Subtype-specific associations between serum lipid profiles and disease severity in patients with amyotrophic lateral sclerosis

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Received November 18, 2025; Accepted February 5, 2026

DOI: 10.3892/br.2026.2141

Abstract. Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disorder. Notably, the differences in lipid metabolism between bulbar- and limb-onset subtypes of ALS remain unclear, particularly in non-Western populations. The present study investigated serum lipid profiles in a Chinese cohort of patients with ALS to explore their associations with disease severity and clinical subtypes. A retrospective, cross-sectional study was conducted, involving 158 patients with ALS and 62 matched healthy controls. Serum lipid parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), small dense LDL cholesterol (sdLDL-c), apolipoprotein A-1 (ApoA1), apolipoprotein B (ApoB) and the TG/HDL ratio, were compared between the groups. Correlation analyses and multivariable linear regression models incorporating phenotype x lipid interaction terms were conducted after adjusting for age, sex, body mass index and disease duration. Patients with ALS exhibited significantly higher TC, TG, LDL, sdLDL-c, ApoA1, ApoB and TG/HDL ratios than controls. Subtype-specific analyses revealed different associations; in bulbar-onset ALS, higher sdLDL-c and TG/HDL ratios were associated with better functional status, whereas higher HDL and ApoA1 levels were negatively correlated with functional status. By contrast, in limb-onset ALS, higher sdLDL-c and ApoB levels were associated with worse function. Interaction analyses confirmed significant phenotype modification for sdLDL-c, TG/HDL ratio, HDL and ApoA1. These results suggest that lipid-severity relationships in ALS vary by subtype, indicating metabolic heterogeneity across phenotypes and supporting the potential of specific lipid parameters as exploratory markers for disease monitoring.

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Abbreviations: ALS, amyotrophic lateral sclerosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense low-density lipoprotein cholesterol; Apo, apolipoprotein

Key words: ALS, clinical subtypes, serum lipid profiles, disease severity, Chinese cohort

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the progressive loss of upper and lower motor neurons, leading to muscle weakness, atrophy, and paralysis. As the disease progresses, patients experience impairments in speech, swallowing, respiration, and limb function, with most succumbing to respiratory failure within 3-5 years of symptom onset (1,2). Clinical heterogeneity is a hallmark of ALS, with bulbar- and limb-onset ALS being the two predominant subtypes. Bulbar-onset ALS manifests with dysarthria and dysphagia due to degeneration in the bulbar regions, while limb-onset ALS is characterized by weakness and fasciculations in the extremities (3-7). These phenotypes differ not only in clinical manifestations but also in prognosis; although less common, bulbar-onset ALS typically exhibits

rapid disease progression and is associated with shorter survival (3-5). Emerging evidence further suggests that subtype-specific pathophysiological features involve distinct neural pathways and genetic risk factors (8-11). However, therapeutic strategies still primarily target ALS as a single entity (12,13), overlooking potential subtype-specific targets.

Dyslipidemia in ALS, characterized by altered cholesterol and triglyceride levels, has been associated with both neuroprotective and deleterious effects, suggesting a multifaceted and context-dependent role in disease pathogenesis (14-18). Some studies report that hyperlipidemia and a higher body mass index may slow disease progression and improve survival (16,19), whereas others associate lipid abnormalities with worse prognosis (20-22). These inconsistencies likely stem from variations in study design, evaluated lipid markers, and patient cohorts. Notably, most studies have treated ALS as a uniform disease, with limited consideration of heterogeneity across clinical subtypes. This gap is significant as bulbar- and limb-onset ALS exhibit distinct clinical trajectories, and emerging evidence indicates potential differences in metabolic mechanisms.

Most existing studies have been conducted in Western populations (14-21), raising uncertainties about the generalizability of the findings to other regions. The regional and ethnic differences in both ALS epidemiology and metabolic risk factors highlight the importance of investigating non-Western cohorts (23-25). While some studies have explored the lipid profiles in Chinese patients with ALS, systematic analyses focusing on subtype-specific associations remain scarce.

In this study, we investigated serum lipid profiles in a Chinese ALS cohort, specifically exploring whether the association with disease severity varied between bulbar- and limb-onset subtypes. Through correlation analyses and multivariable interaction models, our objective was to determine if lipid parameters have subtype-specific effects on functional impairment. These analyses provide new insights into the metabolic heterogeneity of ALS and may contribute to the development of more tailored prognostic assessments and management strategies across clinical subtypes.

Materials and methods

Patients and ethical considerations. This retrospective, cross-sectional study analyzed clinical data from patients with ALS and age- and sex-matched healthy controls treated between March 2022 and July 2024 at the Hubei Provincial Hospital of Traditional Chinese Medicine, China. The study 158 patients with ALS showing clinical and electrophysiological signs of both upper and lower motor neuron involvement, following the revised Gold Coast criteria (26). Exclusion criteria included patients diagnosed with a history of neurological disorders that could impact the assessment, such as brain injury, stroke, alcohol/substance-related disorders, depression, and major psychiatric conditions. Comprehensive demographic and clinical data were collected during the initial visit. The severity of ALS was evaluated using the revised ALS Functional Rating Scale (ALSFRS-R) (27). Disease onset was defined as the patient-reported time of the initial symptoms, i.e., the first paresis in spinal-onset ALS or speech/swallowing disturbances in bulbar-onset ALS. Additionally, 62 age- and sex-matched Healthy controls (HCs) were retrospectively enrolled from the Hubei Provincial Hospital of Traditional Chinese Medicine. All participants provided written informed consent. The study received approval from the Ethics Committee of the Hubei University of Chinese Medicine (approval no. HBZY1022-C42-02). Fig. 1 illustrates the study design flowchart.

Blood test. Blood samples from patients with ALS and healthy individuals were collected between 7:00 a.m. and 10:00 a.m. following an overnight fast of 8 h. Serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), small dense LDL cholesterol (sdLDL-c), apolipoprotein A-1 (ApoA1), and apolipoprotein B (ApoB) were measured using an automatic biochemical analyzer (ADVIA 2400; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), following the manufacturer's protocols.

Statistical analysis. Descriptive statistics were employed to summarize the patient characteristics. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were compared between subgroups utilizing an independent-samples t-test, while non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were compared employing the χ^2 test. One-way ANOVA with Tukey's post-hoc test was utilized for multiple group comparisons, and Spearman's correlation analyses were conducted to evaluate the relationships between serum lipid biomarkers and disease severity.

To assess whether the relationships between lipid parameters and ALS severity varied by clinical subtype, we conducted distinct multivariable linear regression models with ALSFRS-R score as the dependent variable. Each lipid parameter was included in the model with an interaction term (phenotype x lipid value). Phenotypes were categorized as 0=limb-onset and 1=bulbar-onset, while sex was categorized as 0=male and 1=female. The models were adjusted for age, sex, body mass index (BMI), and disease duration. Regression coefficients with 95% confidence intervals and P-values were reported. Statistical analyses were performed using JASP software (JASP Team, Amsterdam, Netherlands). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic and clinical characteristics. The characteristics of the patients with ALS and HCs are summarized in Table I. The ALS cohort comprised 158 patients (105 males, 53 females) with an average age of 53.01±10.84 years at examination. Among these, 30 presented with bulbar onset, while 128 had limb onset. The most prevalent age group was 49-59 years (38.6%). Only 22.8% of the patients were from Hubei province, whereas the remaining 77.2% were individuals from other regions of China who sought diagnosis and treatment at the Hubei Provincial Hospital of Traditional Chinese Medicine. The average age at symptom onset was 50.7±10.7 years. The median diagnostic delay was 11 months, and the median disease duration at assessment was 21.4 months.

Table I. Comparison of demographic and clinical characteristics between patients with ALS and HCs.

Characteristic	Patients with ALS (n=158)	HCs (n=62)
Sex, male/female	105/53	35/27
BMI, kg/m^2	23.22±3.92	24.15±3.49
Age at interview, years[a]	53.01±10.84	49.96±12.18
Age of onset, years[a]	50.67±10.65	NA
Site of onset, spinal/bulbar	128/30	NA
Diagnostic delay, months[a]	11.0 (6.06-19.38)	NA
Disease duration, months[a]	21.4 (10.42-37.65)	NA
ALSFRS-R score[a]	36.0 (30.0-41.0)	NA

[a]Data are presented as the mean ± SD or median (Q1-Q3). ALS, amyotrophic lateral sclerosis; NA, not applicable; HCs, healthy controls; BMI, body mass index; ALSFRS-R, ALS Functional Rating Scale.

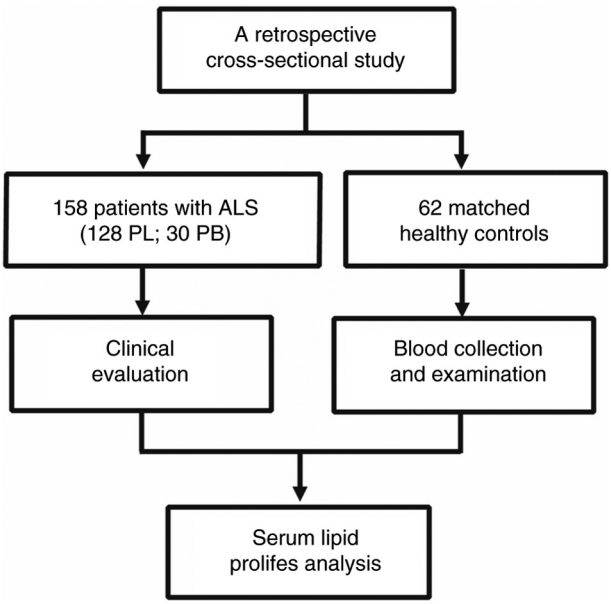

Figure 1. Flow chart of the study design. ALS, amyotrophic lateral sclerosis; PL, patients with limb-onset ALS; PB, patients with bulbar-onset ALS.

The control group comprised 62 individuals (35 males, 27 females) with a mean age of 49.96±12.18 years. No significant variations in age or sex were observed between patients and controls. The mean BMI was slightly lower in ALS patients (23.22±3.92 kg·m^{-2}) compared with controls (24.15±3.49 kg·m^{-2}), although this variance was not statistically significant.

Blood lipid levels in patients with ALS. Compared with controls, patients with ALS exhibited significantly elevated serum levels of TC, TG, LDL, sdLDL-c, ApoA1, ApoB, and the TG/HDL ratio (Fig. 2). Stratification by disease duration revealed that patients with a disease duration exceeding 12 months demonstrated higher levels of TC, TG, LDL, sdLDL-c, and ApoB compared with both controls and patients with a duration of less than 12 months. Particularly, TG levels and the TG/HDL ratio were significantly higher in patients with longer disease duration than in those with shorter disease duration (Fig. 3).

Correlation of total cholesterol with ALS severity. A significant negative correlation was observed between TC and ALSFRS-R scores (r_s=-0.3113, P=0.0005), indicating that higher cholesterol was associated with greater functional impairment (Fig. 4). No significant correlations were observed for TG, LDL, sdLDL-c, ApoA1, ApoB, or the TG/HDL ratio at diagnosis (Fig. 4).

Blood lipid levels according to the site of disease onset. To assess whether lipid profiles differed by clinical phenotype, patients with ALS were categorized according to the onset site. The limb-onset cohort comprised 87 males and 41 females, with a median age of 51.5 years, a diagnostic delay of 7.8 months, and a disease duration of 16.4 months at the time of sampling. In contrast, the bulbar-onset group consisted of 18 males and 12 females with a median age of 50.0 years, a diagnostic delay of 8.4 months, and a disease duration of 26.6 months. Notably, patients with bulbar-onset ALS exhibited a significantly prolonged disease duration compared to those with limb-onset ALS (P=0.030), while displaying slightly lower ALSFRS-R scores (P=0.111). There were no significant differences were observed in sex distribution (P=0.405), age (P=0.710), diagnostic delay (P=0.148) or BMI (P=0.741) between the two subgroups (Table II).

Limb-onset patients had higher proportions of elevated LDL and sdLDL-c levels compared with bulbar-onset patients (Table II). Both subgroups demonstrated significantly elevated TC, TG, and ApoB levels in comparison to the controls, while HDL and ApoA1 levels were similar. Notably, TG, sdLDL-c, and the TG/HDL ratio were elevated in limb-onset patients compared with bulbar-onset patients (Fig. 5).

Associations between lipid profiles and disease severity by subtypes. Correlation analyses indicated subtype-dependent associations between lipids levels and ALS severity. In both subgroups, higher TC was associated with lower ALSFRS-R scores (limb-onset: r_s=-0.2977, P=0.0028; bulbar-onset: r_s=-0.4036, P=0.0454). Among bulbar-onset patients, TG (r_s=0.4292, P=0.0255), sdLDL-c (r_s=0.5158, P=0.0285), and TG/HDL ratio (r_s=0.4201, P=0.0291) exhibited positive correlations with ALSFRS-R scores, whereas HDL (r_s=-0.3988, P=0.0394) and ApoA1 (r_s=-0.4304, P=0.0404) were inversely

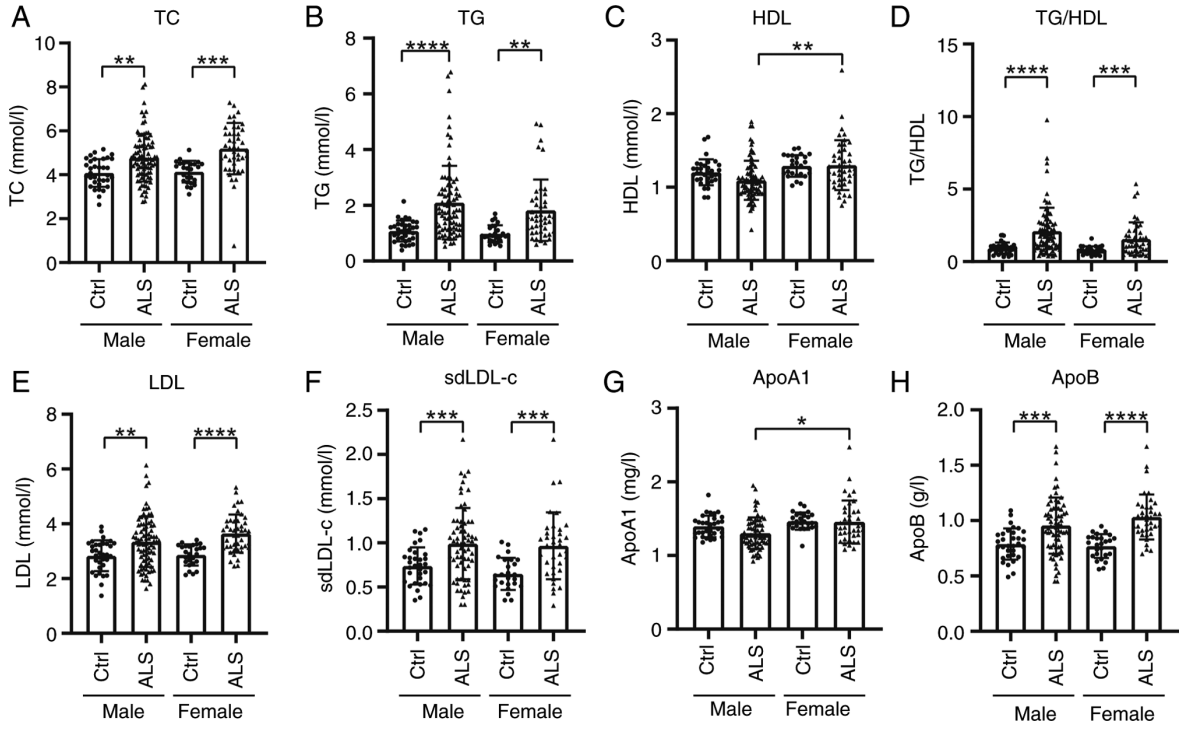

Figure 2. Serum lipid profiles in patients with ALS by sex. Serum lipid levels of (A) TC, (B) TG, (C) HDL, (D) TG/HDL, (E) LDL, (F) sdLDL-c, (G) ApoA1 and (H) ApoB in patients with ALS and Ctrls, categorized by sex. ****P<0.0001; ***P<0.001; **P<0.01; *P<0.05. ALS, amyotrophic lateral sclerosis; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein; Ctrl, control.

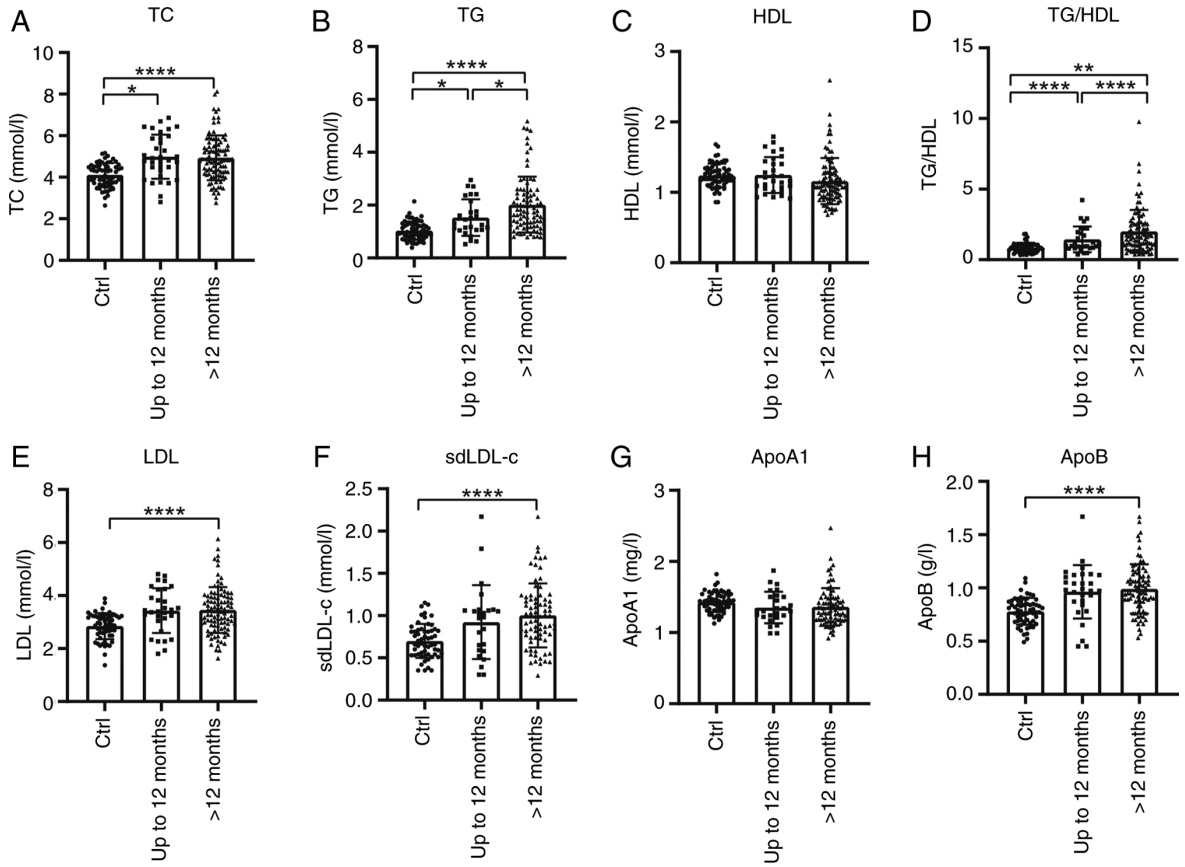

Figure 3. Serum lipid profiles in patients with ALS based on disease duration. Serum lipid levels (A) TC, (B) TG (B), (C) HDL, (D) TG/HDL, (E) LDL, (F) sdLDL-c, (G) ApoA1 and (H) ApoB in patients with ALS and Ctrls, categorized by disease duration (up to 12 months vs. >12 months). ****P<0.0001; **P<0.01; *P<0.05. ALS, amyotrophic lateral sclerosis; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein; Ctrl, control.

Table II. Demographic and clinical characteristics of the patients with ALS.

Characteristic	Phenotype		P-value
	Limb-onset ALS (n=128)	Bulbar-onset ALS (n=30)	
Sex, male/female	87:41	18:12	0.405
BMI, kg/m^{2}[a]	23.37±4.29	22.68±3.34	0.741
Age at interview, years[a]	51.5 (43.25-56.75)	50.0 (44.0-57.0)	0.710
Diagnostic delay, months[a]	7.83 (4.03-14.88)	8.4 (4.31-15.83)	0.148
Disease duration, months[a]	16.4 (4.94-29.54)	26.6 (16.68-42.71)	0.030
ALSFRS-R score[a]	40 (31-43)	32 (2-41)	0.111
Increased total cholesterol	40.0%	33.3%	-
Increased triglycerides	48.5%	48.1%	-
Increased HDL	17.2%	18.5%	-
Increased LDL	53.6%	37.0%	-
Increased sdLDL-c	15.7%	5.6%	-
Increased ApoA1	13.1%	14.3%	-
Increased ApoB	7.1%	4.8%	-

[a]Data are presented as mean ± SD or median (Q1-Q3). HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL cholesterol; Apo, apolipoprotein; ALS, amyotrophic lateral sclerosis; BMI, body mass index; ALSFRS-R, ALS Functional Rating Scale.

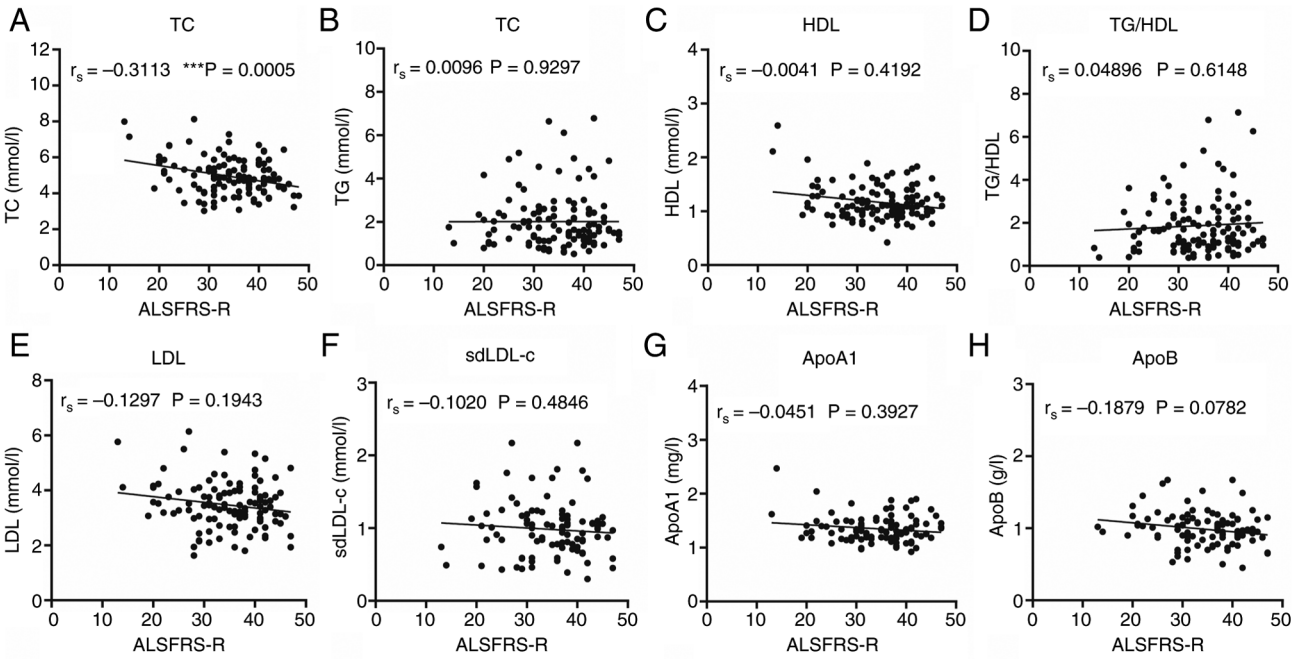

Figure 4. Correlations between serum lipid levels and ALSFRS-R scores. Correlations between serum lipid levels of (A) TC, (B) TG (B), (C) HDL, (D) TG/HDL, (E) LDL, (F) sdLDL-c, (G) ApoA1 and (H) ApoB and ALSFRS-R scores at diagnosis. A significant negative correlation is highlighted between (A) TC and ALSFRS-R scores (r_s=-0.3113; P=0.0005). ***P<0.001. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein.

correlated. In limb-onset patients, sdLDL-c (r_s=-0.2451, P=0.0295) and ApoB (r_s=-0.2487, P=0.0255) showed negative correlations with ALSFRS-R scores, while other lipid measures (TG, HDL, LDL) showed no significant associations (Fig. 6).

To further assess whether these associations differed significantly between phenotypes, we conducted multivariable linear regression analyses incorporating interaction terms (phenotype x lipid level), and adjusting for age, sex, BMI, and disease duration. Significant phenotype-lipid interactions were identified for sdLDL-c (β=12.223, P=0.038), TG/HDL ratio (β=4.620, P=0.019), ApoA1 (β=-13.618, P=0.020), and HDL (β=-11.963, P=0.006) (Table III). Simple slope analysis showed that higher sdLDL-c and TG/HDL ratios were associated with better functional

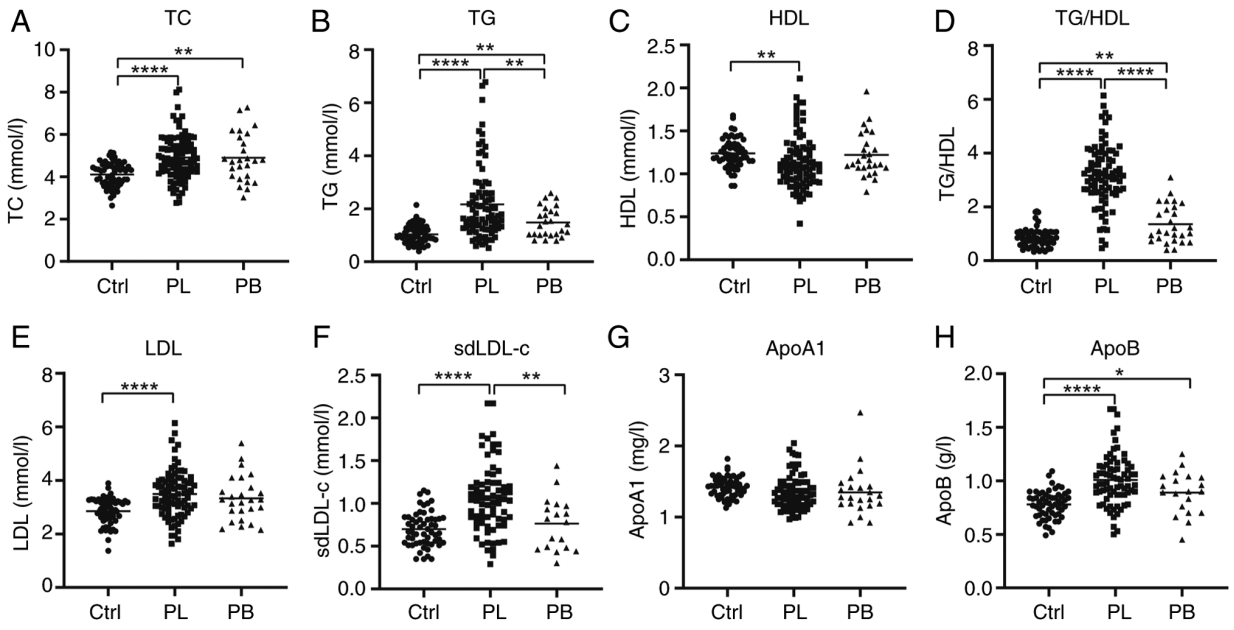

Figure 5. Subgroup analysis of serum lipids levels in PL and PB. Serum lipid levels of (A) TC, (B) TG (B), (C) HDL, (D) TG/HDL, (E) LDL, (F) sdLDL-c, (G) ApoA1 and (H) ApoB in PL and PB compared to Ctrls. ****P<0.0001; **P<0.01; *P<0.05. ALS, amyotrophic lateral sclerosis; PL, patients with limb-onset ALS; PB, patients with bulbar-onset ALS; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein; Ctrl, control.

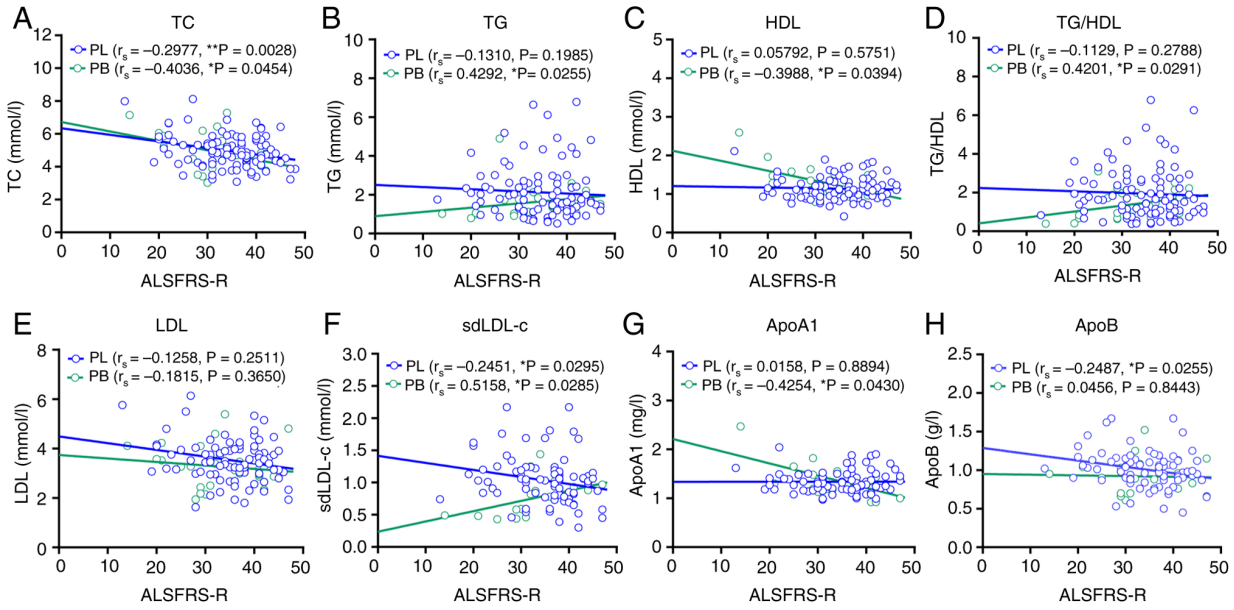

Figure 6. Correlations between serum lipid levels and ALSFRS-R scores in PL and PB. Correlations between serum lipid levels of (A) TC, (B) TG (B), (C) HDL, (D) TG/HDL, (E) LDL, (F) sdLDL-c, (G) ApoA1 and (H) ApoB and ALSFRS-R scores in PL and PB. **P<0.01; *P<0.05. ALS, amyotrophic lateral sclerosis; PL, patients with limb-onset ALS; PB, patients with bulbar-onset ALS; ALSFRS-R, ALS Functional Rating Scale; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein.

status in bulbar-onset patients but not in limb-onset patients (Fig. 7A and B). In contrast, HDL and ApoA1 levels exhibited stronger negative associations with ALSFRS-R scores in bulbar-onset cases (Fig. 7C and D). No significant interactions were detected for TC, TG, ApoB, or LDL (Table III; Fig. S1).

Together, these results suggest that certain lipid parameters, particularly sdLDL-c, the TG/HDL ratio, HDL, and ApoA1, may exhibit subtype-specific associations with ALS severity.

Discussion

This study demonstrates dyslipidemia in a Chinese ALS cohort and reveals that the associations between lipid levels and functional severity are modified by clinical subtype. In bulbar-onset ALS, higher sdLDL-c levels and TG/HDL ratios were associated with better functional status, whereas higher HDL and ApoA1 levels tended to correlate with worse outcomes. In contrast, in limb-onset ALS, higher sdLDL-c

Table III. Multivariable linear regression analyses of the interaction effects between ALS phenotype and lipid parameters on functional severity (ALSFRS-R score).

Model	Lipid parameter	β for interaction (phenotype x lipid)	95% CI	P-value
1	TC	-0.288	-2.654-2.079	0.810
2	TG	2.759	-0.616-6.134	0.108
3	HDL	-11.963	-20.442 to -3.484	0.006
4	LDL	-0.534	-4.144-3.075	0.770
5	sdLDL-c	12.223	0.713-23.732	0.038
6	ApoA1	-13.618	-25.090 to -2.146	0.020
7	ApoB	3.144	-11.572-17.859	0.673
8	TG/HDL ratio	4.620	0.773-8.468	0.019

Results from multivariable linear regression models with ALSFRS-R score as the dependent variable. Separate multivariable linear regression models were fitted for each lipid parameter. All models were adjusted for age, sex, body mass index and disease duration. Phenotype was coded as 0=limb-onset and 1=bulbar-onset; sex was coded as 0=male and 1=female. Regression coefficients (β), 95% CI values and P-values are reported. Interaction terms represent phenotype x lipid parameter. P<0.05 was considered statistically significant. CI, confidence interval; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL-c, small dense LDL-cholesterol; Apo, apolipoprotein.

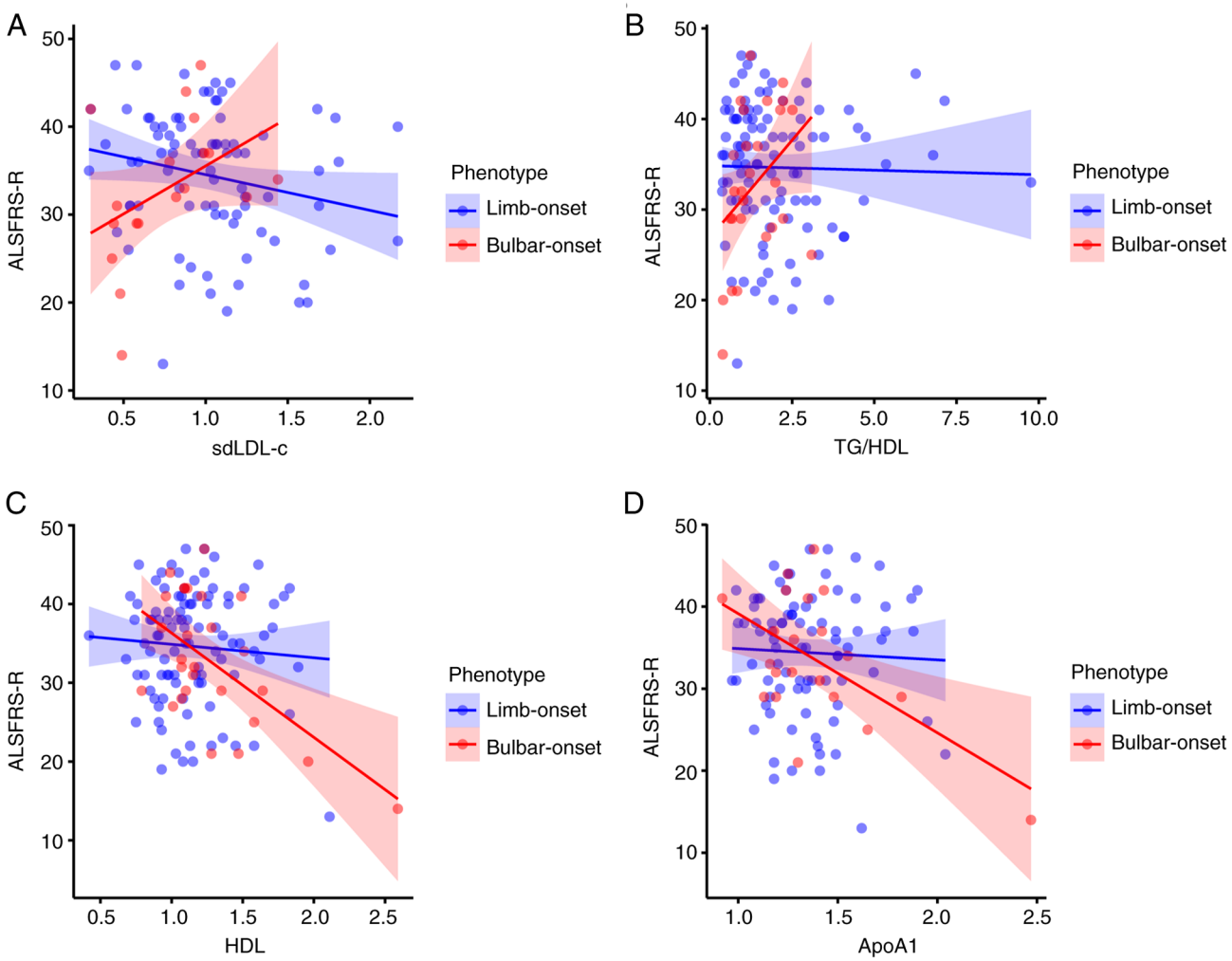

Figure 7. Interaction effects of phenotype and lipid parameters on ALSFRS-R score. (A) Interaction between phenotype and sdLDL-c levels. (B) Interaction between phenotype and TG/HDL ratio. (C) Interaction between phenotype and HDL levels. (D) Interaction between phenotype and ApoA1 levels. Plots are derived from multivariable linear regression models adjusted for age, sex, body mass index and disease duration. The red line represents the bulbar-onset phenotype and the blue line represents the limb-onset phenotype. Shaded areas represent 95% confidence intervals. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale; TG, triglycerides; HDL, high-density lipoprotein; sdLDL-c, small dense low-density lipoprotein-cholesterol; Apo, apolipoprotein.

and ApoB levels were associated with greater functional impairment, whereas other lipid measures showed no significant association. These findings extend the observations from Western cohorts and underscore the importance of accounting for clinical heterogeneity when investigating metabolic alterations in ALS.

Altered lipid metabolism has long been recognized as a feature of ALS, reflecting the high energy demands of denervated and atrophic muscle tissues (28). Lipids serve as major energy substrates, and their imbalance may influence both systemic metabolism and neuronal vulnerability (29). Previous studies in Western populations have reported inconsistent results regarding dyslipidemia in patients with ALS. Some studies have linked elevated lipid levels, particularly triglycerides, to improved survival and slower progression, whereas others have found no significant association or even adverse effects (21,22,30-32). These inconsistencies may arise from methodological differences, variation in disease stage, and unaccounted phenotypic diversity. Evidence from Asian cohorts provides additional context for these discrepancies. Early studies from southwestern China have reported no significant lipid differences between patients with ALS and controls (33). However, more recent Chinese studies have observed negative correlations between total cholesterol or LDL-c levels and ALSFRS-R scores, and between ApoB or Lp(a) levels and respiratory function, suggesting that lipid imbalance accompanies disease severity (34). Another large Chinese cohort found lower HDL and total cholesterol levels but higher LDL/HDL ratios, consistent with stage-related metabolic shifts (35). Our findings partially align with these results but further reveal subtype-specific lipid signatures, indicating that metabolic adaptations differ between bulbar- and limb-onset ALS. Similar heterogeneity has been observed in non-Western populations. In Japanese cohorts, higher total cholesterol, LDL, and triglyceride levels were associated with slower disease progression (36), supporting our observation that elevated lipid levels may reflect compensatory metabolic responses. Conversely, Nakamura *et al* (25) reported that high HDL levels predict poor prognosis, paralleling our finding of a negative association between HDL and functional status. In South Korea, lipid depletion, especially in men, suggests accelerated lipid consumption (37), and CT-based analyses have demonstrated that fat depletion (adipopenia) independently predicts poor survival (38). Collectively, these findings, together with our data, indicate that dyslipidemia is a shared metabolic feature of ALS; however, its clinical implications vary by ethnicity, sex, and phenotype, reflecting diverse adaptive responses to neurodegeneration.

The inverse relationship between cholesterol and ALSFRS-R scores observed in this study supports growing evidence that cholesterol homeostasis may play a role in disease progression. Cholesterol is a structural component of neuronal membranes and a precursor of signaling molecules such as steroid hormones and oxysterols (39,40). Disturbances in cholesterol regulation have been implicated in ALS through multiple molecular pathways. Dysregulation of the LXR/RXR signaling pathways and polymorphisms in lipid-related genes such as *APOE* and *SREBP2* have been associated with altered lipid metabolism and neuronal stress responses in ALS (41,42). Furthermore, TDP-43, a central protein in ALS pathology, modulates SREBP2-dependent cholesterol metabolism, suggesting a mechanistic link between lipid dysregulation and neurodegeneration (43,44). Large-scale genome-wide association studies have also identified elevated total cholesterol as a potential risk factor for ALS (45), further reinforcing the role of lipid homeostasis in disease susceptibility.

Our subtype-specific analysis provides further insight into metabolic diversity in ALS. In patients with bulbar-onset ALS, we observed that higher levels of sdLDL-c and TG/HDL ratio were associated with better functional status, potentially indicating a compensatory lipid mobilization response to the heightened metabolic stress in this subgroup (46). This observation aligns with the concept that individuals with bulbar-onset ALS, who typically experience faster disease progression, may rely on enhanced lipid utilization to meet elevated energy demands (4,5). Conversely, in limb-onset ALS, elevated levels of sdLDL-c and ApoB were linked to poorer functional status, suggesting that lipid accumulation in this subgroup could contribute to exacerbate the disease burden. These opposing trends underscore the idea that lipid dysregulation in ALS is not uniform, but is likely context-dependent, with the clinical phenotype and metabolic dynamics playing a critical role (46). Similarly, previous reports have noted that elevated triglyceride level or BMI may predict longer survival, whereas high HDL levels have been associated with poorer outcomes (15,16,25). This finding reinforces the notion that lipid dysregulation in ALS is phenotype-specific with distinct metabolic responses to neuronal degeneration in bulbar-onset and limb-onset ALS. Bulbar-onset ALS may rely on lipid mobilization as an adaptive response to rapid degeneration, whereas limb-onset ALS may exhibit lipid accumulation, reflecting a passive metabolic adaptation to impaired muscle function. These contrasting trends highlight the importance of clinical heterogeneity when interpreting lipid alterations in patients with ALS.

These findings emphasize the significance of considering ALS as a metabolically heterogeneous disorder rather than a singular disease entity. Lipid signatures specific to subtypes could potentially function as biomarkers for monitoring disease progression and categorizing patients in clinical studies. Apart from their biomarker potential, lipid changes may hold therapeutic relevance. Increasing evidence indicates that maintaining metabolic balance can influence ALS outcomes. Nutritional and metabolic strategies, such as high-calorie or high-fat diets, have demonstrated positive effects in SOD1(G86R) ALS mouse models and in small clinical trials, improving energy balance, tolerance, and occasionally survival (47-49). Recent reviews highlight that energy deficits and lipid depletion accelerate neurodegeneration, while replenishing lipid availability might offer neuroprotective effects (8,50). Although our study did not establish causation, the identified subtype-specific correlations suggest that personalized metabolic or dietary interventions tailored to specific phenotypes could complement future pharmacological approaches in ALS management.

Despite these insights, this study has several limitations. First, the retrospective, cross-sectional design limits causal inference. Since the data were extracted from existing clinical records, the analysis has been subject to missing

information, unrecorded confounders, and potential selection bias. Therefore, our findings should be viewed as hypothesis-generating rather than confirmatory, pending validation in prospective longitudinal cohorts. Second, the relatively small sample size of the bulbar-onset subgroup (n=30) may have affected the statistical stability of the subtype-specific associations. Given this modest number, the observed trends should be interpreted with caution, as they may reflect random variations rather than robust effects. Nonetheless, the internal consistency across analyses and biological plausibility lend support to the reliability of the main findings. Future studies with larger, multicenter cohorts are required to confirm these subtype-specific metabolic patterns and to assess their generalizability across populations. Finally, our study focused on conventional lipid metrics; future research incorporating advanced lipidomics and longitudinal designs is crucial to unravel the precise temporal dynamics and molecular mechanisms of lipid dysregulation across ALS subtypes.

In conclusion, our study identified dyslipidemia as a prevalent feature of ALS and revealed subtype-specific associations between lipid parameters and functional impairment. These findings suggest that the metabolic pathways differ between bulbar- and limb-onset ALS, reflecting distinct pathophysiological mechanisms. Integrating metabolic profiling into ALS research may improve the prognostic accuracy and support the development of personalized management strategies tailored to each clinical phenotype.

Acknowledgements

The authors would like to thank Dr YouYun Zhao (Department of Clinical Laboratory, Hubei Provincial Hospital of Traditional Chinese Medicine) for helping with the collection of clinical data.

Funding

This work was supported by the National Natural Science Foundation of China Grants (grant no. 82575246), the Hubei Provincial Department of Education Science and Technology Research Program Young Talent Project (grant no. Q20232010), the Hubei University of Chinese Medicine Doctoral Startup Fund (grant no. 100501080740), the Key Research and Development Program of Hubei Province (grant no. 2022BCA055) and the Hubei Provincial Hospital of Traditional Chinese Medicine (grant no. 2021YJKT-24).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LC conceived and designed the study, collected and analyzed the data, interpreted the results and drafted the manuscript. GC contributed to study design, data interpretation and critically revised the manuscript. JZ and HH participated in data acquisition and analysis, and contributed to manuscript revision. AX and TZ assisted with data collection and organization, and participated in data analysis. YZ and HL contributed to study design and clinical data acquisition, and critically revised the manuscript. LC, YZ and HL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethical Committee of Hubei University of Chinese Medicine approved this study (approval no. HBZY1022-C42-02). The principal author has received consent forms from the participants in this study and has them on file. All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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