecule to study in the context of autoimmune diseases. The effects of TBS-1 have been extensively investigated in numerous autoimmune disease studies [15–18]. Researchers have explored its impact on disease pathogenesis, disease activity, and potential therapeutic implications. TBS-1 was found to be upregulated in patients with branchiocardiac inflammatory myopathy (BCIM) associated with systemic sclerosis (SSc). TBS-1 and serum from patients with BCIM-SSc promoted proliferation and upregulation of the extracellular matrix in fibroblasts [16]. TBS-1 could mediate cellular communication to propagate inflammation and thrombus formation in antiphospholipid syndrome (APS) [17]. TBS-1 deficient mice were found to develop inflammation in the conjunctiva and experience a loss of goblet cell secretion, similar to that seen in patients with Sjögren's syndrome [18].

TBS-1 may serve as an immunomodulator contributing to the pathogenesis of various autoimmune diseases. However, there were few studies about the roles of TBS-1 in pSLE. Consequently, the objective of this study was to investigate the potential of TBS-1 as a biomarker for pSLE and evaluate its correlation with clinical characteristics and other laboratory tests in pSLE patients.

Methods and materials

Study populations

A total of 112 pSLE patients and 50 healthy controls (HCs) were enrolled between Jan 2022 and Jun 2023 at West China Second University Hospital, Sichuan University. All the pSLE patients included in the study met the diagnostic criteria of the 2021 Chinese Guidelines for the Diagnosis and Treatment of Childhood-onset Systemic Lupus Erythematosus [19]. The disease activity was assessed according to the SLE Disease Activity Index (SLEDAI) scoring system as outlined in the Chinese Guideline, classifying disease activity as mild (SLEDAI: 0–6), moderate (SLEDAI: 7–12) and severe (SLEDAI ≥ 13). This study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University (Approval No. 2023 – 289).

Laboratory tests

Laboratory and clinical findings were collected from the medical database of West China Second University Hospital, Sichuan University. These included parameters such as blood cell count, liver and renal function, coagulation function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum levels of immunoglobulins (IgG, IgM, IgA) and complement, as well as antiphospholipid antibodies. Additionally, demographic information, organ involvement, and medical history were also gathered for the participants in the study.

TBS-1 measurement

Remnant plasma samples obtained from routine clinical tests were collected and stored at – 80 °C until measurements of TBS-1. Plasma TBS-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Human TBS-1 ELISA Kit, CUSABIO, Wuhan, China) according to the manufacturer's instructions. Samples were tested in duplicate. The five-parameter logistic (5-PL) fitted standard curve was generated to calculate the TBS1 concentration based on the website of GainData® (arigo's ELISA Calculator) (https://www.arigobio.cn/ELISA-calculator).

Statistical analysis

The statistical significance was assessed using the independent Student t-test, Mann–Whitney U test, Chi-square test, as appropriate. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for data with abnormal distribution. Spearman's correlation was performed to determine the relationship between TBS-1 and other variables. The receiver operator characteristic (ROC) curve analysis was used to determine the optimal cut-off value of TBS-1 for distinguishing between pSLE patients and HCs. The cut-off value was determined by employing the Youden index, a reliable method commonly utilized to define the cut-off value in numerous articles [20–22]. The data analyses were calculated using SPSS version 22.0 statistical software (SPSS Inc., Chicago, Illinois, USA) or GraphPad Prism 9 (GraphPad Software Inc.). All statistical tests were two-sided, and *P*-values of less than 0.05 were considered statistically significant.

Results

Characteristics of pSLE and HCs

Detailed clinical and laboratory characteristics are presented in Table 1. A total of 112 pSLE patients (102 females and 10 males) and 50 HCs (46 females and 4

Table 1 Clinical characteristics of pSLE patients

	pSLE($n=112$)
Demography	
Sex(male, %)	10(8.93%)
Age(mean ± SD)	11.76 ± 2.79
Clinical manifestations, n (%)	
Facial erythema	69(69.00%)
Sun allergy	22(23.66%)
Oral ulcers	34(35.42%)
Hair loss	23(24.73%)
Renal involvement	64(62.75%)
Hematological involvement	38(50.00%)
Musculoskeletal involvement	28(29.47%)
Cardiovascular involvement	14(21.21%)
Nervous system involvement	24(35.29%)
Gastrointestinal involvement	10(13.33%)
Pulmonary involvement	8(12.12%)
Laboratory(mean ± SD)	
TBS-1(ng/mL)	42196.69 ± 43324.94
WBC(10^9/L)	7.56 ± 3.36
Lymphocyte count(10^9/L)	1.75 ± 1.01
PLT count(10^9/L)	254 ± 125.8
HGB(g/L)	120 ± 521.4
C3(g/L)	0.78 ± 0.41
C4(g/L)	0.16 ± 0.10
C1q(g/L)	18.36 ± 4.92
IgG(g/L)	9.46 ± 5.21
IgA(g/L)	1.36 ± 0.77
IgM(g/L)	0.93 ± 0.50
IgE(g/L)	172.71 ± 298.1
ESR(mm/h)	16.6 ± 18.61
CRP(mg/L)	2.15 ± 8.02
ALT(g/L)	29.79 ± 21.81
AST(g/L)	27.95 ± 11.19
Tbil(umol/L)	9.09 ± 5.79
Dbil(umol/L)	2.89 ± 2.55
ALP(U/L)	119.11 ± 82.92
GGT(U/L)	36.40 ± 55.49
BUN(mmol/L)	6.36 ± 4.68
Cr(umol/L)	49.80 ± 23.85
UA(umol/L)	333.16 ± 106.88
TG(mmol/L)	0.57 ± 2.1
TC(mmol/L)	4.9 ± 3.32
LDL(mmol/L)	2.8 ± 1.6
HDL(mmol/L)	1.91 ± 1.17
PT(s)	11.86 ± 3.58
APTT(s)	28.05 ± 5.45
TT(s)	17.83 ± 1.49
Fbg(mg/dL)	299.39 ± 132.32

SD = standard deviation; WBC = white blood cell; PLT = platelets; HGB = hemoglobin; C3 = complement 3; C4 = complement 4; C1q = complement C1q; IgG = immunoglobulin G; IgA = immunoglobulin A; IgM = immunoglobulin M; IgE = immunoglobulin E; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; Dbil = direct bilirubin; ALP = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase; BUN = blood urea nitrogen; Cr = creatinine; UA = uric acid; TG = triglyceride; TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time; Fbg = fibrinogen; pSLE = pediatric-onset Systemic lupus erythematosus

males) were enrolled in this study. There were no significant differences in the distributions of gender and age between pSLE patients and HCs (both $P>0.05$). According to the SLEDAI score, the study group was categorized into three groups: mild disease activity group ($n=50$), moderate disease activity group ($n=19$) and severe disease activity group ($n=36$). Among the 112 pSLE patients, the renal system ($n=64$), hematological system ($n=38$) and nervous system ($n=24$) were the most frequently affected systems as shown in Table 1. The most common symptoms observed in the pSLE group were facial erythema ($n=69$), hypocomplementemia ($n=61$), proteinuria ($n=44$), hematuria ($n=30$) and pyuria ($n=30$).

Plasma TBS-1 levels are significantly lower in pSLE

The workflow diagram outlining the methodology of this study can be seen in Fig. 1. Plasma TBS-1 level in patients with pSLE (26778 ng/mL, IQR: 9875–59011) was significantly lower than that in HCs (100583 ng/mL, IQR: 58327–189547) ($P<0.0001$) (Fig. 2A). ROC curve analysis was performed for TBS-1 to distinguish between pSLE patients and HCs. The area under curve (AUC) for TBS-1 was determined to be 0.845 (95%CI: 0.785–0.905, $P<0.0001$) and the optimal cut-off was 49,937 ng/mL with a sensitivity of 84%, and a specificity of 70.5% based on the Youden index (Fig. 2B).

Characteristics of patients with pSLE according to TBS-1 levels

Subsequently, patients with pSLE were categorized into two groups, namely TBS-1-positive (TBS-1+) and TBS-1-negative (TBS-1–), using a predefined cut-off value (Fig. 2C). The clinical and laboratory characteristics of these two groups are presented in Fig. 3 and Table S1. Compared to TBS-1 + patients, TBS-1 – patients exhibited significant reductions in hemoglobin (HGB), IgM and fibrinogen (Fbg) levels (Fig. 3A). However, apart from these findings, both TBS-1 + and TBS-1 – patients demonstrated similar laboratory characteristics, including blood cell count, C3, C4, ESR, CRP, alanine

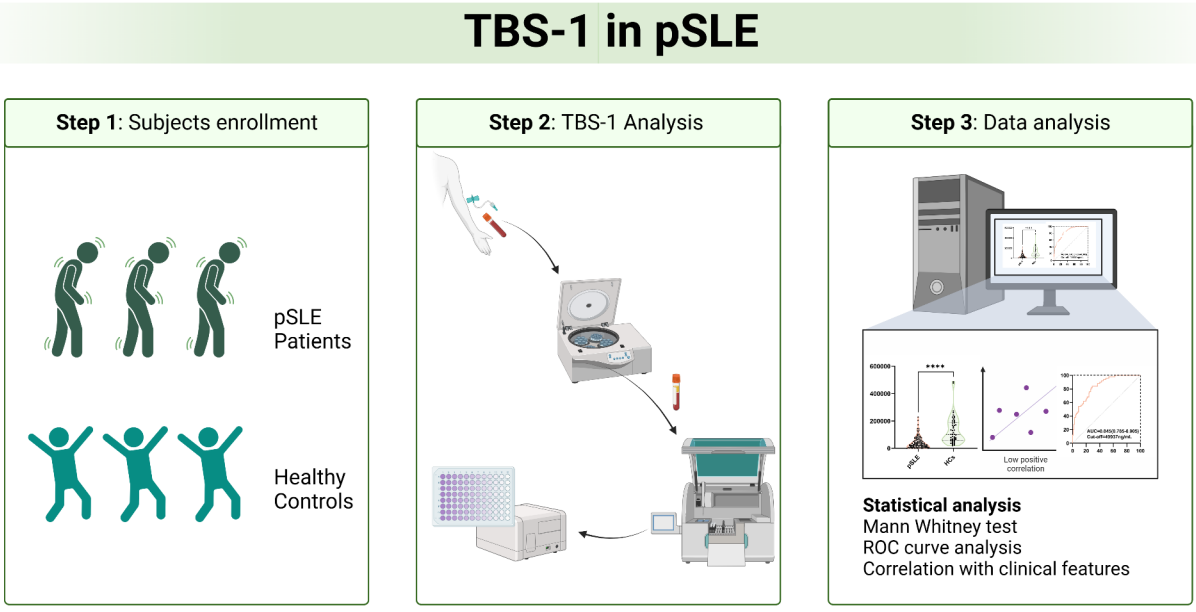

Fig. 1 The workflow diagram of this study (created with BioRender.com)
TBS-1 = thrombospondin-1; pSLE = pediatric-onset systemic lupus erythematosus; ROC = receiver operator characteristic

aminotransferase, creatinine, among others, with no observed statistically significant differences (P>0.05) (Figure S1).

Regarding clinical relevance, no significant differences were observed. TBS-1 – patients displayed a higher proportion of renal involvement, hematological involvement, and gastrointestinal involvement compared to TBS-1 + patients. Furthermore, the proportion of pulmonary involvement in the TBS-1 – patients was approximately twice that of the TBS-1 + patients (Fig. 3B); nevertheless, these differences did not reach statistical significance (P>0.05). We have further classified organ involvement in pSLE into two categories: common organ involvement and rare organ involvement. Commonly affected organs include the skin, kidney, brain, joint and peripheral blood. Rare organ involvement encompasses the heart, lungs, liver, pancreas, and others. Figure 3C of the Sankey plot demonstrates the disparities in organ involvement between the TBS-1 + and TBS-1 – patients. It was observed that the TBS-1 – patients exhibited a higher prevalence of both common (94.8% vs. 84.4%) and rare (22.1% vs. 15.6%) organ involvement compared to the TBS-1 + patients, suggesting a potential association between TBS-1 and the risk of organ involvement in pSLE.

The comparison of TBS-1 levels between the groups with and without clinical manifestations was summarized in Table S2. Similar to the previous analysis involving laboratory parameters, a significant difference in TBS-1 levels was found between the groups with and without hemolytic anemia (22442ng/mL, IQR:7288-40211ng/mL vs. 37844ng/mL, IQR:18701-74618ng/mL, P = 0.025). The TBS-1 levels in pSLE patients with antinuclear antibody (ANA) titers greater than 1:320 were significantly lower compared to pSLE patients with ANA titers equal to or less than 1:320, and this difference was statistically significant (23092 ng/mL, IQR: 9020–47112 ng/mL vs. 36034 ng/mL, IQR: 16547–74306 ng/mL, P = 0.042).

Correlations of TBS-1 with laboratory parameters

We conducted further investigations to explore the relationship between TBS-1 levels and various laboratory parameters, aiming to assess the effectiveness of TBS-1 as a biomarker for pSLE (Fig. 4A). Our findings revealed positive correlations between TBS-1 levels and specific laboratory characteristics, namely: hemoglobin (r = 0.2076, P = 0.0303), IgM (r = 0.2452, P = 0.0098), and Fbg (r = 0.4536, P = 0.0104) (Fig. 4B). Conversely, no statistically significant correlations were observed between TBS-1 levels and other laboratory parameters.

Discussion

The pathogenesis of SLE involves the abnormal activation of immune cells, increased expression of pro-inflammatory cytokines, and impaired clearance of apoptotic cells [23]. These factors play a crucial role in the development and progression of disease. While previous studies have suggested that TBS-1 can exhibit either pro-inflammatory or anti-inflammatory properties depending on the specific context [24, 25], its role in SLE, particularly in pediatric SLE, remains largely unexplored. Therefore, the objective of this study is to investigate the involvement of TBS-1 in the development of SLE, with a specific focus on pSLE. By examining the expression and activity

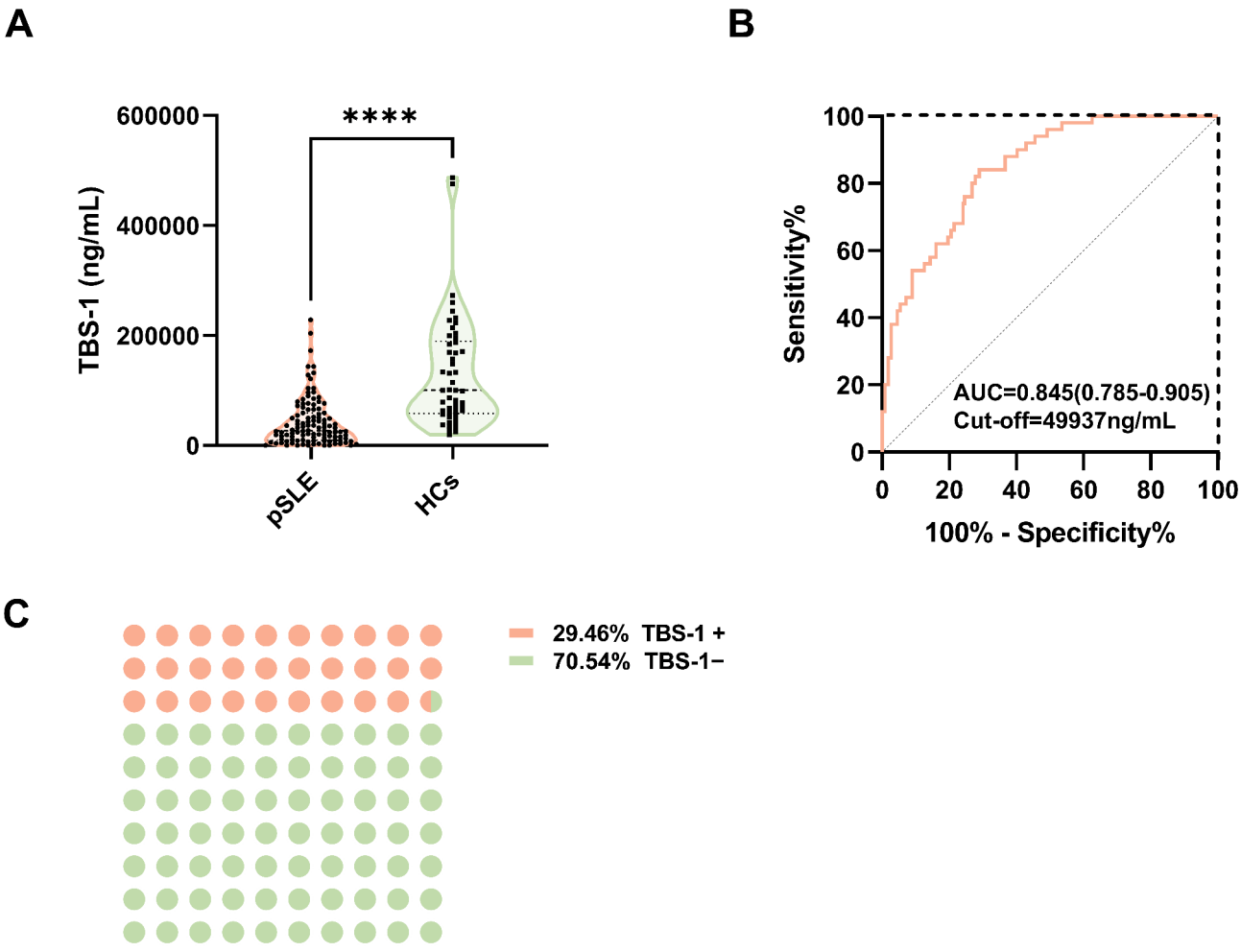

Fig. 2 The TBS-1 levels in the pSLE and HCs group. (**A**) Comparison of TBS-1 in the plasmas of the pSLE and HCs group. (**B**) ROC curve for the TBS-1 between the pSLE and HCs group. (**** $P < 0.0001$). (C) The distribution of patients with TBS-1-positive (TBS-1+) and TBS-1-negative (TBS-1−) pSLE according to the cut-off value

TBS-1 = thrombospondin-1; pSLE = pediatric-onset systemic lupus erythematosus; HCs = healthy controls; ROC = receiver operator characteristic; AUC = area under curve

of TBS-1 in pSLE patients, we aim to shed light on its potential contribution to the pathogenesis of the disease. To the best of our knowledge, this study represents the pioneering attempt to explore the correlation between plasma TBS-1 levels and pSLE.

In this study, we measured the plasma levels of TBS-1 in both pSLE patients and HCs. Our findings demonstrated a significant reduction in TBS-1 levels among pSLE patients when compared to HCs. This finding suggests a potential dysregulation of TBS-1 in the context of pSLE. Furthermore, we sought to explore the clinical relevance of TBS-1 in pSLE patients. Our investigation uncovered a significant correlation between the decreased TBS-1 levels and a decline in IgM, HGB, and Fbg levels. This finding suggests that the reduced TBS-1 levels may be associated with alterations in these laboratory parameters, indicating its potential involvement in the disease process of pSLE. However, it is important to note that we did not observe a significant correlation between TBS-1 levels and the explicit SLEDAI score, which is commonly used to measure disease activity in SLE patients. This suggests that TBS-1 may not directly correlate with disease activity as assessed by SLEDAI.

Angiogenesis serves as an indicator of activity in chronic inflammatory conditions like SLE and atherosclerosis [26]. Previous research has indicated that TBS-1 can impede angiogenesis by inhibiting the adhesion and activation of leukocytes and endothelial cells, thereby mitigating inflammation [27–29]. Based on this knowledge, it is hypothesized that the decreased expression of TBS-1 in pSLE patients may contribute to increased angiogenesis, thereby promoting disease activity in SLE. These findings suggest that TBS-1 may play an immunomodulatory role in the autoimmune processes involved in pSLE.

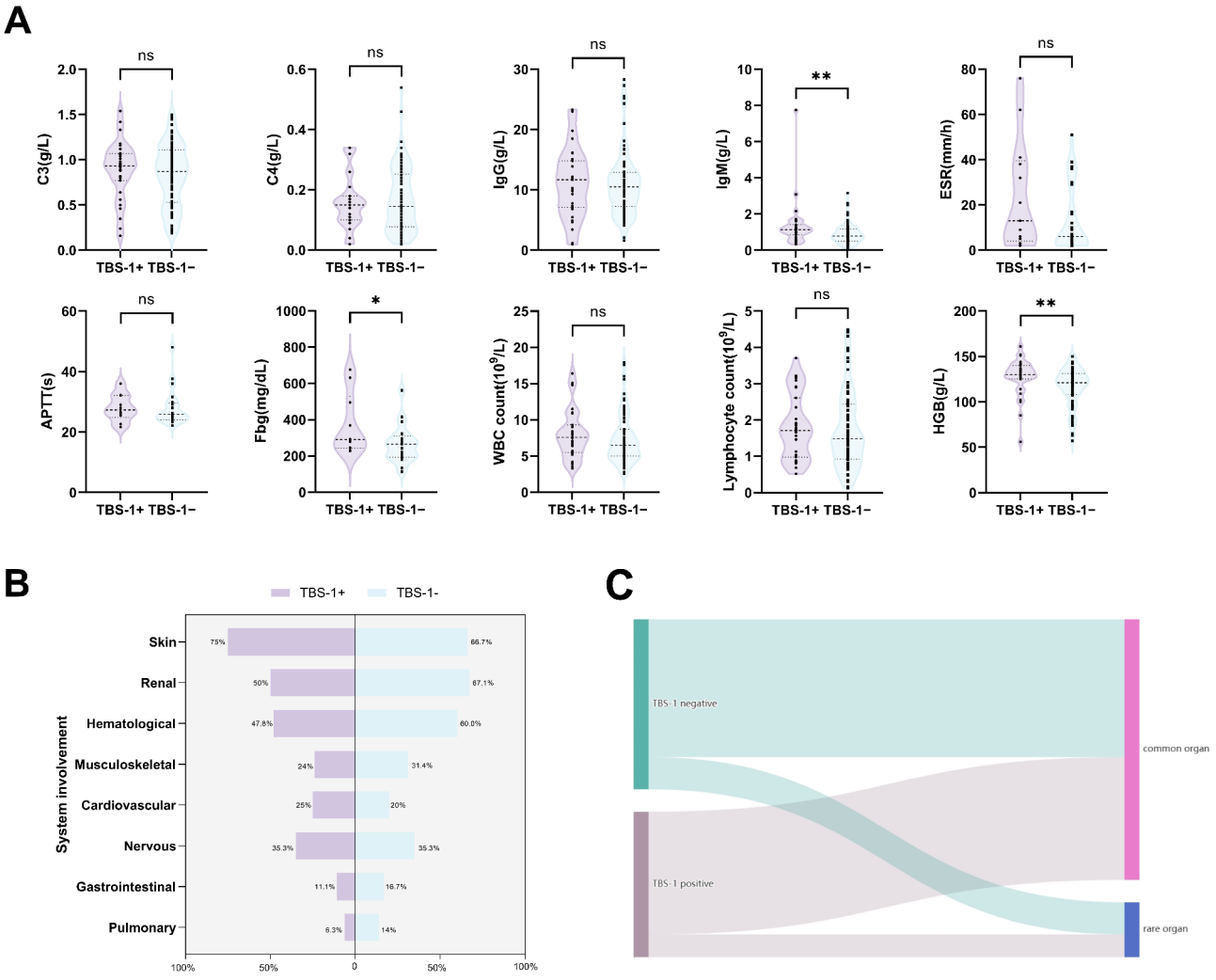

Fig. 3 Comparison of the clinical features between patients with TBS-1-positive (TBS-1+) and TBS-1 negative (TBS-1−) pSLE. (**A**) Violin plots for the comparison of the laboratory test results (C3, C4, IgG, IgM, ESR, APTT, Fbg, WBC count, Lymphocyte count, HGB) between TBS-1 + and TBS-1 − patients. (*$P < 0.05$, **$P < 0.01$, ns = not statistically significant). (**B**) Comparison of the system involvement between TBS-1 + and TBS-1 − patients. (**C**) Sanky plot summarizes the organ involvement between TBS-1 + and TBS-1 − patients

C3 = complement 3; C4 = complement 4; IgG = immunoglobulin G; IgM = immunoglobulin M; ESR = erythrocyte sedimentation rate; APTT = activated partial thromboplastin time; Fbg = fibrinogen; WBC = white blood cell; HGB = hemoglobin; TBS-1 = thrombospondin-1; pSLE = pediatric-onset systemic lupus erythematosus

Furthermore, while there have been studies examining the association of serological detection of TBS-1 in adult SLE [15], notable variations in performance have been observed between adults and children. In our study, we did not find a significant difference in TBS-1 levels between the group of patients with lupus nephritis and the group without lupus nephritis. This discrepancy differs from the findings of the most recent study conducted in adults with lupus nephritis [30]. Our findings also differ from studies that have reported significant differences in TBS-1 levels between active renal SLE and active non-renal SLE [6]. It emphasizes the importance of considering such variations and the need for further research to accurately understand the role of TBS-1 in different subsets of SLE patients, particularly in pediatric cases and those with renal involvement.

High-titer ANA is a characteristic feature of pSLE at the time of diagnosis [31, 32]. In our study, we observed that pSLE patients with ANA titers greater than 1:320 exhibited significantly lower TBS-1 levels compared to pSLE patients with ANA titers equal to or less than 1:320. However, we did not find significant differences in TBS-1 levels between the groups based on anti-double-stranded (anti-dsDNA) antibodies positivity or negativity. These findings diverge from the results of correlation studies between TBS-1 and anti-dsDNA antibodies in adult SLE patients [15]. These discrepancies highlight the potential differences in TBS-1 expression and its clinical

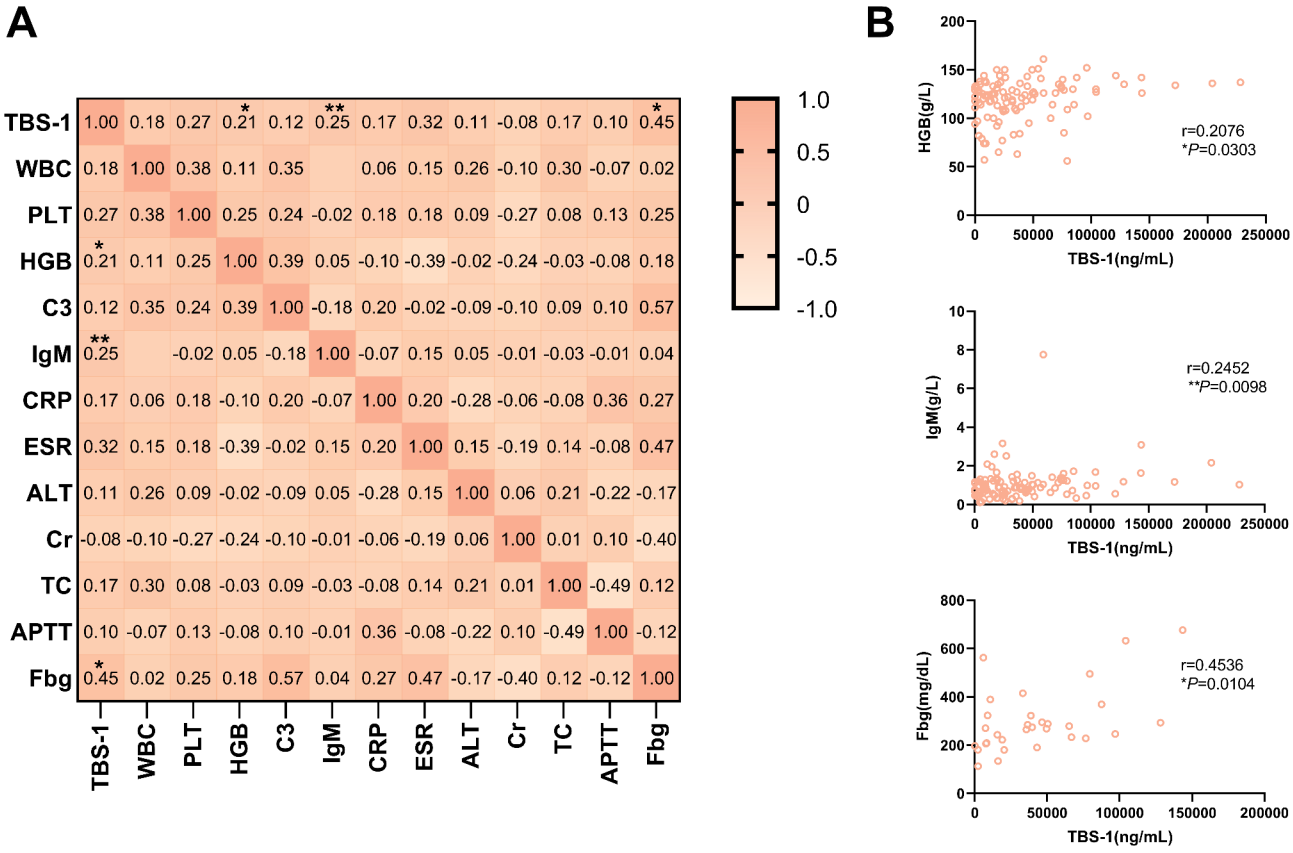

Fig. 4 The correlation between TBS-1 levels and clinical features. (**A**) Heatmap for the correlation between TBS-1 levels and clinical features. (*$P < 0.05$, **$P < 0.01$). (**B**) Scatter plots display the statistically significant correlation between laboratory parameters (IgM, Fbg, HGB) and TBS-1 levels
C3 = complement 3; IgM = immunoglobulin M; CRP = C- reactive protein; ESR = erythrocyte sedimentation rate; ALT = alanine aminotransferase; Cr = creatinine; TC = total cholesterol; APTT = activated partial thromboplastin time; Fbg = fibrinogen; WBC = white blood cell; PLT = platelets; HGB = hemoglobin; TBS-1 = thrombospondin-1

implications between pediatric and adult populations with SLE.

Recent research has highlighted the significance of hematological manifestations in SLE patients, as these manifestations contribute to increased in-hospital mortality [33]. These manifestations include lymphopenia, anemia, and thrombocytopenia [33]. It has been suggested that TBS-1 is particularly released by activated platelets, suggesting that the decreased plasma TBS-1 levels in pSLE patients may be secondary to reduced platelet counts. However, in our pSLE patients' group, we did not observe a direct correlation between TBS-1 levels and platelet counts. This implies that the decreased plasma levels of TBS-1 in these patients may have been caused by reduced platelet activation and degranulation, rather than a decrease in platelet count [34]. Moreover, while anti-cardiolipin antibodies (ACL) have been reported to induce chronic platelet activation in SLE patients [35], we did not identify a correlation between TBS-1 levels and ACL. Additionally, research has suggested that HGB can stimulate platelet activation and act as a regulator for the release of TBS-1 [36]. In our study, we observed a positive correlation between TBS-1 levels and HGB levels. Furthermore, we found that pSLE patients with concurrent anemia had lower levels of TBS-1 compared to those without anemia. Further research is needed to explore the specific cellular sources of TBS-1 in pSLE and to better understand its potential implications.

However, our study has limitations for the absence of a disease control group, such as another non-lupus autoimmune disease, primarily due to the low prevalence of other autoimmune conditions in children. Otherwise, TBS-1 levels were only measured at baseline, and any alterations in TBS-1 levels following treatment remain unknown.

These findings highlight the potential significance of TBS-1 in pSLE and its association with specific laboratory parameters. It is imperative to elucidate the underlying mechanisms and clinical implications of TBS-1 dysregulation in pSLE, as well as explore its potential as a biomarker for disease monitoring and as a target for therapeutic interventions.

Conclusion

In light of the current data, the efficacy of TBS-1 as a biomarker in pSLE diverged from its performance in adult SLE. In summary, TBS-1 shows potential as a biomarker for pSLE, particularly in hematological manifestations. Further investigations are essential to delve into the immunomodulatory roles of TBS-1 in the autoimmune pathways of pSLE.

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area the under-curve
BUN	Blood urea nitrogen
C1q	Complement 1q
C3	Complement 3
C4	Complement 4
CI	Confidence interval
Cr	Creatinine
CRP	C-reactive protein
CYSC	Cystatin C
Dbil	Direct bilirubin
ESR	Erythrocyte sedimentation rate
Fbg	Fibrinogen
GGT	Gamma-glutamyl transpeptidase
HCs	Healthy controls
HDL	High-density lipoprotein
HGB	Hemoglobin
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQR	Interquartile range
LDL	Low-density lipoprotein
PLT	Platelet
pSLE	Pediatric-onset systemic lupus erythematosus
PT	Prothrombin time
ROC	Receiver operator characteristic
SD	Standard deviation
SLEDAI	Systemic lupus erythematosus disease activity index
Tbil	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
TT	Thrombin time
UA	Uric acid
WBC	White blood cell count

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05542-7 .

Supplementary Material 1

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Not applicable.

Author contributions

CL contributed to data analysis and manuscript drafting. LY and MZ designed the experiment and performed statistical analysis. JL and ZL were responsible for sample and data drafting. TL and YJ provided research supervision and critically revised the manuscript for important intellectual content. All authors have reviewed and approved the final version of the manuscript and take full responsibility for its accuracy and integrity.

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Data availability

Data will be made available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of West China Second University Hospital, Sichuan University (Approval No. 2023 – 289). Written informed consents were obtained from all participants' parents or other legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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