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Serum BAFF level is associated with the presence and severity of coronary artery disease and acute myocardial infarction

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Abstract

Objective The aim of this study was to investigate the relationship between circulating levels of B cell activating factor (BAFF) and the presence and severity of coronary artery disease (CAD) and acute myocardial infarction (AMI) in humans, as its biological functions in this context remain unclear.

Methods Serum BAFF levels were measured in a cohort of 723 patients undergoing angiography, including 204 patients without CAD (control group), 220 patients with stable CAD (CAD group), and 299 patients with AMI (AMI group). Logistic regression analyses were used to assess the association between BAFF and CAD or AMI.

Results Significantly elevated levels of BAFF were observed in patients with CAD and AMI compared to the control group. Furthermore, BAFF levels exhibited a positive correlation with the SYNTAX score ($r=0.3002$, $P<0.0001$) and the GRACE score ($r=0.5684$, $P<0.0001$). Logistic regression analysis demonstrated that increased BAFF levels were an independent risk factor for CAD (adjusted OR 1.305, 95% CI 1.078–1.580) and AMI (adjusted OR 2.874, 95% CI 1.708–4.838) after adjusting for confounding variables. Additionally, elevated BAFF levels were significantly associated with a high GRACE score (GRACE score 155 to 319, adjusted OR 4.297, 95% CI 1.841–10.030). BAFF exhibited a sensitivity of 75.0% and specificity of 71.4% in differentiating CAD patients with a high SYNTAX score, and a sensitivity of 75.5% and specificity of 72.8% in identifying AMI patients with a high GRACE score.

Introduction

Coronary artery disease (CAD) and acute myocardial infarction (AMI) are the leading causes of mortality and morbidity worldwide. [1, 2] Timely identification of CAD and AMI is essential for preventing stenosis progression and reducing mortality. The diagnosis of CAD usually relies on clinical symptoms or invasively angiography findings. However, conventional serum biomarkers like cardiac troponin and creatine kinase, have limited diagnostic utility for severe CAD as they may exhibit high concentrations during the acute stage. [3] Therefore, there is an urgent need to discover novel biomarkers for

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Conclusion Circulating BAFF levels serve as a valuable diagnostic marker for CAD and AMI. Elevated BAFF levels are associated with the presence and severity of these conditions, suggesting its potential as a clinically relevant biomarker in cardiovascular disease.

Keywords BAFF, Coronary artery disease, Acute myocardial infarction, Biomarker, GRACE score

risk stratification and early detection of CAD and AMI to avert cardiovascular events.

B cell-activating factor of the TNF family (BAFF, also known as TNFSF13B) is a type II membrane protein that and a recent addition to the TNF ligand family. [4] It plays a pivotal role in cellular differentiation, survival, programmed cell death, and immune responses. Initially identified for its impact on B cell survival and development, [5] BAFF has been found to regulate atherogenesis by controlling antibody and cytokine production in rodent models. Mouse B cells can be classified into two distinct groups: B1 and B2, based on specific cell surface markers. [6] B1 cells primarily inhibit atherosclerosis development through the secretion of IgM, [7] while B2 cells are generally considered to contribute to the pathological progression of atherosclerosis by producing pathogenic IgG. [8] The influence of BAFF on B cells and its role in regulating atherosclerosis progression have been extensively investigated. [9] However, the relationship between BAFF, CAD, and AMI remains unclear. Consequently, the objective of this study is to assess the association between serum BAFF levels and the presence and severity of CAD and AMI. We aim to provide valuable insights into the impact of BAFF on cardiovascular function through our study findings.

Materials and methods

Study population

A total of 723 patients who underwent coronary angiography (CAG) due to angina pectoris or cardiovascular disease symptoms between January 2016 and December 2019 at Ruijin Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, were included. Exclusion criteria comprised previous myocardial infarction (MI) or percutaneous coronary intervention (PCI), severe heart failure, cardiogenic shock, cancer, acute infectious diseases, viral diseases, autoimmune diseases, and other physical disabilities. Patients aged ≥ 18 years were enrolled in this study.

They were divided into three groups base on angiographic finding: control (CON) group ($n=204$) with normal or near-normal coronary arteries on angiography (stenosis < 50%); stable CAD group ($n=220$) with left main coronary artery stenosis ≥ 50% or at least one epicardial main coronary artery stenosis ≥ 75%;[10] and AMI group ($n=299$), which was defined as ST-segment elevation or non-ST-segment elevation myocardial infarction according to international guidelines. [11]

The study was approved by the Ruijin Hospital ethics committee (2018−183), and written informed consent was obtained from all participants. This study is registered at ClinicalTrials.gov (Identifier: NCT05450757). The study protocol complies with the ethical guidelines of the Declaration of Helsinki.

Clinical assessments

Demographic and clinical data, including age, sex, disease history, and physical examination, were collected through face-to-face interviews at baseline. Transthoracic echocardiography and laboratory tests were performed on the second day after admission. Patients received standard care according to current guidelines, including dual antiplatelet therapy and statins. [12, 13] Various parameters, such as glucose and lipid levels, liver and renal function, electrolytes, and cardiac troponin I (cTnI), were measured at the central laboratory of Ruijin Hospital. Body mass index (BMI) was calculated using baseline height and weight measurements. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. [14]

Evaluation for SYNTAX score and GRACE score

The severity of CAD and AMI was assessed using the SYNTAX score and GRACE score, respectively. The SYNTAX (synergy between percutaneous coronary intervention with TAXUS stent and cardiac surgery) score was calculated based on coronary angiography results to assess the severity and complexity of atherosclerotic lesions. Based on the SYNTAX score, CAD patients were categorized into low risk (<23), intermediate risk (23 to 32), or high risk (>32).15.

The GRACE (The Global Registry of Acute Coronary Events) score, obtained online at https://www.outcomes-umassmed.org/grace/, was utilized to determine the severity of AMI. patients into low risk (49 to 125), intermediate risk (126 to 154), or high risk (155 to 319). These scores provide valuable information for assessing the severity of CAD and AMI, aiding in risk stratification and clinical decision-making.

Blood sampling and analysis

During coronary angiography, blood samples were collected from the catheter. These samples were processed within a maximum of 2 h. After centrifugation at 2000 rpm for 15 min, the supernatant liquid was carefully extracted and stored at -80 °C for future use.

The analysis of serum BAFF levels was performed using a Human BAFF ELISA kit (catalog number: CSB-E11912h) obtained from CUSABIO. It is worth noting that all samples were anonymized prior to being handled by laboratory technicians to ensure confidentiality and unbiased analysis.

Statistical analysis

All statistical analyses were conducted using SPSS 22.0 (IBM, Armonk, NY, USA) and R language software (version 4.1.1). Descriptive statistics were used to summarize the baseline characteristics of the entire cohort. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were expressed as counts and percentages. To compare continuous variables, either one-way ANOVA or the Kruskal-Wallis test was employed, depending on the distributional assumptions. The differences in categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate.

Spearman's correlation analysis was performed to examine the association between BAFF and clinical data. The BAFF levels were either log-transformed or divided into tertiles for further analysis. Logistic regression models were utilized to determine the predictive value of serum BAFF concentration in CAD and AMI. Three types of logistic regression models were employed: unadjusted, partially adjusted, and fully adjusted. The partially adjusted model included adjustments for age and gender (with female as the reference category), while the fully adjusted model incorporated additional adjustments for age, gender, body mass index (BMI), smoking status (with non-smoking as the reference category), hypertension (with no hypertension as the reference category), diabetes mellitus (with no diabetes mellitus as the reference category), hyperlipidemia (with no hyperlipidemia as the reference category), white blood cells (WBC), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), myoglobin (MYO), and estimated glomerular filtration rate (eGFR).

Furthermore, a restricted cubic spline (RCS) model with four knots (at the 5th, 25th, 75th, and 95th percentiles) was employed to explore the nonlinear dose-response relationship between BAFF and the risk of a high GRACE score. Receiver operating characteristic (ROC) curves were generated, and the optimal cut-off points with the greatest sensitivity and specificity were determined using Youden's index. The area under the ROC curve (AUC) was calculated to assess the discriminative ability of BAFF in predicting CAD or AMI. All statistical tests were two-tailed, and a P-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 723 patients undergoing CAG were recruited for this study, and they were categorized into CON group, CAD group, and AMI group, based on the results of their angiography (Fig. 1). The clinical characteristics of these patients were presented in Table 1. Among the three groups, individuals in the AMI group exhibited several notable differences compared to the CON and CAD groups. Specifically, the AMI group had a higher proportion of male participants, as well as a higher mean age and a higher prevalence of obesity. Additionally, patients with AMI showed elevated levels of white blood cells (WBC), high-sensitivity C-reactive protein (hs-CRP),

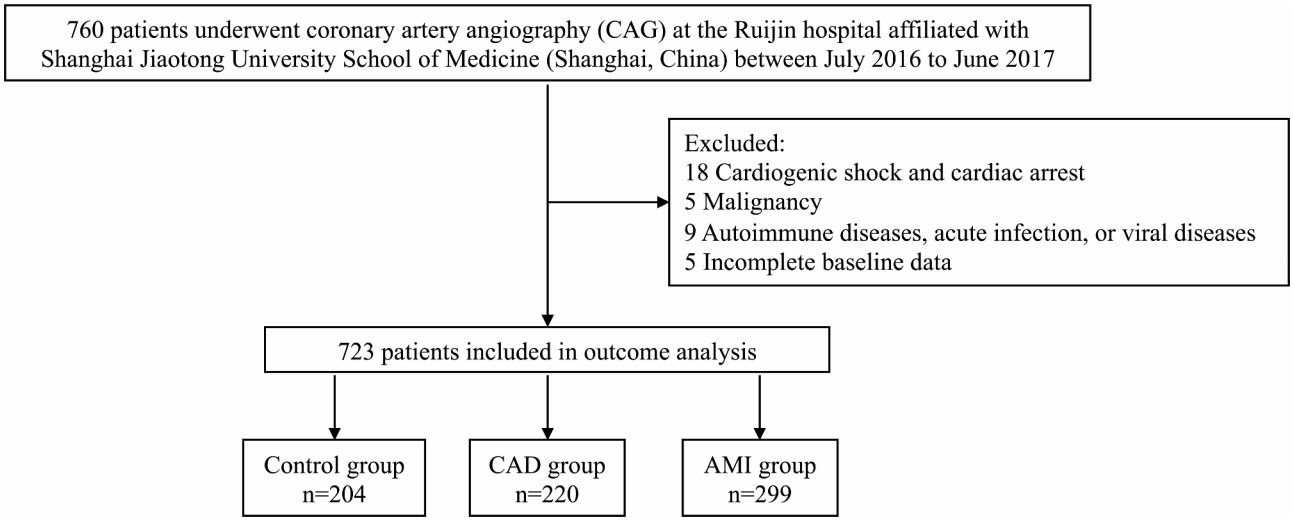

Fig. 1 Study Flowchart. **Abbreviation** CAD, coronary artery disease AMI: acute myocardial infarctions

Table 1 Baseline characteristics for the entire cohort

	Total (*n* = 723)	CON (*n* = 204)	CAD (*n* = 220)	AMI (*n* = 299)	*P* value
Demographic characteristics					
Age (years)	64.66 ± 10.42	62.92 ± 8.53	65.24 ± 8.46	65.43 ± 12.57 *	0.018
Male, sex (n, %)	543(75.1)	140(68.6)	166(75.5) *	237(79.3) *	0.025
BMI (kg/m^2)	24.59 ± 3.32	25.08 ± 3.68	24.82 ± 3.33	24.08 ± 2.98 *†	0.002
Smoking (n, %)	315(43.6)	85(41.7)	95(43.2)	135(45.2)	0.734
Alcohol (n, %)	167(23.1)	54(26.5)	38(17.3)	75(25.1)	0.046
Heart Rate (beats/minute)	80.31 ± 13.26	78.94 ± 10.32	77.64 ± 10.21	83.21 ± 16.18 *†	< 0.001
Systolic pressure (mmHg)	131.86 ± 21.29	135.33 ± 19.48	139.45 ± 18.97	123.91 ± 21.46 *†	< 0.001
Diastolic pressure (mmHg)	76.04 ± 12.79	76.82 ± 11.93	76.84 ± 12.37	74.92 ± 13.60	0.142
Medical history					
Hypertension (n, %)	430(59.5)	125(61.3)	132(60.0)	173(57.9)	0.732
Diabetes (n, %)	201(27.8)	45(22.1)	74(33.6) *	82(27.4) *	0.029
Dyslipidemia (n, %)	148(20.5)	24(11.8)	36(16.4)	88(29.4) *	< 0.001
Lab. Examination					
BAFF (ng/ml)	0.79(0.50–1.10)	0.59(0.38–0.81)	0.74(0.44–1.01) *	1.00(0.67–1.54) *†	< 0.001
WBC (×10^9/L)	6.80(5.30-9.00)	5.80(4.83–6.92)	6.00(4.90–7.05)	9.20(7.10–11.20) *†	< 0.001
Hemoglobin (g/L)	138.00(128.00-148.00)	142.00(133.00-150.00)	136.50(127.00-147.00) *	137.00(122.00-147.00) *	< 0.001
Platelet (×10^9/L)	185.00(154.00-218.00)	174.00(144.25–209.00)	189.00(161.00-223.75) *	190.00(157.50–221.00) *	0.001
hs-CRP (mg/L)	1.20(0.52–3.52)	0.68(0.35–1.57)	0.75(0.35–1.74)	3.00(1.07–7.96) *†	< 0.001
HbA1c (%)	5.90(5.60–6.60)	5.80(5.60–6.20)	5.90(5.57–6.70)	6.00(5.65–6.80) *	0.004
Fasting glucose (mmol/L)	5.64(5.12–6.64)	5.46(5.01–6.01)	5.59(5.14–6.38) *	6.09(5.24–7.33) *†	< 0.001
Triglyceride (mmol/L)	1.26(0.91–1.79)	1.20(0.90–1.70)	1.23(0.90–1.80)	1.29(0.97–1.82)	0.269
Total cholesterol (mmol/L)	4.12(3.41–4.93)	3.99(3.36–4.56)	3.85(3.21–4.75)	4.58(3.72–5.36) *†	< 0.001
HDL-C (mmol/L)	1.09(0.93–1.30)	1.14(0.96–1.35)	1.09(0.92–1.34)	1.05(0.92–1.25) *	0.004
LDL-C (mmol/L)	2.57(1.89–3.19)	2.39(1.87–2.96)	2.23(1.62–2.93)	2.87(2.22–3.52) *†	< 0.001
Lp(a) (mmol/L)	0.14(0.07–0.31)	0.14(0.06–0.28)	0.14(0.07–0.34)	0.14(0.07–0.29)	0.306
Creatine (μmol/L)	80.00(70.00–94.00)	78.00(69.25–88.75)	80.00(70.00-94.75)	81.00(70.00-100.00) *	0.042
Cystatin C (mg/L)	1.04(0.91–1.21)	1.05(0.92–1.18)	1.03(0.92–1.18)	1.04(0.91–1.29)	0.691
eGFR (mL/minute/1.73m^2)	84.05(70.28–93.93)	86.70(75.15–95.48)	82.75(71.03–92.30) *	82.75(62.43–94.80) *	0.011
NT-proBNP (pg/ml)	139.15(47.45-663.05)	77.15(27.78-238.48)	68.95(30.35-162.93)	614.95(152.85-2,026.00) *†	< 0.001
CK-MB (mg/L)	3.70(1.40–67.0)	1.30(0.90–1.98)	2.10(1.40–5.10) *	107.60(26.30–275.00) *†	< 0.001
myoglobin (ng/ml)	36.10(22.70-177.20)	24.10(18.33–31.35)	26.70(19.03–39.75)	345.30(98.50-1,053.10) *†	< 0.001
cTnI (ng/L)	0.38(0.01–12.97)	0.01(0.01–0.01)	0.21(0.06–0.49) *	20.27(6.06–61.22) *†	< 0.001
Syntax score	11.00(0.00-21.5)	0.00(0.00–0.00)	12.00(7.00-22.75) *	19.00(12.00–27.00) *†	< 0.001
Echocardiography					
LVEF (%)	61.96 ± 9.00	65.92 ± 7.78	65.66 ± 7.07	56.47 ± 8.20 *†	< 0.001
LAD (mm)	38.36 ± 4.32	39.06 ± 4.98	38.10 ± 4.13	38.08 ± 3.91 *	0.028
LVEDD (mm)	49.05 ± 4.54	49.15 ± 5.16	48.61 ± 4.40	49.31 ± 4.16	0.213
LVESD (mm)	32.31 ± 5.59	31.06 ± 5.66	31.02 ± 5.98	34.13 ± 4.69 *†	< 0.001
Medication					
Aspirin (n, %)	606(83.8)	111(54.4)	206(93.6) *	289(96.7) *†	< 0.001
Clopidogrel (n, %)	417(57.7)	32(15.7)	134(60.9) *	251(83.9) *†	< 0.001
Ticagrelor (n, %)	79(10.9)	1(0.5)	39(17.7) *	39(13.0) *	< 0.001
Statins (n, %)	650(89.9)	149(73.0)	218(99.1) *	283(94.36) *	< 0.001
Anticoagulants (n, %)	138(19.2)	26(12.7)	6(2.7) *	107(35.8) *†	< 0.001
ACEI/ARB (n, %)	434(60.0)	88(43.1)	102(46.4)	244(81.6) *†	< 0.001

Table 1 (continued)

	Total (*n* = 723)	CON (*n* = 204)	CAD (*n* = 220)	AMI (*n* = 299)	*P* value
Demographic characteristics					
Beta blockers (n, %)	504(69.7)	104(51.0)	132(60)	268(89.6) *†	< 0.001
Nitrates (n, %)	193(26.7)	35(17.2)	52(23.6)	106(35.5) *†	< 0.001

Values are mean ± SD, n (%), or median (interquartile range)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BAFF, B-cell activating factor; BMI, body mass index; CK-MB, creatine kinase-MB isoenzyme; cTnI, Cardiac troponin I; eGFR, estimated glomerular filtration; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C reactive protein; LAD, left atrial diameter; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell

* for significant difference compared to control group

† for significant difference compared to CAD group

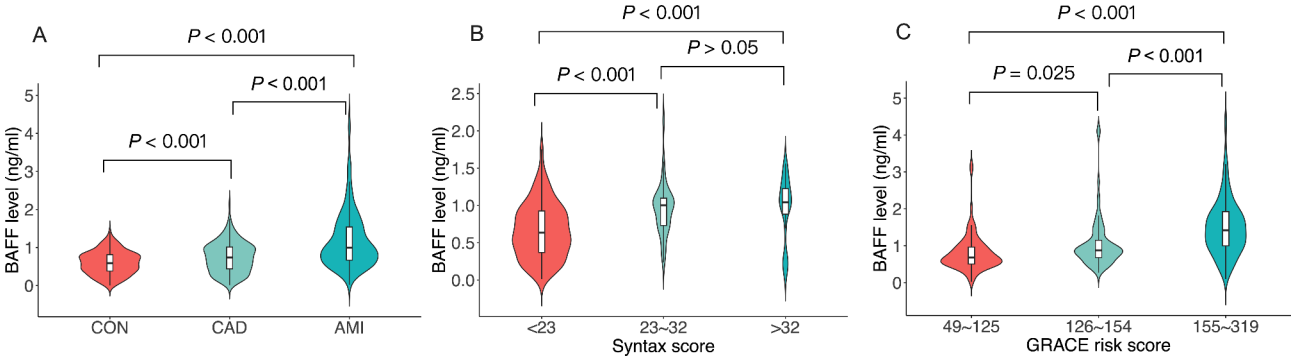

Fig. 2 The concentration of serum BAFF in different groups. (**A**) Comparison of serum BAFF levels in CAD, AMI, or control group; (**B**) Serum BAFF levels in different groups stratified by SYNTAX score; (**C**) Serum BAFF levels in different groups stratified by GRACE score. **Abbreviation** BAFF, B-cell activating factor; CAD, Coronary artery disease; AMI, Acute myocardial infarction; SYNTAX score, Synergy Between Percutaneous Coronary Intervention score; GRACE score, Global Registry of Acute Coronary Events score

N-terminal pro-brain natriuretic peptide (NT-proBNP), and creatine kinase-MB isoenzyme (CK-MB).

Conversely, they had lower levels of high-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), left atrial diameter, and left ventricular end systolic diameter (LVESD). Despite a higher proportion of statin use, the AMI group still exhibited higher triglyceride levels compared to the CON and CAD groups. These findings are consistent with the clinical presentation of patients with acute myocardial infarction.

Serum BAFF levels between groups

In comparison with the control group, serum BAFF concentrations in CAD and AMI groups showed a gradual increase trend (control group: 0.59 [0.38–0.81], CAD group: 0.74 [0.44–1.01], AMI group: 1.00 [0.67–1.54]) (Fig. 2A).

In CAD group, compare with low risk (SYNTAX score < 23) patients, circulating BAFF levels were significant increase in high risk (SYNTAX score 23 to 32) patients (SYNTAX score < 23 group: 0.63 [0.37–0.93], SYNTAX score 23 to 32 group: 1.00 [0.73–1.10], SYNTAX score > 23 group: 1.04 [0.82–1.24]) (Fig. 2B).

In AMI group, compare with low risk (GRACE score 49 to 125) patients, circulating BAFF levels were significant increase in high risk (GRACE score155 to 319) patients (GRACE score 49 to 125 group: 0.68 [0.50–0.97], GRACE score 126 to 154 group: 0.88 [0.68–1.16], GRACE score155 to 319 group: 1.44 [0.99–1.92]) (Fig. 2C).

Correlations of circulating BAFF levels and clinical data

The levels of BAFF levels exhibited positive correlation with age (r=0.2241, P<0.0001) (Fig. 3A), WBC (r=0.2268, P<0.0001) (Fig. 3C) and hs-CRP levels (r=0.2517, P<0.0001) (Fig. 3D). Conversely, BAFF levels showed a negative correlation with LVEF (r = -0.2686, P<0.0001) (Fig. 3B), indicating a potential involvement of BAFF in inflammation and cardiac function.

Moreover, the Spearman's correlation analysis found that there was a statistically significant but weak positive correlation between the BAFF levels and SYNTAX score (r=0.3002, P<0.0001) (Fig. 3E). Circulating BAFF levels were positively correlated with GRACE score. (r=0.5684, P<0.0001) (Fig. 3F), suggesting a potential correlation of BAFF and severity of CAD and AMI.

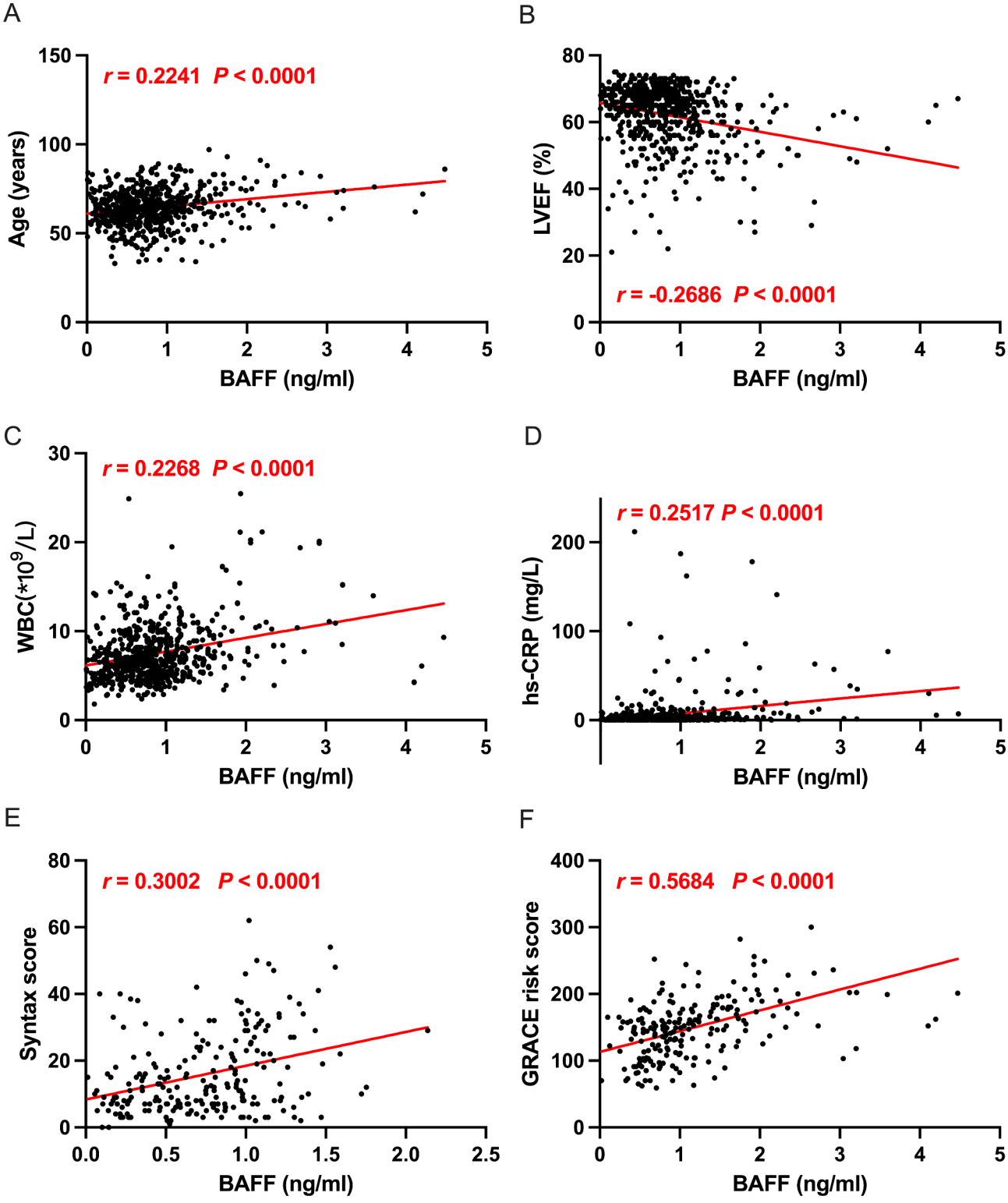

Fig. 3 Dot plot showing the relationship between BAFF and clinical data. (**A**) correlation between BAFF and age; (**B**) correlation between BAFF and LVEF; (**C**) correlation between BAFF and WBC; (**D**) correlation between BAFF and hs-CRP; (**E**) serum BAFF levels were positively associated with SYNTAX score in CAD group; (**F**) serum BAFF levels were positively associated with GRACE score in AMI group. **Abbreviation** BAFF, B-cell activating factor; LVEF, left ventricular ejection fraction; hs-CRP, high sensitivity C reactive protein; WBC, white blood cell; CAD, Coronary artery disease; AMI, Acute myocardial infarction; SYNTAX score, Synergy Between Percutaneous Coronary Intervention score; GRACE score, Global Registry of Acute Coronary Events score

Associations of BAFF levels and presence and severity of CAD and AMI

Univariate and multivariate logistic regression models were constructed to analyze the Associations of BAFF and the presence and severity of CAD and AMI. As shown in Table 2, in the CAD and control groups, high levels of circulating BAFF were significantly associated with CAD (adjusted odds ratio [OR] 1.305, 95% CI 1.078–1.580), as a continuous log-transformed variable, adjusted for the full model including age, sex, BMI, smoking, history of hypertension, history of diabetes, history of dyslipidemia, WBC, hs-CRP, NT-proBNP, and MYO. To further demonstrate this relationship, the BAFF levels were separated into three groups according to tertiles. There was a three-fold increased risk (adjusted OR 3.179, 95% CI 1.830–5.524) in the fully adjusted model in tertile 3 compared to tertile 1. However, circulating BAFF levels was associated with severe CAD only in unadjusted raw model (SYNTAX score > 32, unadjusted OR 4.129, 95% CI 1.433–11.893), not fully adjusted model (SYNTAX score > 32, adjusted OR 3.299, 95% CI 0.967–11.254).

In addition, the multivariable-adjusted ORs for the association of circulating BAFF levels and the presence and severity of AMI are shown in Table 3. When analyzed as a continuous variable, in CAD and AMI groups, high levels of circulating BAFF were significantly related to the presence of AMI (adjusted OR 2.874, 95% CI 1.708–4.838). Using the tertile 1 group as a reference, the risk of AMI for the tertile 3 groups was a three-fold higher (adjusted OR 3.335, 95% CI 1.493–7.452).

Of note, after adjusting for various conventional influencing factors (Covariates in the model included age, sex, BMI, smoking, history of hypertension, history of DM, history of dyslipidemia, WBC, hs-CRP, NT-proBNP, MYO, and eGFR), the BAFF as a categorical variable was still significantly related to a high GRACE score (GRACE score 155 to 319, adjusted OR 4.297, 95% CI 1.841–10.030). Additionally, the results of the RCS showed a dose−response relationship between the BAFF and the risk of a high GRACE score ($P_{for\ non-linearity} < 0.0005$, $P_{overall} < 0.0001$; Fig. 4).

The predictive performance of the BAFF for presence and severity of CAD and AMI

The ROC curves were used to evaluate the diagnostic efficacy of serum BAFF levels for presence and severity of CAD and AMI. The ROC curves of BAFF suggested that the BAFF be valuable in predicting the incidence of CAD and AMI (Fig. 5A and B). The AUC was 0.605 and 0.683, respectively. BAFF had 38.2% sensitivity, 85.8% specificity for identifying CAD, and 33.8% sensitivity, 95.0% specificity for identifying AMI.

Furthermore, the AUC was 0.690 and had sensitivity of 75.0% and specificity of 71.4% of differentiating CAD patients with a high SYNTAX score (Fig. 5C). The AUC was 0.766 and had sensitivity of 75.5% and specificity of 72.8% of differentiating AMI patients with a high GRACE score (Fig. 5D). These results demonstrated the BAFF has the certain predictive value for predicting presence and severity of CAD and AMI.

Table 2 Association of serum BAFF with the presence and severity of CAD

	Unadjusted OR (95%CI)	*P* value	Adjusted for model 1 OR (95%CI)	*P* value	Adjusted for model 2 OR (95%CI)	*P* value
CAD						
log_2BAFF per SD	1.304 (1.087–1.565)	0.004	1.310 (1.090–1.573)	0.004	1.305 (1.078–1.580)	0.006
BAFF tertiles						
T1	1 (Ref)		1 (Ref)		1 (Ref)	
T2	0.724 (0.487–1.076)	0.724	0.741 (0.496–1.107)	0.143	0.709 (0.465–1.082)	0.111
T3	3.300 (1.959–5.560)	< 0.001	3.203 (1.889–5.432)	< 0.001	3.179 (1.830–5.524)	< 0.001
SYNTAX score ≥ 33						
log_2BAFF per SD	1.652 (0.965–2.829)	0.067	1.640 (0.947–2.841)	0.078	1.398 (0.770–2.538)	0.271
BAFF tertiles						
T1	1 (Ref)		1 (Ref)		1 (Ref)	
T2	0.378 (0.071–2.013)	0.254	0.369 (0.069–1.977)	0.244	0.316 (0.054–1.849)	0.201
T3	4.129 (1.433–11.893)	0.009	3.998 (1.373–11.640)	0.011	3.299 (0.967–11.254)	0.057

The BAFF and abnormal distribution data were transformed into logarithmic form. The OR is shown as 1 SD

Model 1 was adjusted for age and sex

Model 2 was adjusted in terms of model1 and BMI, smoking, history of hypertension, history of diabetes, history of dyslipidemia, WBC, hs-CRP, NT-proBNP, MYO, and eGFR

Abbreviation: BAFF, B-cell activating factor; BMI, body mass index; hs-CRP, high sensitivity C reactive protein; WBC, white blood cell; DM, diabetes mellitus; eGFR, estimated glomerular filtration; NT-proBNP, N-terminal pro-brain natriuretic peptide; MYO, myoglobin; OR odds ratio; CI, confidence interval. RCS restricted cubic spline, GRACE risk score, Global Registry of Acute Coronary Events score; BAFF, B-cell activating factor; AMI, Acute myocardial infarction

Table 3 Association of serum BAFF with the presence and severity of AMI

	Unadjusted OR (95%CI)	*P* value	Adjusted for model 1 OR (95%CI)	*P* value	Adjusted for model 2 OR (95%CI)	*P* value
AMI						
log_2BAFF per SD	2.103 (1.703–2.598)	< 0.001	2.106 (1.704–2.602)	< 0.001	2.874 (1.708–4.838)	0.002
BAFF tertiles						
T1	1 (Ref)		1 (Ref)		1 (Ref)	
T2	0.800 (0.549–1.166)	0.245	0.805 (0.551–1.174)	0.260	0.589 (0.260–1.332)	0.203
T3	2.499 (1.730–3.610)	< 0.001	2.489 (1.722–3.597)	< 0.001	3.335 (1.493–7.452)	0.003
GRACE score 155 to 319						
log_2BAFF per SD	3.078 (2.183–4.340)	< 0.001	2.177 (1.513–3.133)	< 0.001	1.771 (1.184–2.648)	0.005
BAFF tertiles						
T1	1 (Ref)		1 (Ref)		1 (Ref)	
T2	2.209 (1.185–4.117)	0.013	1.547 (0.770–3.106)	0.220	1.409 (0.651–3.052)	0.384
T3	11.227 (5.808–21.704)	< 0.001	5.891 (2.850-12.179)	< 0.001	4.297 (1.841–10.030)	0.001

The BAFF and abnormal distribution data were transformed into logarithmic form. The OR is shown as 1 SD

Model 1 was adjusted for age and sex

Model 2 was adjusted in terms of model1 and BMI, smoking, history of hypertension, history of diabetes, history of dyslipidemia, WBC, hs-CRP, NT-proBNP, MYO, and eGFR

Abbreviation BAFF, B-cell activating factor; BMI, body mass index; hs-CRP, high sensitivity C reactive protein; WBC, white blood cell; DM, diabetes mellitus; eGFR, estimated glomerular filtration; NT-proBNP, N-terminal pro-brain natriuretic peptide; MYO, myoglobin; OR odds ratio; CI, confidence interval. RCS restricted cubic spline, GRACE risk score, Global Registry of Acute Coronary Events score; BAFF, B-cell activating factor; AMI, Acute myocardial infarction

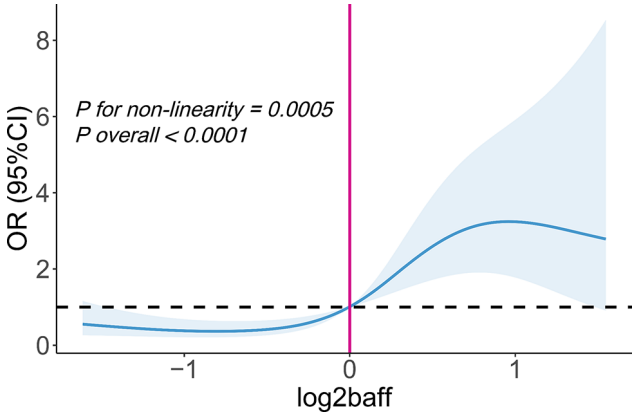

Fig. 4 Restricted cubic spline for the odds ratio of a high GRACE score in AMI group. Note: Restricted cubic spline curve was carried out with 4 knots at 5th, 25th, 75th and 95th percentiles of baseline BAFF levels. The reference point was the median of the BAFF in the 299 AMI participants. The solid line represented point estimation on the association of BAFF with GRACE score 155 to 319, and the shaded portion represented 95% CI estimation. Covariates in the model included age, sex, BMI, smoking, history of hypertension, history of DM, history of dyslipidemia, WBC, hs-CRP, NT-proBNP, MYO, and eGFR. *Abbreviation* BAFF, B-cell activating factor; AMI, acute myocardial infarction; BMI, body mass index; hs-CRP, high sensitivity C reactive protein; WBC, white blood cell; DM, diabetes mellitus; eGFR, estimated glomerular filtration; NT-proBNP, N-terminal pro-brain natriuretic peptide; MYO, myoglobin; CI, confidence interval, GRACE score, Global Registry of Acute Coronary Events score

Discussion

This study demonstrated that patients diagnosed with CAD or AMI exhibited elevated levels of serum BAFF compared to patients with normal coronary angiography findings. Additionally, BAFF levels were positively correlated with both the SYNTAX score and GRACE score, which are indicators of the severity of CAD and AMI, respectively. Importantly, our study revealed that increased levels of circulating BAFF were independently associated with the presence of CAD, AMI, and a high GRACE score. To the best of our knowledge, this is the first study to specifically investigate the relationship between BAFF and the presence and severity of CAD/AMI in human subjects. These findings provide compelling evidence that circulating BAFF serves as a predictive biomarker for the presence and severity of CAD and AMI. These findings underscore the significance of BAFF in patients presenting with chest pain and suggest its potential clinical utility.

The SYNTAX score is a comprehensive angiographic tool used to evaluate the complexity of CAD by considering anatomical risk factors. [16] By analyzing angiographic variables, this score characterizes coronary artery disease qualitatively and quantitatively. [17] Higher SYNTAX scores indicate more intricate diseases and increased potential for major adverse cardiovascular events. [15, 18] However, calculating the SYNTAX score relies on invasive coronary angiography findings. On the other hand, the GRACE risk score is a robust model for predicting short- and long-term mortality and reinfarction following acute coronary syndrome (ACS). [19] However, it does not incorporate biomarkers that reflect the diverse pathophysiological processes observed in ACS patients. Therefore, there is an urgent need for novel biomarkers that can noninvasively assess the severity of CAD and AMI before undergoing coronary angiography. Such biomarkers would be valuable for early risk stratification and could potentially influence the choice of therapeutic approaches and patient management.

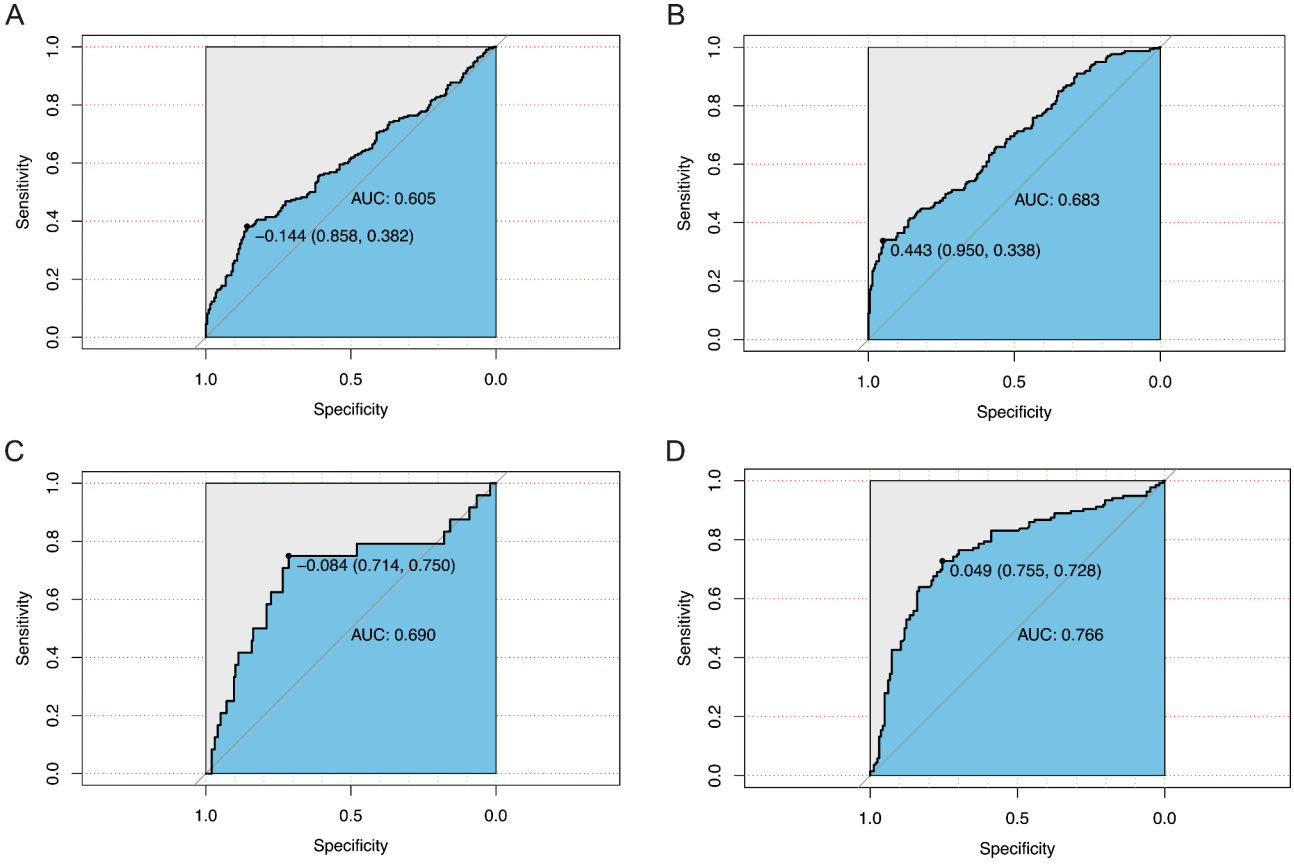

Fig. 5 Receiver operating characteristic curves for the diagnostic accuracy of BAFF for presence and severity of CAD and AMI. (**A**) Receiver operating characteristic curves for the diagnostic accuracy of BAFF for CAD; (**B**) Receiver operating characteristic curves for the diagnostic accuracy of BAFF for AMI; (**C**) Receiver operating characteristic curves for the diagnostic accuracy of BAFF for SYNTAX score ≥ 33; (**B**) Receiver operating characteristic curves for the diagnostic accuracy of BAFF for GRACE score 155 to 319. *Abbreviation* BAFF, B-cell activating factor; AUC, Area under the curve; CAD, Coronary artery disease; AMI, Acute myocardial infarction; GRACE score, Global Registry of Acute Coronary Events score; SYNTAX score, Synergy Between Percutaneous Coronary Intervention score

Evidence indicates that inflammation induced by innate immunity and adaptive immunity plays an indispensable role in the pathological mechanism of CAD and AMI. [20–22] The immune response and inflammatory process in the post-MI period are regulated by different classes of immune cells, cytokines, and chemokines. B cells are thought to participate in the progression of atherosclerosis and eventually AMI. Recent studies identified B2 cells as a pro-atherogenic B cell subgroup that could significantly enhance the development of atherosclerosis by driving T cell activation and secreting pro-inflammatory cytokines, including TNF-α. [23, 24] Germinal center-derived IgG antibodies produced by follicular B cells and T-B cell interactions promote atherosclerosis. [25, 26] Antibodies produced by B cells are crucial in atherosclerosis, IgM, IgG, and IgA are present in atherosclerotic plaques. [27] Autoantibodies that bind specific antigens, including oxLDL, [28] ApoB [29] and stressed endothelial cells [30] might be a significant cause of the development of atherosclerotic cardiovascular diseases. In summary, B cells are involved in the determination of the fate of atherosclerotic plaques.

The rationale for examining BAFF as a biomarker in this study stems from its role as a TNF family molecule predominantly produced by myeloid cells. BAFF, along with its receptors, plays a crucial role in regulating B cell maturation and maintaining B cell homeostasis. [31, 32] Previous research has investigated BAFF in autoimmune diseases such as rheumatoid arthritis and lupus, [33, 34] which are associated with an increased risk of premature atherosclerosis and heart attacks. [35] Evidence suggests that the proliferation and activation status of B cells are significant factors in determining the risk of cardiovascular disease (CVD). [36] Studies conducted in hyperlipidemic atherosclerotic mice have implicated BAFF in the development of atherosclerotic lesions, particularly vulnerable lesions that are prone to rupture and cause heart attacks. [25] Our previous studies suggested that higher BAFF levels in the acute phase are an independent predictor of the incidence of MACEs in patients with STEMI. [37] Therefore, in this study, the researchers

chose to investigate BAFF as a potential biomarker to assess its association with the presence and severity of CAD and AMI, aiming to provide insights into its role and potential clinical applications in patients with chest pain.

In the present study, we found that subjects with AMI had the highest serum BAFF levels. And those have a high GRACE score (155 to 319) also had the highest BAFF levels. Indeed, previous studies conducted on rodent models have provided further insights into the role of BAFF in atherosclerosis and cardiovascular health. Deletion of the BAFF receptor (BAFFR) in these models has been shown to attenuate the progression of atherosclerosis, suggesting a protective effect. [38] However, interestingly, neutralizing BAFF using an anti-BAFF antibody has been found to induce advanced atherosclerosis in mice lacking apolipoprotein E ($Apoe^{-/-}$) or low-density lipoprotein receptor ($Ldlr^{-/-}$), indicating a complex and context-dependent role for BAFF in atherosclerosis development. The dynamic changes in myocardial B cells observed in an ischemia-reperfusion (IR) model further support the involvement of B cells and BAFF in cardiac injury and repair processes. The increase in myocardial B cells following IR injury, peaking between days 3 and 5, suggests their potential contribution to the inflammatory response and subsequent healing. [21] BAFF producers, including neutrophils and macrophages, infiltrate the heart shortly after myocardial injury which might be the primary cellular source of elevated BAFF in AMI or IR injury. [21] Moreover, participants with higher serum BAFF levels tended to have higher SYNTAX scores. Mechanistically, depletion of B2 but not B1a cells in a BAFFR-deficient mouse model could attenuate atherosclerosis, [8] BAFF can also augment B2 cell replication and viability, which might partly explain the worse diseases in patients with higher BAFF levels. [39]

After being fully adjusted for several common risk factors in the Logistic regression model, our research found that the elevation of BAFF was not only associated with CAD (Log [2] BAFF: adjusted OR 1.305, 95% CI 1.078–1.580) but also AMI (log [2]BAFF: adjusted OR 2.874, 95% CI 1.708–4.838). Additionally, the BAFF as a categorical variable was still significantly related to a high GRACE score (GRACE score 155 to 319, adjusted OR 4.297, 95% CI 1.841–10.030), establishing a relationship between BAFF levels and severity of AMI for the first time. However, after adjustment for potential clinical confounders, the highest tertile BAFF was not associated with a high SYNTAX score might cause by a bias that was attributed to the number of SYNTAX score > 32 in each group being quite small. *Furthermore, it is noteworthy that BAFF demonstrates a relatively low predictive sensitivity for CAD and AMI, while exhibiting a higher specificity. This characteristic of being a biomarker with low sensitivity and high specificity holds significant practical implications. In the context of disease screening or early diagnosis, a high specificity test can effectively minimize unnecessary treatment or overtreatment of healthy individuals, while also ensuring that genuinely ill individuals are not misdiagnosed as healthy. However, it is important to recognize that the trade-off for high specificity is the potential for BAFF to miss detecting some individuals with the disease. Therefore, careful consideration of BAFF's utility is essential to ensure the accuracy and practicality of the test.*

In all, the above results suggest that BAFF might be involved in the fate of atherosclerotic plaques by influencing immune response and inflammation, associated with the severe pathological change of coronary artery. It is important that the cardiovascular field be cognizant of potential effects of modulating B-cell activity on CAD patients.

Limitations

The present study has several limitations that should be taken into consideration. First, it is important to acknowledge that this study was conducted at a single center with a relatively small sample size. Therefore, the generalizability of the findings may be limited, and there is a need for validation in larger, multicenter cohort studies to confirm the results. Second, due to the observational nature of the study, a causal relationship between BAFF levels and the presence and severity of CAD and AMI cannot be established. The findings demonstrate an association but do not provide evidence of causality. Third, the control group consisted of subjects with chest pain and normal coronary angiography results, which may introduce bias. Ideally, healthy controls without any chest pain symptoms would have been more appropriate. Fourth, despite adjusting for known CAD risk factors, there is still a possibility of residual confounding influencing the results. Other unmeasured or unknown confounding factors may have affected the association between BAFF levels and cardiovascular outcomes. Fifth, a single measurement of BAFF levels was obtained in this study, which may not fully capture the dynamic changes that could occur over time. Serial evaluations of BAFF levels at different time points would provide more comprehensive information and could be considered in future studies. Finally, the exact role of BAFF in cardiovascular disease is still not fully understood, and there are conflicting findings in the existing literature. Further research is needed to elucidate the underlying mechanisms of BAFF in the pathogenesis of AMI and to determine whether it has a harmful or protective effect in cardiovascular disease.

Conclusions

This study demonstrated that elevated serum BAFF concentration was positively associated with the incidence of CAD and AMI and with the severity of the disease. Consequently, BAFF could be a novel biomarker to assist in the diagnosis of CAD and AMI and to determine the severity of the disease. More studies or trials are needed to determine whether therapy with BAFF/BAFFR would benefit clinical patients.

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Author contributions
ZYC, ZYW and YKC designed this study. LY performed the echocardiography. ZBZ, JWN, RD, XQW, JZZ, and FHD performed PCI and collected blood samples. ZYC, ZYW, HYX and YKC collected and analyzed the data. YYW, HYX, and YKC performed the statistical analysis. YYW, ZYW and YKC wrote the manuscript. RYZ, YYW, and XXY made critical revisions to the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (2018 – 183). The patients/participants provided their written informed consent to participate in this study. All the methods included in this study are in accordance with the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interest
The authors declare no competing interests.

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