Research Square

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Lipid Metabolism Markers in Relation to Brucella Spondylitis: A Multicenter Cross- Sectional Study

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Abstract

Background

During brucellosis, Brucella evades host immune response to survive and multiply within macrophages, eventually triggering a systemic inflammatory response. Spondylitis is among the most common complications of brucellosis. While inflammation and dyslipidemia are closely intertwined, the association between lipid metabolism markers and Brucella spondylitis (BS) remains unclear.

Objective

This study investigates the potential relationship between various lipid metabolism markers and BS.

Methods

A multicenter cross-sectional approach is adopted, covering 702 brucellosis patients admitted to two infectious disease hospitals in Hohhot and Xing'an League between May 2022 and March 2024. Multivariable logistic regression models and restricted cubic spline (RCS) analysis were employed to examine the independent association and dose-response relationship between lipid markers and BS. Subgroup analyses were performed based on age, sex, disease stage, and comorbidities, complemented by interaction testing. The discriminatory performance and clinical net benefit were evaluated using calibration curves, and decision curve analysis.

Results

Of the 702 patients, 296 (42.2%) were diagnosed with BS. Multivariable logistic regression and RCS analysis revealed a linear positive association of HDL-C with BS (OR = 1.992; 95% CI 1.229–3.228) and linear negative associations of MHR (OR = 0.298; 95% CI 0.148–0.599), AIP (OR = 0.446; 95% CI 0.256–0.776), and AI (OR = 0.819; 95% CI 0.728–0.922) with BS ($P \leq 0.005$). Subgroup analysis suggested that the association of HDL-C with BS was more significant in patients under 60 and those in the acute/subacute phase.

Conclusion

The results demonstrate a positive association between HDL-C and BS, and negative associations of MHR, AIP, and AI with BS. Elevated HDL-C warrants caution regarding increased spondylitis risks in patients under 60 and those in the acute/subacute phase. These findings support stratified management across populations and infection types, potentially improving outcomes.

Background

Brucella spondylitis (BS) is among the most severe complications of Brucellosis [1], posing a high public health risk in low-income countries, even in China [2]. Consequences of this disease include vertebral bone destruction, abscess formation, irreversible neurological deficits, and in rare cases, mortality [3–5]. The pathogenesis involves the hematogenous seeding of vertebral bodies by *Brucella*, and the resultant endoplasmic reticulum stress and amplified secretion of pro-inflammatory cytokines (e.g., *IL-6* and *TNF-α*) often induce granuloma formation and chronic infection [6, 7]. Eventually, bone destruction and spinal lesions ensue. Advanced age, delayed diagnosis, and exacerbated systemic inflammation promote BS onset and progression. Infection-driven inflammation is rarely an isolated process. Extensive evidence suggests that *IL-6* and *TNF-α* inhibit lipoprotein lipase and promote hepatic synthesis of very-low-density lipoprotein (VLDL), thereby inducing dyslipidemia [8–10]. These findings imply a possible inflammation-driven “lipid dysregulation-bone imbalance” network in BS patients. For one thing, inflammation directly stimulates osteoclast-mediated bone resorption, akin to the bone damage in other inflammatory bone diseases [11]. For another, concomitant dyslipidemia may also modulate bone metabolism.Clinical evidence supports this hypothesis. Marked dyslipidemia was reported in acute brucellosis, with significantly lower HDL-C levels than healthy controls [12]. Research in related fields also classified hyperlipidemia among the most common cardiovascular risk factors in axial spondyloarthritis [13]. Collectively, these findings point to an inflammation-driven “lipid dysregulation-bone homeostasis imbalance” cross-network.

Common clinical markers for lipid metabolism assessment include low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, and total cholesterol (TC), as well as derived composite indices. The monocyte-to-HDL cholesterol ratio (MHR)[14], atherogenic index of plasma (AIP) [15], and atherogenic index (AI) [16] have recently attracted academic attention due to their potential relevance in bone metabolic diseases. MHR reportedly reflects skeletal homeostasis imbalance under chronic inflammation [17], while AIP is negatively associated with vertebral fracture risk, with sex-specific differences [18]. Nonetheless, the association between these markers and BS has not yet been validated.

Accordingly, this study analyzes the independent associations of lipid metabolism markers and their derived indices with BS from an “inflammation-metabolism” perspective. Meanwhile, their dose-response relationships are explored, thus offering quantifiable clues for early BS screening strategies.

Methods

Research Design

Data were collected from 1,131 brucellosis patients from infectious disease hospitals in Hohhot and Xing'an League between May 2022 and March 2024. All patients met the diagnostic criteria detailed in the 2019 *Brucellosis Diagnostic Standards* [19]. The inclusion criteria included documented epidemiological history and clinical symptoms, plus at least one of: (1) isolation of Brucella from blood

or other specimens; (2) serum agglutination test (SAT) titer ≥ 1:100 (++), or ≥ 1:50 (++) with disease duration > 1 year; (3) Coombs test titer ≥ 1:400 (++). The exclusion criteria are individuals aged < 18 years (*n* = 22); those with tuberculosis, viral hepatitis, skeletal deformities, or other relevant conditions; those taking lipid-modifying medications at admission (*n* = 76); and those with missing lipid test results (*n* = 331). A total of 702 patients were eligible **(**Fig. 1**).**

Data Collection and Definition

The MHR, AIP, and AI were calculated as follows: MHR = Monocyte Count / HDL-C [20]; AIP = $\log_{10}$(TG/HDL-C) [21]; AI = (TC —HDL-C)/HDL-C [22].

BS was diagnosed in brucellosis patients manifesting spinal redness, swelling, heat, pain, or limited mobility, supported by confirmatory imaging findings; diagnosis was verified by two attending physicians and a radiologist based on MRI, CT, or X-ray.

General characteristics of the patients included demographics (age, sex) and personal history (alcohol consumption, smoking). Smoking and alcohol consumption histories were defined as previous or current ones. Medication history, dietary habits, and physical activity were not incorporated. Laboratory data covered lipid profile (TC, TG, HDL-C, LDL-C) and C-reactive protein (CRP). Comorbidities included diabetes and hypertension. Diabetes and hypertension were diagnosed per the 2021 ADA Standards [23] and the Adult Hypertension Guidelines [24], respectively.

Statistical Analyses

Continuous variables were expressed as mean ± *SD* or median (IQR) and compared by t-test or Mann-Whitney U test, as appropriate. Categorical variables were presented as percentages and compared by χ^2 or Fisher's exact test. The associations between lipid indices and BS were assessed using logistic regression across the unadjusted model (Model 1), the model adjusted for age and sex (Model 2), and the model additionally adjusted for smoking, alcohol consumption, diabetes, hypertension, and disease stage (Model 3). Linear trends were formally assessed, and restricted cubic splines (RCS) with smooth curve fitting were employed to explore potential nonlinear relationships. Subgroup analyses were performed by age (< 60 *vs.* ≥ 60 years), sex, disease stage (acute/subacute vs. chronic), diabetes, and hypertension. Multivariable models within each subgroup were fitted, and the interactions were tested. The subgroup analysis results were presented as forest plots. All analyses were conducted in SPSS 25.0 and R 4.4.2.

Results

Baseline Characteristics of the Studied Population

Of the 702 enrolled participants, 296 (42.2%) had BS. In the BS group, 154 (52.0%) were < 60, whereas 142 (48.0%) were ≥ 60; and 208 (70.3%) were male. The diabetes prevalence was significantly higher in the BS group (10.5%, $P < 0.05$). Hypertension prevalence showed no significant difference across groups. Meanwhile, BS patients showed higher HDL-C but lower MHR, AIP, and AI (all with $P \leq 0.01$). The CRP levels were also higher in the BS group ($P = 0.022$). TC and LDL-C did not differ significantly between groups ($P > 0.05$) (Table 1).

Table 1
Demographic data and baseline characteristics of the two groups (*n* = 702).

Variables	**Total**	**BS**	**Non-BS**	***P***
	***n* = 702**	***n* = 296**	***n* = 406**	
Age group, (%)				<0.001
<60	434(61.8)	154(52.0)	280(69.0)	
≥ 60	268(38.2)	142(48.0)	126(31.0)	
Gender, (%)				0.163
Male	473(67.4)	208(70.3)	265(65.3)	
Female	229(32.6)	88(29.7)	141(34.7)	
Disease Staging, (%)				0.095
Acute/Subacute	441(62.8)	184(62.3)	257(63.3)	
Chronic	261(37.2)	112(37.8)	149(36.7)	
Smoking history, (%)				0.289
Yes	278(39.6)	124(41.9)	154(37.9)	
No	424(60.4)	172(58.1)	252(62.1)	
Alcohol consumption, (%)				0.510
Yes	124(17.7)	49(16.6)	75(18.5)	
No	578(82.3)	247(83.4)	331(81.5)	
Hypertension, (%)				0.272
Yes	261(37.2)	117(39.5)	144(35.5)	
No	441(62.8)	179(60.5)	262(64.5)	
Diabetes, (%)				0.008
Yes	52(7.4)	31(10.5)	21(5.2)	
No	650(92.6)	265(89.5)	385(94.8)	
TC, mmol/L	4.20(3.68,4.86)	4.22(3.67,4.85)	4.17(3.70,4.88)	0.910
TG, mmol/L	1.27(0.95,1.75)	1.21(0.90,1.62)	1.36(0.99,1.83)	0.006

TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; MHR: monocyte to high-density lipoprotein cholesterol Ratio; AIP: atherogenic index of plasma; AI: atherogenic index

Variables	Total	BS	Non-BS	*P*
	***n* = 702**	***n* = 296**	***n* = 406**	
LDL-C, mmol/L	2.68(2.22,3.17)	2.64(2.21,3.04)	2.74(2.22,3.25)	0.058
HDL-C, mmol/L	1.04(0.84,1.29)	1.11(0.90,1.33)	1.01(0.80,1.25)	0.001
CRP, mg/L	7.6(2.0,21.0)	9.5(2.60,21.58)	5.8(1.7,20.6)	0.022
MHR	0.36(0.25,0.55)	0.34(0.23,0.49)	0.39(0.27,0.59)	0.001
AIP	0.08 (-0.11,0.30)	0.05(-0.14,0.24)	0.13(-0.08,0.34)	0.001
AI	3.02(2.25,3.95)	2.72(2.16,3.67)	3.29(2.41,4.14)	<0.001

TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; MHR: monocyte to high-density lipoprotein cholesterol Ratio; AIP: atherogenic index of plasma; AI: atherogenic index

Association between Lipid Metabolism Markers and BS

Univariate analysis indicated associations of MHR, AIP, AI, and HDL-C with BS, which were confirmed by multivariable analysis: MHR (OR = 0.298; 95% CI 0.148–0.599; *P* = 0.001), AIP (OR = 0.446; 95% CI 0.256–0.776; *P* = 0.004), AI (OR = 0.819; 95% CI 0.728–0.922; *P* = 0.001), HDL-C (OR = 1.992; 95% CI 1.229–3.228; *P* = 0.005)(Table 2).

Table 2
Association of lipid metabolism markers with BS (n = 702).

MHR	Model 1[a]	*P*	Model 2[b]	*P*	Model 3[c]	*P*
	OR (95%CI)		**OR (95%CI)**		**OR (95%CI)**	
	0.363(0.191–0.690)	**0.002**	**0.330(0.169–0.646)**	**0.001**	**0.298(0.148–0.599)**	**0.001**
AIP	0.415(0.244–0.706)	0.001	0.485(0.282–0.833)	0.009	0.446(0.256–0.776)	0.004
AI	0.814(0.726–0.912)	< 0.001	0.836(0.744–0.938)	0.002	0.819(0.728–0.922)	0.001
TG	0.912(0.775–1.073)	0.268	0.958(0.816–1.123)	0.594	0.934(0.792–1.102)	0.420
HDL-C	2.002(1.286–3.115)	0.002	1.882(1.194–2.964)	0.006	1.992(1.229–3.228)	0.005
CRP	1.009(0.995–1.022)	0.217	1.004(0.991–1.019)	0.531	1.005(0.991–1.020)	0.473

[a] Model 1, No adjustment for any potential influence factors. [b] Model 2, Adjusted for sex and age. [c] Model 3, Adjusted for smoking history, alcohol consumption, diabetes, disease staging, and

hypertension.

RCS analysis, adjusted for age, sex, smoking, alcohol, diabetes, hypertension, and disease stage, indicated linear relationships between all four lipid metabolism markers and BS, with no evidence of significant nonlinearity or threshold (Fig. 2). Specifically, HDL-C demonstrated a linear positive association with BS, i.e., higher HDL-C was associated with greater risks of BS. In contrast, MHR, AIP, and AI showed linear negative associations with BS risk, i.e., increased levels of these markers corresponded to lower risks of BS. In summary, the studied population predominantly exhibited linear associations between the four lipid metabolism markers and BS risks, without notable nonlinear dose-response patterns or thresholds.

Subgroup Analysis

No significant interactions were detected across subgroups (all with interaction $P > 0.05$), and the influencing directions were consistent (Fig. 3). Statistical significance of the associations varied: MHR's negative association was significant in men, non-diabetics, and various age/stage subgroups; AIP's negative association was more consistent in the age ≥ 60, women, hypertensives, non-diabetics, and acute/subacute phase subgroups; AI's negative association was the broadest, lacking significance only in the men, diabetics, and chronic phase subgroups; HDL-C's positive association was mainly seen in the men, age < 60, hypertensives, non-diabetics, and acute/subacute phase subgroups.

Performance Evaluation and Clinical Utility Analysis of the BS Model

The four markers showed promise for identifying BS. The calibration curve (Fig. 4A) demonstrated good robustness, confirmed by bootstrap (200 resamples) and Hosmer-Lemeshow test ($\chi^2 = 10.99$, $df = 8$, $P = 0.202$). Precision-recall curves (Fig. 4B) showed the superior discrimination of the combined model over single markers. Decision curve analysis (DCA; Fig. 4C) revealed a net benefit of all markers over "no intervention" across the threshold of 0-0.45, with the greatest net benefit from the combined model.

Discussion

This study systematically examined the associations of lipid metabolism markers and derived indices with BS in brucellosis patients. The results showed that HDL-C was independently positively associated with BS, whereas MHR, AIP, and AI were independently negatively associated, all of which were linear dose-response relationships. The significance of association varied by age and disease stage, with more active lipid changes in patients < 60 and those in the acute/subacute phase, providing a basis for stratified management to improve prognosis.

BS prevalence in this study (42.2%) is notably higher than that reported by Liu et al. in Ningxia (29.49%) [25] and that in the domestic multicenter study by Shi et al. (16.6%) [26], indicating a high disease burden that requires intensified management. Higher diabetes prevalence and CRP levels in the BS group further

suggest that combined metabolic and inflammatory burdens contribute to BS [27, 28]. Future research should dive deeper into the role of lipid dysregulation in BS onset and progression.

The positive HDL-C association with BS, a linear dose-response relationship, may be explained by several mechanisms. First, the infection may remodel the HDL proteome [29, 30], and the resultant dysfunctional HDL loses anti-inflammatory and antioxidant capacities [31, 32] while indirectly promoting bone resorption via immune cell modulation [33]. *Brucella's* unique invasion mode in BS may amplify this effect [34]. Second, the systemic inflammation subsides as infection localizes, which reduces HDL consumption and increases compensatory synthesis [35]. As such, peripheral HDL-C is elevated. Hence, the observed relationship likely reflects HDL dysfunction and compensatory changes rather than a protective effect. Similar observations were reported in rheumatoid arthritis, HIV, and periodontitis [36, 37].

The BS group's lower MHR than the non-BS group may reflect a unique "consumption-dilution" dual effect. Following Brucella invasion into the spine, monocytes migrate to the infectious focus and participate in granuloma formation, thus depleting functional monocytes in the peripheral blood [38]. Meanwhile, the subsidence of systemic inflammation upon infection localization leads to compensatory increases in HDL-C synthesis [35]. Together, these two mechanisms lower MHR, producing a "pseudo-reduction". Thus, a decreased MHR in BS should not be interpreted as reduced inflammation or lower risk; instead, it may signal progression of focal spinal infection. Previous studies have reported a negative association between MHR and osteoporosis [39–41].

Regarding AIP and AI, the metabolic alterations observed in BS should not be viewed as indicators of decreased atherosclerotic risks. Rather, they represent an "infection-driven lipid paradox" [42] that is unlikely to be a passive epiphenomenon of inflammation; instead, it reflects the active exploitation of host lipid metabolism by Brucella to facilitate focal spinal infections [43, 44]. The findings from non-infectious populations, linking AIP negatively with vertebral fractures [18] and trabecular bone score [45], can provide cross-disease support for this interpretation.

Subgroup differences may arise from variations in lipid metabolic activity and baseline inflammatory burden. Patients below 60 exhibit more robust immune responses, where dyslipidemia is more likely to activate pro-inflammatory pathways [46, 47]. In contrast, older patients often have chronic comorbidities that obscure the lipid-BS associations [48]. In the acute/subacute phase, infection-triggered metabolic reprogramming for immune defense enhances lipid turnover [49, 50]. With decelerated *Brucella* replication in the chronic phase, metabolism shifts toward low-inflammation homeostasis [51], and lipid changes attenuate [52]. Hence, clinical interpretation of these markers must consider patient age and disease stage.

This study is not free from limitations. The cross-sectional design precludes causal inference and proves ineffective in capturing dynamic lipid changes. Due to data limitations, key lifestyle confounders (e.g., medication use, diet, and physical activity) were not analyzed, potentially biasing the results. Prospective

cohort studies with multiple control groups and comprehensive lifestyle data are warranted to validate these findings.

Conclusions

BS prevalence was high among brucellosis patients, warranting clinical attention. MHR, AIP, and AI showed linear negative associations with BS, whereas HDL-C showed a linear positive association. Elevated HDL-C in patients below 60 and in the acute/subacute phase indicate heightened spondylitis risks. These findings provide a basis for stratified management of dyslipidemia across populations and infection phases. We recommend systematic lipid profile monitoring and MHR and AIP calculations, with age and disease duration integrated into the interpretation framework, to improve prognosis and reduce adverse outcomes in brucellosis.

Abbreviations

BS
Brucella spondylitis
MHR
Monocyte to High-density lipoprotein Cholesterol Ratio
AIP
Atherogenic Index of Plasma
AI
Atherogenic Index
TG
Triglyceride
TC
Total cholesterol
HDL-C
High-density lipoprotein cholesterol
LDL-C
Low-density lipoprotein cholesterol
CRP
C-reactive protein
RCS
Restricted cubic splines
OR
Odds ratio
CI
Confidence interval

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Review Committee of Inner Mongolia Medical University (Approval Number: YKD202503002). Due to the retrospective nature of the study and the use of anonymized clinical data that did not contain personally identifiable information, the requirement for obtaining written informed consent from participants was waived by the above Ethics Committee.

Consent for publication

Not applicable, because the study did not include any data that could identify an individual person.

Competing interests

The authors declare no competing interests.

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Author Contribution

YL, H-QZ, P-FZ,Y-LW, X-LJ,CW,TW and X-MW drafted the plan for data analysis; H-QZ and Y-LW conducted the data analysis; YL, Y-LW.and H-QZ drafted the manuscript; YL, H-QZ, Y-LW, and P-FZ. contributed to data interpretation and discussion; X-MW contributed to discussion and extensively reviewed and edited the manuscript,All authors read and approved the final manuscript.

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Data Availability

The current study data are not publicly available but can be obtained from the corresponding authors upon request, where appropriate.

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Figures

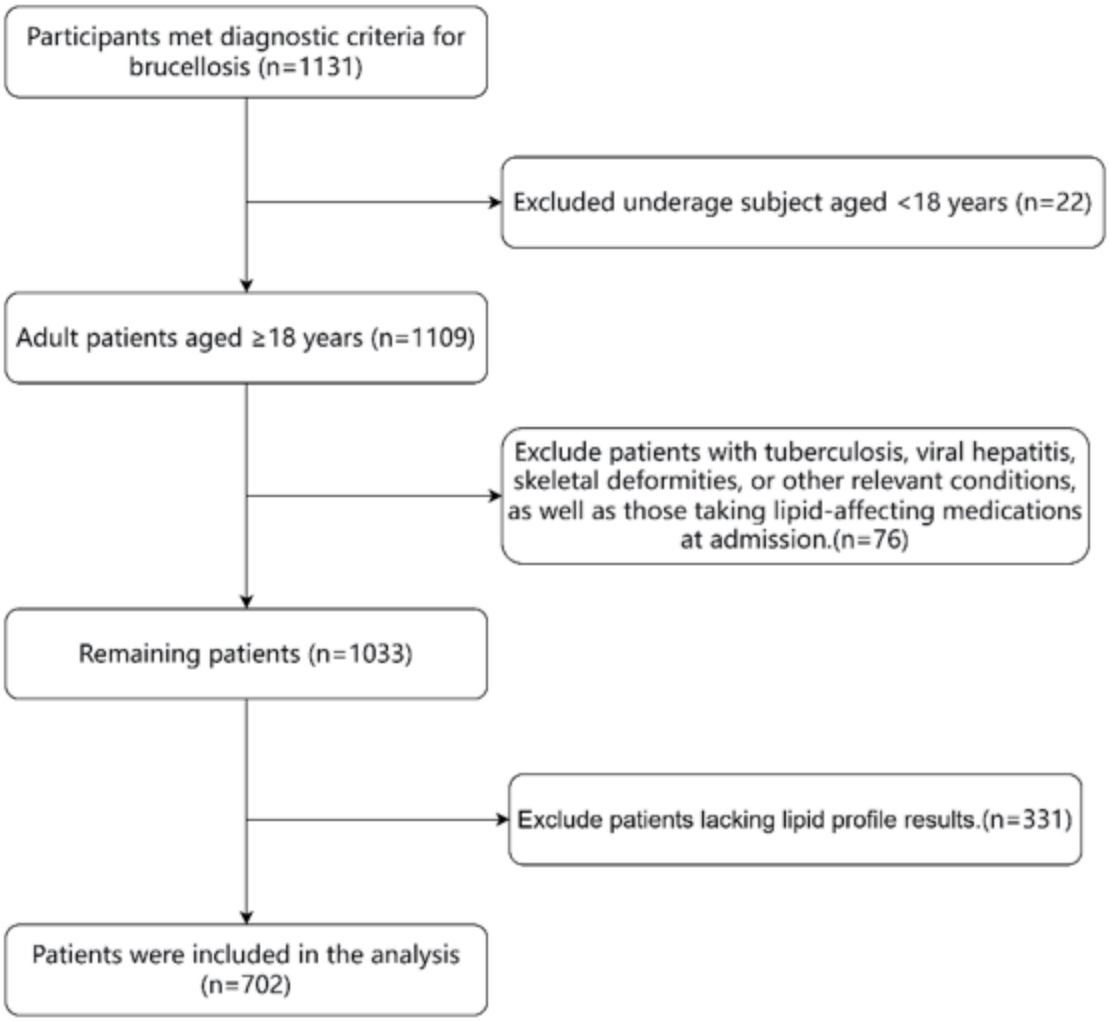


Figure 1

Flow chart of participant enrollment in the study.

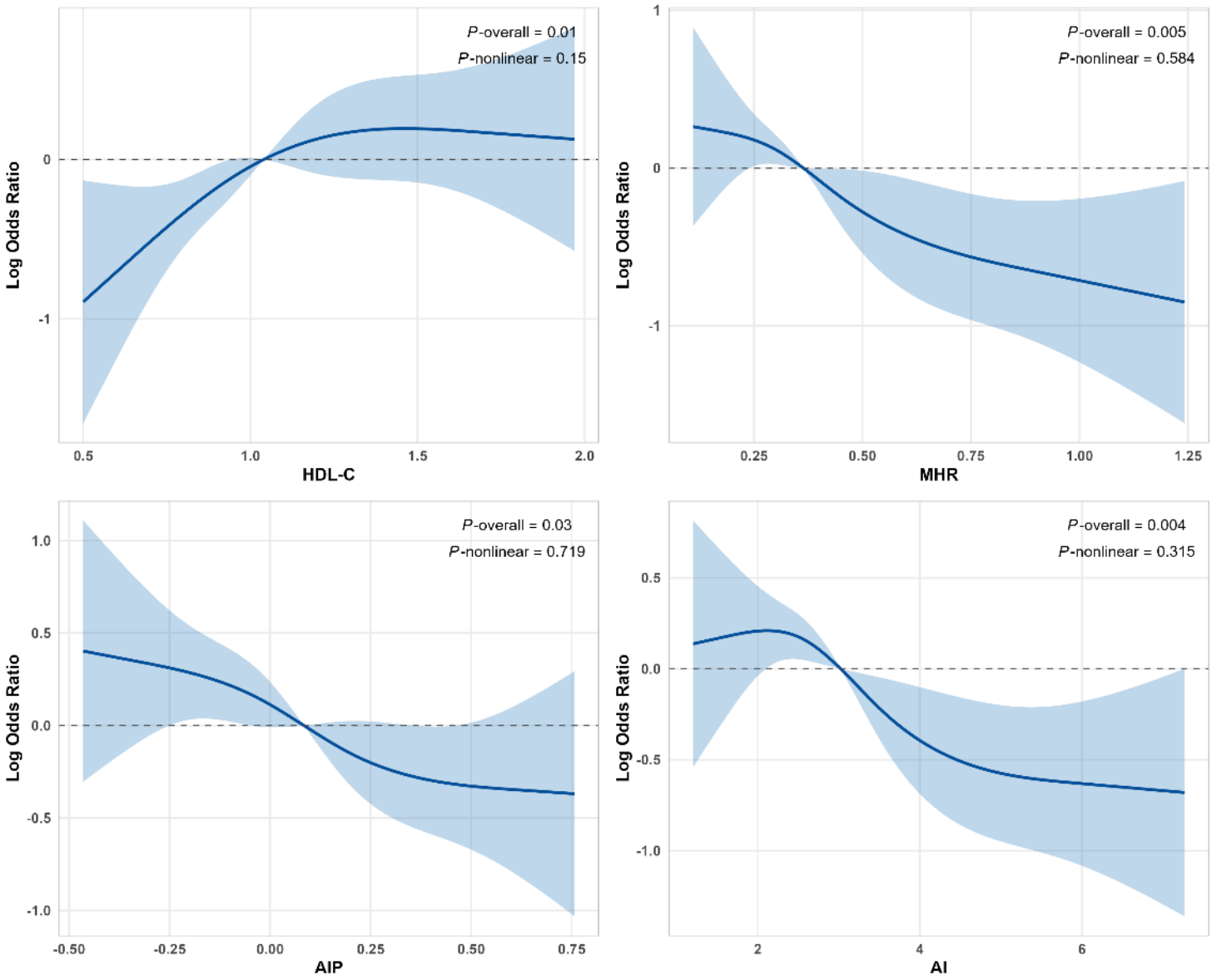


Figure 2

RCS for the association of MHR, AIP, AI, and HDL-C with BS. Solid blue line: fitted relationship; light blue shading: 95% CI.

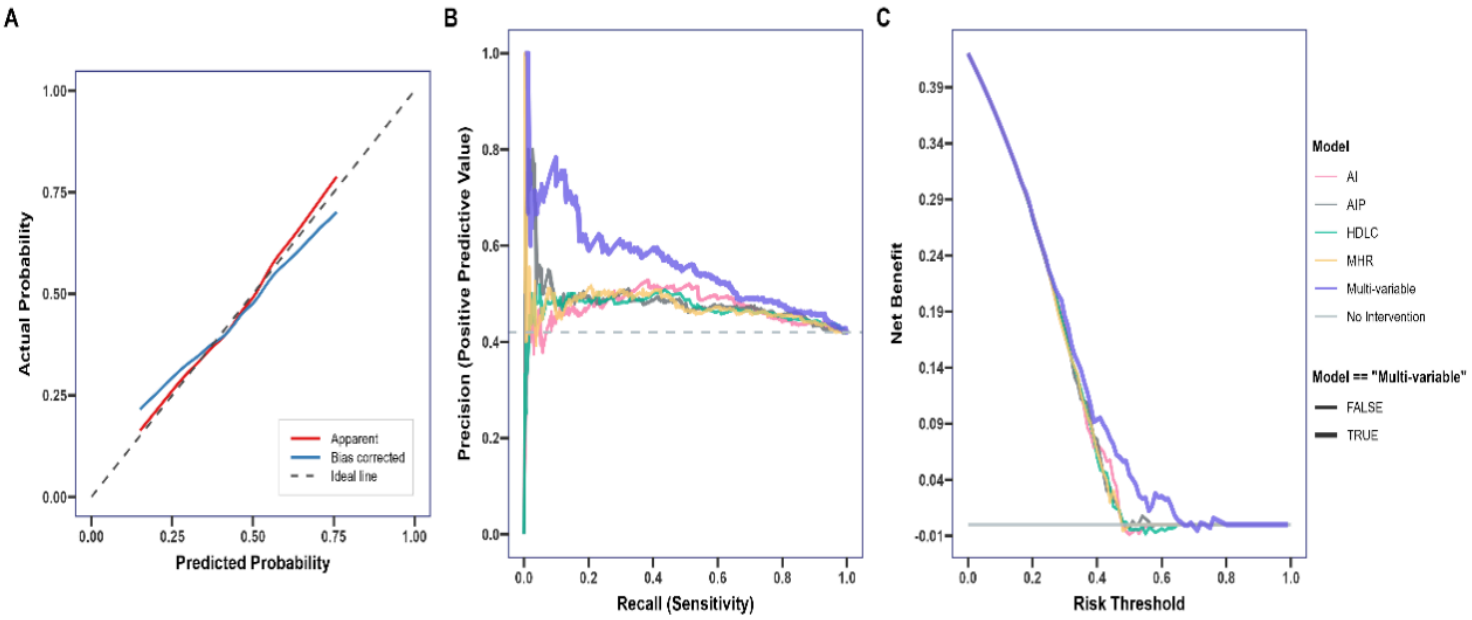
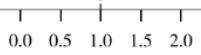


Figure 3

Model performance and clinical utility for BS identification. (A) Calibration curve of the combined diagnostic model. (B) Precision-Recall (PR) curve. (C) DCA.

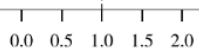
MHR

Subgroup	OR（95%CI）	P	P for Interaction
Overall	0.298 (0.148, 0.599)	0.001	
Gender			0.587
male	0.303 (0.139, 0.661)	0.003	
female	0.206 (0.040, 1.071)	0.06	
Age			0.265
< 60	0.282 (0.109, 0.730)	0.009	
⩾60	0.330 (0.113, 0.958)	0.041	
Hypertension			0.327
Yes	0.141 (0.041, 0.479)	0.002	
No	0.439 (0.182, 1.059)	0.067	
Diabetes			0.995
Yes	0.203 (0.020, 2.092)	0.18	
No	0.302 (0.143, 0.635)	0.002	
Disease staging			
acute+subacute	0.329 (0.148, 0.732)	0.006	0.432
chronic	0.196 (0.042, 0.911)	0.038	



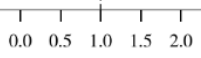
AIP

Subgroup	OR（95%CI）	P	P for Interaction
Overall	0.446 (0.256, 0.776)	0.004	
Gender			0.206
male	0.580 (0.295, 1.140)	0.114	
female	0.256 (0.094, 0.696)	0.008	
Age			0.239
< 60	0.587 (0.304, 1.135)	0.114	
⩾60	0.224 (0.078, 0.644)	0.005	
Hypertension			0.493
Yes	0.303 (0.123, 0.746)	0.009	
No	0.571 (0.277, 1.176)	0.129	
Diabetes			0.077
Yes	0.024 (0.002, 0.375)	0.08	
No	0.532 (0.298, 0.948)	0.032	
Disease staging			0.257
acute+subacute	0.363 (0.175, 0.750)	0.006	
chronic	0.636 (0.262, 1.544)	0.317	



AI

Subgroup	OR(95%CI)	P	P for Interaction
Overall	0.819 (0.728, 0.922)	0.001	
Gender			0.186
male	0.870 (0.753, 1.004)	0.057	
female	0.707 (0.563, 0.888)	0.003	
Age			0.99
< 60	0.835 (0.721, 0.967)	0.016	
⩾60	0.783 (0.634, 0.968)	0.024	
Hypertension			0.68
Yes	0.766 (0.631, 0.930)	0.007	
No	0.850 (0.729, 0.992)	0.039	
Diabetes			0.942
Yes	0.750 (0.511, 1.103)	0.143	
No	0.823 (0.724, 0.935)	0.003	
Disease staging			
acute+subacute	0.774 (0.665, 0.902)	0.001	0.171
chronic	0.924 (0.759, 1.125)	0.432	



HDL-C

Subgroup	OR（95%CI）	P	P for Interaction
Overall	1.992 (1.229, 3.228)	0.005	
Gender			0.635
male	1.921 (1.053, 3.507)	0.003	
female	2.280 (0.998, 5.207)	0.051	
Age			0.509
< 60	1.903 (1.032, 3.510)	0.039	
⩾60	2.101 (0.936, 4.719)	0.072	
Hypertension			0.911
Yes	2.342 (1.101, 4.983)	0.027	
No	1.872 (0.978, 3.584)	0.058	
Diabetes			0.876
Yes	4.788 (0.633, 36.218)	0.129	
No	1.946 (1.176, 3.220)	0.01	
Disease staging			0.082
acute+subacute	2.920 (1.505, 5.666)	0.002	
chronic	1.183 (0.564, 2.482)	0.656	

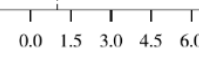


Figure 4

Subgroup analysis of the association between MHR, AIP, AI, HDL-C, and BS.