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RESEARCH ARTICLE

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Serum brain-derived neurotrophic factor in coronary heart disease: Correlation with the T helper (Th)1/Th2 ratio, Th17/regulatory T (Treg) ratio, and major adverse cardiovascular events

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) exerts protective roles against dyslipidemia, atherosclerosis, and inflammation in cardiovascular diseases; meanwhile, it retards $CD4^+$ T cell differentiation into T helper (Th)1 and Th17 cells. Hence, this study aimed to investigate the linkage of serum BDNF with Th1/Th2 ratio, Th17/regulatory T (Treg) ratio, and major adverse cardiovascular events (MACE) risk in the coronary heart disease (CHD) patients.

Methods: This prospective study detected serum BDNF in 210 CHD patients, 50 disease controls (DCs), and 50 healthy controls (HCs) using an enzyme-linked immunosorbent assay. For CHD patients only, the proportion of Th1, Th2, Th17, and Treg cells in blood $CD4^+$ T cells was calculated by flow cytometry.

Results: The BDNF varied among CHD patients, DC, and HC ($p < 0.001$). Specifically, BDNF was declined in CHD patients compared with DCs ($p < 0.001$) and HCs ($p < 0.001$). In CHD patients, BDNF was negatively related to Th1 cells ($p = 0.031$), Th1/Th2 ratio ($p = 0.026$), Th17 cells ($p = 0.001$), and Th17/Treg ratio ($p = 0.002$). Concerning the prognosis, BDNF was reduced in patients with MACE occurrence compared to patients without MACE occurrence ($p = 0.006$). Furthermore, BDNF showed a trend (lacked statistical significance) to relate to longer MACE-free survival ($p = 0.059$). Besides, BDNF was related to the absence of obesity ($p = 0.019$), decreased total cholesterol ($p = 0.043$), low-density lipoprotein cholesterol ($p = 0.019$), C-reactive protein ($p = 0.012$), and Gensini score ($p = 0.005$).

Conclusion: Serum BDNF negatively correlates with Th1/Th2 ratio, Th17/Treg ratio, and estimates lower MACE risk in CHD patients.

KEYWORDS
brain-derived neurotrophic factor, coronary heart disease, major adverse cardiovascular events, Th1/Th2 ratio, Th17/Treg ratio

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1 | INTRODUCTION

Coronary heart disease (CHD), characterized by the presence of atherosclerosis in coronary arteries, is a prevalent cardiovascular disease (whose prevalence reaches 0.60%) and the foremost leading cause of mortality in China.[1–4] Based on CHD pathogenetic factors (including atherosclerosis plaque, excessive inflammation, lipid dysfunction, etc.), numerous interventions have been developed, which contain coronary revascularization, angiotensin inhibitor therapy, antiplatelet and lipid therapy, etc.[5–7] Unfortunately, the 4-year MACEs rate ranges from 24.06% to 40.11%, implying that the clinical outcomes of many CHD patients are still not ideal.[8–10] Therefore, exploring some potential biomarkers is helpful for identifying disease risk and improving the clinical management of CHD.

Brain-derived neurotrophic factor (BDNF), belonging to the neurotrophin family, exerts a beneficial role in several biological processes, including regulating $CD4^+$ T cell differentiation, lipid and glucose metabolism, angiogenesis, inflammatory response, etc.[11–14] For instance, a previous study finds that BDNF suppresses T helper (Th)1 and Th17 cell activation in the central nervous system.[15] Another study notices that BDNF could ameliorate the progression of atherosclerosis in diabetes mellitus-accelerated atherosclerosis mouse models.[16] In addition, some studies suggest that BDNF has the potency to alleviate inflammatory injury and regulate dyslipidemia in pre-clinical stroke models.[17–19] Considering that the aforementioned $CD4^+$ cell differentiation, dyslipidemia, atherosclerosis, and inflammation are closely related to the initiation and progression of CHD, BDNF might be a protective factor in CHD patients.[20,21] Recently, a study has found that BDNF level is reduced in CHD patients compared with HCs.[22] Another study shows that BDNF is negatively related to interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and the Gensini score in CHD patients.[23] However, the associations of BDNF with T cell differentiation and prognosis in CHD patients are still unknown presently.

Hence, this study aimed to investigate the correlation of serum BDNF with Th1/Th2, Th17/Treg balance, and MACE risk in CHD patients.

2 | METHODS

2.1 | Subjects

In this research, a total of 210 CHD patients were serially recruited from March 2019 to August 2021. The recruitment criteria were: (i) diagnosed with CHD by coronary angiography[24]; (ii) >18 years old; and (iii) willing to cooperate actively. The exclusion criteria were: (i) complicated with cerebral or peripheral vascular disease; (ii) complicated with hematologic malignancies or solid cancers; and (iii) pregnant or lactating females. During the same period, a total of 50 patients with unexplained chest pain and diagnosed as non-CHD by coronary angiography were recruited as disease controls (DC). A total of 50 healthy subjects without any abnormality in the physical examination were recruited as HC. This research obtained the approval of the Ethics Committee, and informed consent was signed by each subject or guardian.

2.2 | Sample collection and examination

For all subjects, peripheral blood samples were collected. Whereafter, the serum samples were isolated by the centrifugation method and were subsequently stored at −80°C. The level of serum BDNF was measured by a commercial Enzyme-linked immunosorbent assay (ELISA) kit (sensitivity: 2.4 pg/ml, range: 15.6–1000 pg/ml, No. Cat. ab212166, Abcam).

In CHD patients only, the proportion of Th1, Th2, Th17, and Treg cells in $CD4^+$ T cells was calculated by flow cytometry (FCM) analysis, using a commercial human Th1/Th2/Th17 phenotyping kit (No. Cat. 560751, BD) and human Regulatory T cell sorting kit (No. Cat. 560753, BD). $CD4^+$ and Interferon-gamma$^+$ (IFN-γ^+) were applied to label Th1 cells, $CD4^+$ and $IL4^+$ were applied to label Th2 cells, $CD4^+$ and IL-$17A^+$ were applied to label Th17 cells, $CD4^+$, $CD25^+$, and Forkhead box protein 3^+ ($FOXP3^+$) were applied to label Treg cells. A fluorescence-activated cell sorting (FACS) flow cytometer was used to detect the proportion of those cells. Meanwhile, ratios of Th1/Th2 and Th17/Treg cells were obtained.

2.3 | Data collection, follow-up, and assessment

Demographics, medical history, and blood biochemical indexes of CHD patients were obtained. The Gensini score was calculated to assess coronary artery stenosis degree.

Standard follow-up in CHD patients was performed until February 2022. The median follow-up duration was 16.2 months (range of 3.3–29.2 months). MACE events were also recorded.[25]

2.4 | Statistics

The clinical data were analyzed statistically by SPSS 24.0 (IBM Crop.). All the figures were plotted by GraphPad 7.0 (GraphPad Software Inc.). In the analysis, we divided the level of serum BDNF into high and low by median in CHD patients. The Wilcoxon rank sum test was used to compare the differences between the two groups. Meanwhile, Kruskal–Wallis H rank-sum test was used to compare the differences among the three groups, and the Bonferroni correction was used for post hoc comparison. To evaluate the correlation between the level of serum BDNF and other continuous variables, spearman's rank correlation analysis was used. The receiver operator characteristic (ROC) curves were plotted to describe the discrimination abilities of the serum BDNF level. The Kaplan–Meier curve was applied to display the MACE-free survival, and the log-rank test was applied for analysis.

3 | RESULTS

3.1 | Clinical characteristics of CHD patients

Two hundred and ten CHD patients consisted of 47 (22.4%) females and 163 (77.6%) males, with a mean age of 63.7 ± 10.4 years (Table 1). The mean body mass index (BMI) was 24.2 ± 3.1 kg/m.^{2} A respective of 146 (69.5%), 85 (40.5%), 48 (22.9%), and 25 (11.9%) patients were accompanied by a history of hypertension, hyperlipidemia, diabetes mellitus (DM), and chronic kidney disease (CKD). The median (interquartile range [IQR]) Gensini score was 29.0 (17.0–49.0). Besides, the median (IQR) proportion of Th1 cells, Th2 cells, Th17 cells, and Treg cells in blood $CD4^+$ T cells were 15.7% (13.3%–18.1%), 10.9% (8.2%–13.9%), 4.4% (3.2%–6.1%), and 4.9% (4.0%–5.9%), accordingly; besides, the respective Th1/Th2 ratio and Th17/Treg ratio were 1.4 (1.1–2.3) and 0.9 (0.6–1.4). The detailed demographic and disease characteristics of CHD patients were listed in Table 1.

3.2 | Serum BDNF level in all subjects

Serum BDNF levels varied among CHD patients, DC, and HC ($p < 0.001$); in detail, the median (IQR) BDNF level of CHD patients, DC, and HC was 6.3 (3.5–8.3) ng/ml, 9.7 (7.2–11.6) ng/ml, and 10.6 (8.5–14.9) ng/ml, correspondingly (Figure 1A). Specifically, serum BDNF level declined in CHD patients compared to DC ($p < 0.001$) and HC ($p < 0.001$), while it only disclosed a decreasing trend (without statistical significance) in DC than that in HC ($p = 0.157$). Concerning the distinguishing value, serum BDNF level could differentiate CHD patients from DC (area under the curve (AUC): 0.762, 95% confidence interval (CI): 0.693–0.831, Figure 1B) and HC (AUC: 0.862, 95% CI: 0.815–0.909, Figure 1C), with the best cut-off point value of 8.095 ng/ml and 7.515 ng/ml, respectively; while its value on distinguishing DC from HC was not ideal, with the best cut-off point value of 6.225 ng/ml (AUC: 0.638, 95% CI: 0.529–0.745, Figure 1D).

3.3 | Correlation of serum BDNF level with Th1/Th2 ratio in CHD patients

Serum BDNF level was negatively correlated with Th1 cells ($r = -0.149$, $p = 0.031$, Figure 2A), and it disclosed a positive correlating trend (lacked statistical significance) with Th2 cells ($r = 0.096$, $p = 0.165$, Figure 2B) in CHD patients; consequently, serum BDNF level was negatively related to Th1/Th2 ratio ($r = -0.154$, $p = 0.026$, Figure 2C).

3.4 | Correlation of serum BDNF level with Th17/Treg ratio in CHD patients

Serum BDNF level was negatively linked with Th17 cells ($r = -0.225$, $p = 0.001$, Figure 3A) and exhibited a positive associating trend

TABLE 1 Clinical characteristics of CHD patients.

Items	CHD patients ($N = 210$)
Demographics	
Age (years), mean ± SD	63.7 ± 10.4
Gender, No. (%)	
Female	47 (22.4)
Male	163 (77.6)
BMI (kg/m^2), mean ± SD	24.2 ± 3.1
History of drink, No. (%)	
No	130 (61.9)
Yes	80 (38.1)
History of smoke, No. (%)	
No	109 (51.9)
Yes	101 (48.1)
Medical history	
History of hypertension, No. (%)	
No	64 (30.5)
Yes	146 (69.5)
History of hyperlipidemia, No. (%)	
No	125 (59.5)
Yes	85 (40.5)
History of DM, No. (%)	
No	162 (77.1)
Yes	48 (22.9)
History of CKD, No. (%)	
No	185 (88.1)
Yes	25 (11.9)
Blood biochemical indexes	
FBG (mmol/L), median (IQR)	6.1 (5.1–6.9)
Scr (μmol/L), median (IQR)	81.8 (73.4–90.5)
SUA (μmol/L), median (IQR)	348.5 (311.5–412.8)
TG (mmol/L), median (IQR)	1.8 (1.1–2.5)
TC (mmol/L), median (IQR)	4.6 (3.9–5.4)
LDL-C (mmol/L), median (IQR)	3.3 (2.5–4.0)
HDL-C (mmol/L), median (IQR)	1.0 (0.8–1.1)
cTnI (ng/ml), median (IQR)	2.2 (1.4–3.5)
CK-MB (ng/ml), median (IQR)	16.8 (9.1–30.9)
CRP (mg/L), median (IQR)	6.0 (4.4–8.7)
Coronary artery stenosis	
Gensini score, median (IQR)	29.0 (17.0–49.0)
Ratio of Th1/Th2 and Th17/Treg	
Th1 cells (%), median (IQR)	15.7 (13.3–18.1)
Th2 cells (%), median (IQR)	10.9 (8.2–13.9)
Ratio of Th1/Th2, median (IQR)	1.4 (1.1–2.3)
Th17 cells (%), median (IQR)	4.4 (3.2–6.1)

(Continues)

TABLE 1 (Continued)

Items	CHD patients (N = 210)
Treg cells (%), median (IQR)	4.9 (4.0–5.9)
Ratio of Th17/Treg, median (IQR)	0.9 (0.6–1.4)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CK-MB, creatine kinase MB; CRP, C-reactive protein; cTnI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SD, standard deviation; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; Th1, T helper 1; Th17, T helper 17; Th2, T helper 2; Treg, regulatory T.

(without statistical significance) with Treg cells ($r = 0.104$, $p = 0.134$, Figure 3B) in CHD patients. Then, serum BDNF level was negatively associated with Th17/Treg ratio ($r = -0.215$, $p = 0.002$, Figure 3C).

3.5 | Correlation with MACE risk in CHD patients

Serum BDNF level was reduced in CHD patients with MACE occurrence compared to CHD patients without MACE occurrence (median (IQR): 4.2 (2.4–6.8) ng/ml vs. 6.4 (3.8–8.5) ng/ml, $p = 0.006$, Figure 4A). Meanwhile, serum BDNF level was related to reduced MACE risk in CHD patients, with the best cut-off point value of 2.695 ng/ml (AUC: 0.672, 95% CI: 0.554–0.791, Figure 4B). Furthermore, serum BDNF showed a positive correlating trend (lacked statistical significance) with MACE-free survival ($p = 0.059$, Figure 4C).

3.6 | Correlation of serum BDNF level with clinical features in CHD patients

Serum BDNF level was related to the absence of fat (BMI ≥28 kg/m^2) in CHD patients ($p = 0.019$), while it was not linked with age, gender, history of drink, smoke, hypertension, hyperlipidemia, DM, or CKD (all $p > 0.050$) (Table 2). Moreover, serum BDNF level was negatively associated with total cholesterol (TC) ($r = -0.140$, $p = 0.043$), low-density lipoprotein cholesterol (LDL-C) ($r = -0.162$, $p = 0.019$), C-reactive protein ($r = -0.173$, $p = 0.012$), and Gensini score ($r = -0.193$, $p = 0.005$) in CHD patients (Table 3).

In addition, serum BDNF was negatively linked with Gensini score in BMI <28 kg/m^2 CHD patients ($r = -0.197$, $p = 0.008$, Figure S1A), while it was not related to Gensini score in BMI ≥28 kg/m^2 CHD patients ($r = -0.169$, $p = 0.355$, Figure S1B).

4 | DISCUSSION

Some evidences have revealed the close relationship between BDNF and CD4$^+$ T-cell lineages.[15,26–28] For instance, a previous study indicates that BDNF rebalances Th1 polarized environment via the wingless-type protein 7a (Wnt7a) signaling pathway.[27] Another

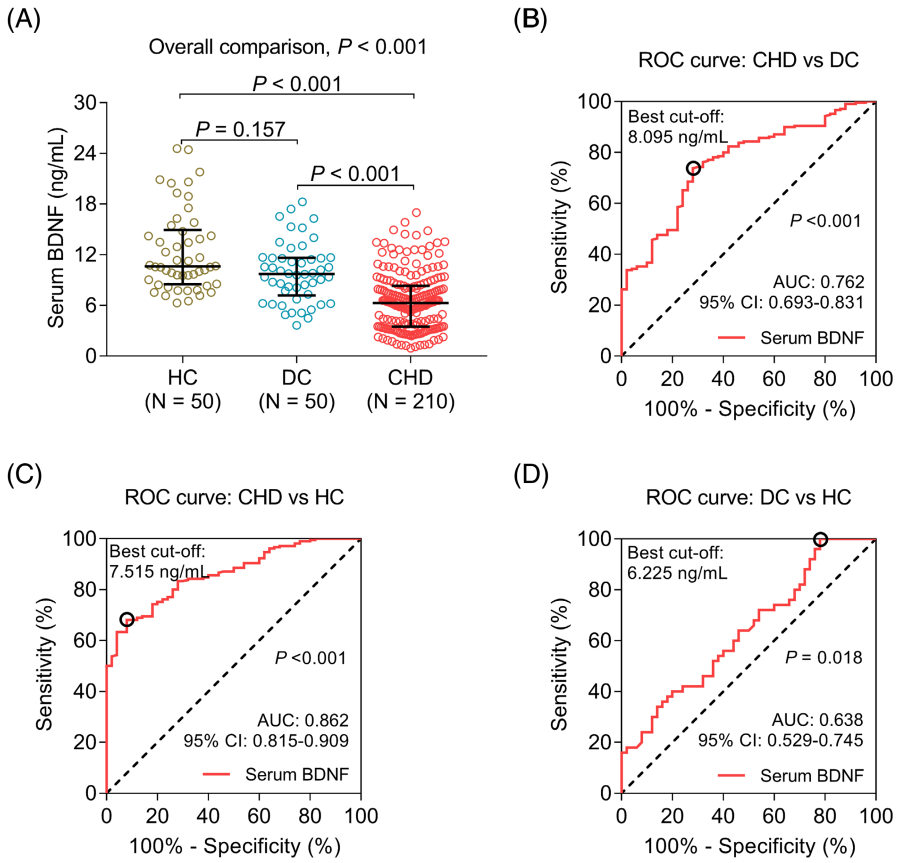

FIGURE 1 Serum BDNF level was declined in CHD patients compared with DCs and HCs. Comparison of serum BDNF level among CHD patients, DCs, and HCs (A). The value of serum BDNF level on distinguishing CHD patients from DCs (B), distinguishing CHD patients from HCs (C), and distinguishing DCs from HCs (D).

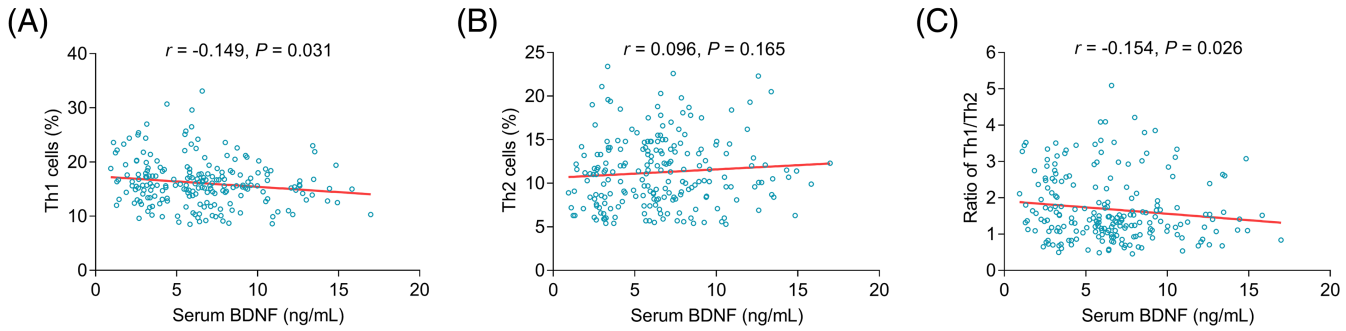

FIGURE 2 Serum BDNF level was negatively linked with Th1 cells and Th1/Th2 ratio in CHD patients. Linkage of serum BDNF level with Th1 cells (A), Th2 cells (B), and Th1/Th2 ratio (C) in CHD patients.

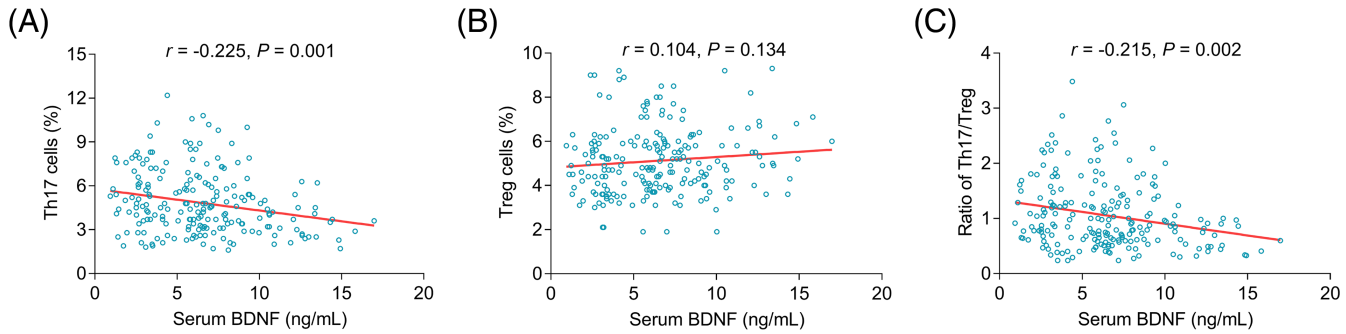

FIGURE 3 Serum BDNF level was negatively linked with Th17 cells and Th17/Treg ratio in CHD patients. Linkage of serum BDNF level with Th17 cells (A), Treg cells (B), and Th17/Treg ratio (C) in CHD patients.

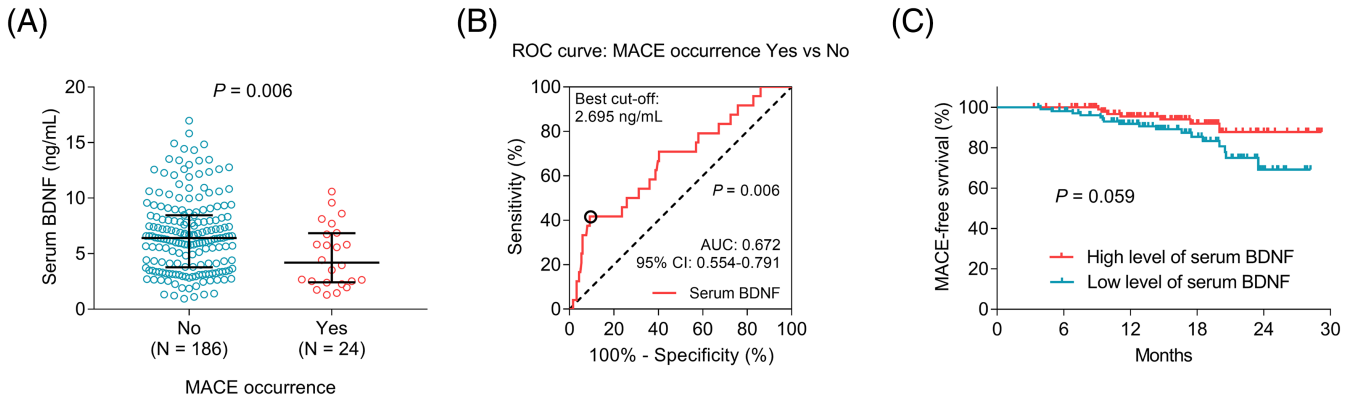

FIGURE 4 Serum BDNF level was negatively linked with MACE risk in CHD patients. Comparison of serum BDNF level between CHD patients with MACE occurrence and CHD patients without MACE occurrence (A), and its value on distinguishing patients with MACE occurrence from patients without MACE occurrence (B). Linkage of serum BDNF level with MACE-free survival in CHD patients (C).

study shows that BDNF deficiency induces Th1 and Th17 cell differentiation in the immune-inflammatory response system (IRS).[28] Since T cell differentiation is also an essential issue involved in the pathogenesis of CHD, BDNF is speculated to be correlated with Th cell balance in CHD patients; however, it lacks relevant exploration. The present study found that serum BDNF level was negatively associated with the Th1/Th2 ratio and Th17/Treg ratio in CHD patients, which could be explained by that: BDNF suppressed $CD4^+$ T cell differentiation into Th1 and Th17 cells; then, it was negatively associated with the proportion of Th1 and Th17 cells.[15,29] Therefore, serum BDNF level was negatively linked with the Th1/Th2 ratio and Th17/Treg ratio in CHD patients.

With respect to the prognostic value of BDNF in patients with cardiovascular and cerebrovascular diseases, a previous study reveals that circulating BDNF level is related to favorable long-term functional outcomes in ischemic stroke patients.[30] Whereas the detailed linkage of serum BDNF level with clinical outcomes in CHD patients is rarely discussed before. In the current study, serum BDNF level was related to ameliorated MACE risk in CHD patients, which could be regarded as a prognostic factor for CHD. Possible

TABLE 2 Correlation of serum BDNF with demographics and medical history of CHD patients.

Items	Serum BDNF (ng/ml), median (IQR)	*p* values
Demographics		
Age		0.519
<60 years	6.4 (3.4–8.5)	
≥60 years	6.2 (3.7–8.0)	
Gender		0.205
Female	6.4 (4.0–9.1)	
Male	6.2 (3.3–8.2)	
BMI		0.019
<28 kg/m^2	6.4 (3.8–8.6)	
≥28 kg/m^2	5.8 (2.7–6.8)	
History of drink		0.451
No	6.4 (3.4–8.4)	
Yes	6.1 (3.4–8.1)	
History of smoke		0.191
No	6.6 (3.7–9.0)	
Yes	5.9 (3.4–7.9)	
Medical history		
History of hypertension		0.571
No	3.9 (2.7–6.3)	
Yes	3.4 (2.5–6.3)	
History of hyperlipidemia		0.096
No	4.1 (2.6–6.5)	
Yes	3.3 (2.1–5.8)	
History of DM		0.130
No	6.4 (3.8–8.4)	
Yes	5.8 (3.1–7.4)	
History of CKD		0.664
No	6.4 (3.5–8.4)	
Yes	5.9 (3.4–8.0)	

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; IQR, interquartile range.

TABLE 3 Correlation of serum BDNF with blood biochemical indexes and coronary artery stenosis of CHD patients.

Items	*R*	*p* values
Blood biochemical indexes		
FBG (mmol/L)	−0.074	0.283
Scr (μmol/L)	−0.116	0.093
SUA (μmol/L)	−0.089	0.198
TG (mmol/L)	−0.125	0.070
TC (mmol/L)	−0.140	0.043
LDL-C (mmol/L)	−0.162	0.019
HDL-C (mmol/L)	0.095	0.171
cTnI (ng/ml)	−0.092	0.183
CK-MB (ng/ml)	−0.035	0.609
CRP (mg/L)	−0.173	0.012
Coronary artery stenosis		
Gensini score	−0.193	0.005

Abbreviations: BDNF, brain-derived neurotrophic factor; CHD, coronary heart disease; CK-MB, creatine kinase MB; CRP, C-reactive protein; cTnI, cardiac troponin I; FBG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride.

reasons might be as follows: (1) BDNF restrained atherosclerosis progression, which ultimately alleviated artery occlusion and ischemic injury of the coronary artery.[31] (2) The anti-dyslipidemia and anti-inflammation function of BDNF protected CHD patients from disease exacerbation. (3) BDNF possessed the cardioprotective effect through improving angiogenesis in ischemic myocardium.[32] Hence, the disease progression of CHD was delayed. Combining the above three aspects, BDNF was negatively linked with MACE risk in CHD patients. However, it was observed that serum BDNF only showed a positive correlating trend (but lacked statistical significance) with MACE-free survival, which might be affected by the relatively short follow-up duration, and some end-point events did not reach.

Furthermore, the protective effect of BDNF on dyslipidemia is also mentioned in previous studies.[23,33,34] For example, one study shows that BDNF is negatively linked with TC and LDL-C in angina pectoris patients.[34] Consistent with the previous studies, this study displayed a negative correlation of serum BDNF level with TC and LDL-C in CHD patients. The probable explanation was listed as follows: BDNF could facilitate lipid consumption and further maintain lipid homeostasis via inhibiting peroxisome proliferator-activated receptor alpha and fibroblast growth factor 21.[35] Therefore, serum BDNF level was negatively associated with TC and LDL-C in CHD patients. Furthermore, this study also noticed that reduced serum BDNF level was linked with elevated BMI in CHD patients, reflecting the anti-obesity role of serum BDNF, which also attributed to its protective role against dyslipidemia.[36]

Some limitations needed to be mentioned in this study. First, the detection of serum BDNF level at multiple time points would be helpful for monitoring the disease progression of CHD; while in the current study, serum BDNF level in CHD patients was only determined after recruitment, and its longitudinal variation was unknown. Secondly, the polarization of macrophages was also reported as an essential factor in the occurrence of atherosclerosis, while the correlation of BDNF with macrophage polarization in CHD patients was not detected in the present study.[37] Thirdly, the underlying mechanism of BDNF in regulating the Th1/Th2 ratio, Th17/Treg ratio, and blood lipid in CHD patients was unidentified in this study.

In summary, serum BDNF relates to restored Th1/Th2 balance, Th17/Treg balance, and ameliorated MACE risk in CHD patients, which might serve as a protective indicator for CHD.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

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

CONSENT TO PARTICIPATE

The informed consent was signed by each subject or guardian.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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