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RESEARCH ARTICLE

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The relation of common inflammatory cytokines with anxiety and depression and their values in estimating cardiovascular outcomes in coronary heart disease patients

Hanmei Lu | **Qinling Yang** | **Yan Zhang**

Department of Critical Care Medicine, Wuhan Asia General Hospital, Wuhan, China

Correspondence
Yan Zhang, Department of Critical Care Medicine, Wuhan Asia General Hospital, No. 300 Taizi Lake North Road, Economic and Technological Development Zone, Wuhan 430000, China.
Email: 13485717@qq.com

Abstract

Background: Inflammatory cytokines are associated with the occurrence and severity of psychological disorders in cerebro-cardiovascular disease patients. This study aimed to investigate the correlation of inflammatory cytokines with anxiety and depression in coronary heart disease (CHD) patients and their values for estimating cardiovascular outcomes.

Methods: Totally, 150 CHD patients and 50 healthy subjects were enrolled. Then, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-10, and IL-17 in their serum samples were detected using ELISA assay; anxiety and depression were assessed by the HADS score. For CHD patients, major adverse cardiac events (MACE) were recorded and evaluated.

Results: CHD patients presented with increased TNF-α (median: 50.0 vs. 37.0 pg/ml, $p < 0.001$), IL-1β (median: 2.7 vs. 2.0 pg/ml, $p < 0.001$), IL-6 (median: 24.7 vs. 24.3 pg/ml, $p = 0.032$), IL-17A (median: 58.6 vs. 43.6 pg/ml, $p < 0.001$), HADS-A score ($p < 0.001$), HADS-D score ($p < 0.001$), anxiety rate ($p < 0.001$), and depression rate ($p < 0.001$) compared to healthy subjects. Then, TNF-α ($p = 0.003$), IL-1β ($p = 0.023$), and IL-17A ($p < 0.001$) were related to elevated HADS-A score. Also, TNF-α ($p = 0.014$) and IL-17A ($p = 0.020$) positively, while IL-10 ($p = 0.047$) negatively related to the HADS-D score in CHD patients. Interestingly, elevated TNF-α and IL-17A were associated with anxiety and depression occurrence in CHD patients (all $p < 0.05$). Inspiringly, only TNF-α high, but not other cytokines, was related to elevated accumulating MACE ($p = 0.041$), while no correlation of anxiety ($p = 0.173$) or depression ($p = 0.068$) with accumulating MACE was observed.

Conclusion: TNF-α and IL-17A correlate with anxiety and depression, while only TNF-α high is related to elevated accumulating MACE in CHD patients.

KEYWORDS
accumulating MACE, coronary heart disease, HADS score, inflammatory cytokines, psychological disorders

Hanmei Lu and Qinling Yang contributed equally to this work.

1 | INTRODUCTION

Coronary heart disease (CHD) places a huge disease burden across the world.[1] Despite applying appropriate management options (such as percutaneous coronary intervention (PCI), coronary artery bypass surgery, dual antiplatelet therapy, etc.), CHD still remains the second leading cause of mortality with approximately 1.57 million deaths in 2018 in China.[2,3] Apart from the high mortality rate, psychological disorders (such as depression, anxiety, etc.) are commonly identified as critical comorbidities of CHD patients.[4,5] One study points out that approximately 32% of CHD patients who received PCI procedures develop anxiety within 3 years.[6] Also, the high prevalence of anxiety and depression in CHD patients impairs their daily function, quality of life, and even long-term health status.[4-6]

Inflammatory cytokines, consisting of pro-inflammatory and anti-inflammatory ones, are closely involved in CHD pathogenesis.[7,8] Also, inflammatory cytokines play a key role in cerebrocardiovascular related psychological disorders, especially in the context of anxiety and depression.[9-11] For instance, inflammatory cytokines cause dysregulation and imbalance of neurotransmitters (such as serotonin, dopamine, etc.) as well as accumulation of neurotoxic metabolites and promotion of neural apoptosis, which further leads to the occurrence of psychological disorders.[10,12-16] Meanwhile, recent clinical studies exhibit that these inflammatory cytokines (such as tumor necrosis factor (TNF)-α and interleukin (IL)-6) are upregulated in acute ischemic stroke (AIS) patients with anxiety and depression.[17-19] Also, these inflammatory cytokines are related to more depressive symptoms in AIS patients.[19] While limited study reports the clinical role of inflammatory cytokines in CHD patients with anxiety and depression.

Hence, this study aimed to detect the level of common inflammatory cytokines (including TNF-α, IL-1β, IL-6, IL-10, and IL-17A) as well as explore their association with depression, anxiety, and cardiovascular-related outcomes in CHD patients.

2 | METHODS

2.1 | Subjects

From January 2018 to June 2021, this study consecutively included 150 CHD patients. The inclusion criteria were as follows: (a) diagnosed as CHD by coronary angiography; (b) more than 18 years old; (c) had ability to complete the assessment of Hospital Anxiety and Depression Scale (HADS); (d) volunteered to provide serum samples; (e) willing to comply with follow-up protocol of the study. The patients who met the following conditions were excluded from the study: (a) unable to understand the study due to severe cognitive impairment or psychiatric disorder; (b) concomitance with poor controlled diseases which seriously affected mental health; (c) had a prior history of cancer or malignant tumor. During the same period, the study also enrolled 50 health subjects with matched age and gender as health controls (HCs). The exclusion criteria for CHD patients were also appreciated for HCs. All subjects provided the written informed consents. The study was permitted by Ethics Committee.

2.2 | Collection and detection

Clinical characteristics and serum samples were obtained from CHD patients at admission, and from HCs after enrollment. After collection, serum was used to detect the levels of inflammatory cytokines by enzyme-linked immunosorbent assay (ELISA) using commercial Human ELISA Kits (Bio-Techne China Co. Ltd., China; DY210-05 for TNF-α, DY201 for IL-1β, DY206 for IL-6, DY217B for IL-10, DY317 for IL-17). The experiments were performed based on the manufacturer's instruction. Briefly, standards and samples were added into the wells, and incubated for 2 h. Then, conjugate (100 μl) was added into the wells, followed by incubation for 1 h. Following that, substrate solution (200 μl) was added into the wells, and incubated for 30 min. Subsequently, stop solution was added into the wells, followed by reading absorbance at 450 nm immediately. Finally, standard curve was made, which was applied to calculate the concentration of unknown samples.

2.3 | Anxiety and depression evaluation

HADS was evaluated on the day of discharge from the hospital for CHD patients, and after enrollment for HCs. The HADS for anxiety (HADS-A) score and HADS for depression (HADS-D) score were used for the assessment of anxiety status and depression status, respectively. The maximum score of HADS-A and HADS-D was 21, respectively. The HADS-A score >7 was considered as anxiety; the HADS-D score >7 was considered as depression.[20]

2.4 | Follow-up and major adverse cardiac events (MACE) evaluation

All CHD patients were followed up regularly until October 30, 2021. During the follow-up, the incidence of MACE was assessed, which was defined as a composite of cardiovascular death, non-fatal myocardial infarction (MI), ischemic stroke, and coronary revascularization.[21] Then, accumulating MACE rate was calculated for study analysis.

2.5 | Statistics

Statistical analysis was fulfilled by SPSS V.22.0 (IBM Corp., USA), and figures were plotted by GraphPad Prism V.7.02 (GraphPad Software Inc., USA). Difference of characteristics between CHD patients and HCs was compared using t test, Chi-square test or Mann–Whitney U test. Correlation of inflammatory cytokines with HADS score and

Gensini score was determined using Spearman's rank correlation test. Correlation of inflammatory cytokines with anxiety status and depression status was evaluated using Mann–Whitney U test. The accumulating MACE rate was elucidated using Kaplan–Meier curve. Correlation of inflammatory cytokines, anxiety status, and depression status with the accumulating MACE rate was analyzed using log-rank test, and each inflammatory cytokine of CHD patients was divided into high and low levels using median in the analysis. Factors affecting accumulating MACE rate were determined using Cox's proportional hazard regression analysis, and independent prognostic factors were screened out from all potential factors using forward-stepwise multivariate Cox's proportional hazard regression analysis. All statistical tests were two-sided. $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Clinical features of CHD patients and HCs

The mean ages of CHD patients and HCs were 61.7 ± 9.4 years and 60.1 ± 4.0 years, separately (Table 1). Moreover, CHD patients consisted of 37 (24.7%) females and 113 (75.3%) males; HCs consisted of 12 (24.0%) females and 38 (76.0%) males. By comparison, most demographic features were similar between CHD patients and HCs (all $p > 0.05$), although CHD patients presented with a higher proportion of hypertension ($p < 0.001$) and hyperlipidemia ($p < 0.001$). Furthermore, the laboratory biochemical indexes and Gensini score of CHD patients are displayed in Table 1.

TABLE 1 Characteristics of CHD patients and HCs

Items	HCs (N = 50)	CHD patients (N = 150)	*p* value
Demographics			
Age (years), mean ± SD	60.1 ± 4.0	61.7 ± 9.4	0.099
Gender, n (%)			0.924
Female	12 (24.0)	37 (24.7)	
Male	38 (76.0)	113 (75.3)	
Hypertension, n (%)			<0.001
No	35 (70.0)	37 (24.7)	
Yes	15 (30.0)	113 (75.3)	
Hyperlipidemia, n (%)			<0.001
No	38 (76.0)	66 (44.0)	
Yes	12 (24.0)	84 (56.0)	
DM, n (%)			0.487
No	41 (82.0)	116 (77.3)	
Yes	9 (18.0)	34 (22.7)	
Smoke, n (%)			0.085
No	33 (66.0)	78 (52.0)	
Yes	17 (34.0)	72 (48.0)	
Blood laboratory detections			
FBG (mmol/L), median (IQR)	—	5.6 (4.8–6.3)	—
Scr (μmol/L), median (IQR)	—	76.3 (66.1–86.1)	—
SUA (μmol/L), median (IQR)	—	337.8 (299.4–394.0)	—
TG (mmol/L), median (IQR)	—	1.7 (0.9–2.3)	—
TC (mmol/L), median (IQR)	—	4.5 (3.9–5.4)	—
LDL-C (mmol/L), median (IQR)	—	3.2 (2.4–4.0)	—
HDL-C (mmol/L), mean ± SD	—	0.9 ± 0.2	—
CRP (mg/L), median (IQR)	—	7.6 (5.5–10.0)	—
Disease factor			
Gensini score, median (IQR)	—	30.5 (15.0–47.0)	—

Abbreviations: CHD, coronary heart disease; CRP, C-reactive protein; DM, diabetes mellitus; FBG, fasting blood glucose; HCs, health controls; 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.

3.2 | Comparison of inflammatory cytokines, anxiety and depression between CHD patients and HCs

TNF-α (median (interquartile range (IQR)): 50.0 (36.4–69.6) pg/ml vs. 37.0 (27.2–54.7) pg/ml, $p < 0.001$, Figure 1A), IL-1β (median (IQR): 2.7 (2.1–3.7) pg/ml vs. 2.0 (1.0–3.1) pg/ml, $p < 0.001$, Figure 1B), IL-6 (median (IQR): 24.7 (21.4–32.6) pg/ml vs. 24.3 (16.1–31.6) pg/ml, $p = 0.032$, Figure 1C), and IL-17A (median (IQR): 58.6 (42.3–85.5) pg/ml vs. 43.6 (33.4–53.9) pg/ml, $p < 0.001$, Figure 1E) were all upregulated in CHD patients compared to HCs, while IL-10 (median (IQR): 84.5 (66.4–121.8) pg/ml vs. 95.7 (72.5–136.2) pg/ml, $p = 0.124$, Figure 1D) was of no difference between CHD patients and HCs.

Moreover, the HADS-A score (7.0 (5.0–9.0) vs. 5.0 (3.0–6.0), $p < 0.001$, Figure 2A), HADS-D score (6.0 (4.0–9.0) vs. 4.0 (2.8–6.0), $p < 0.001$, Figure 2B), anxiety rate (42.7% vs. 10.0%, $p < 0.001$, Figure 2C), and depression rate (33.3% vs. 8.0%, $p < 0.001$, Figure 2D) were all increased in CHD patients compared to HCs.

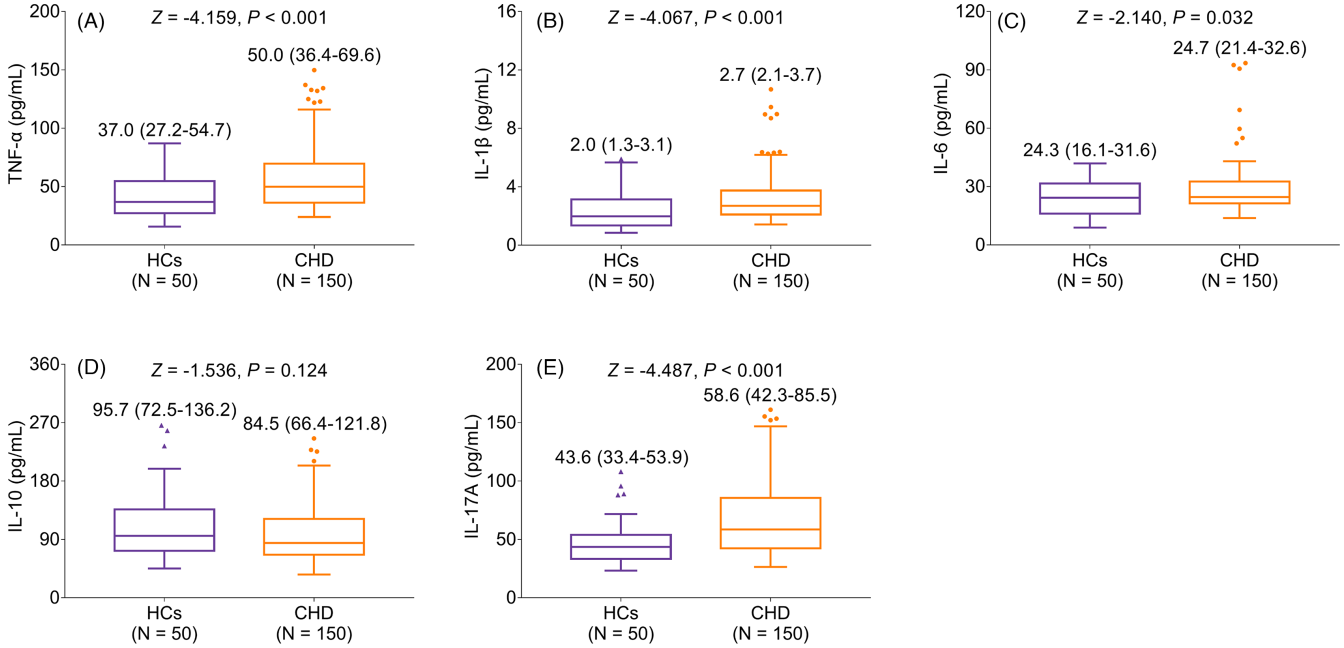


FIGURE 1 Pro-inflammatory cytokines were elevated in CHD patients. Comparison of TNF-α (A), IL-1β (B), IL-6 (C), IL-10 (D), and IL-17A (E) between CHD patients and HCs

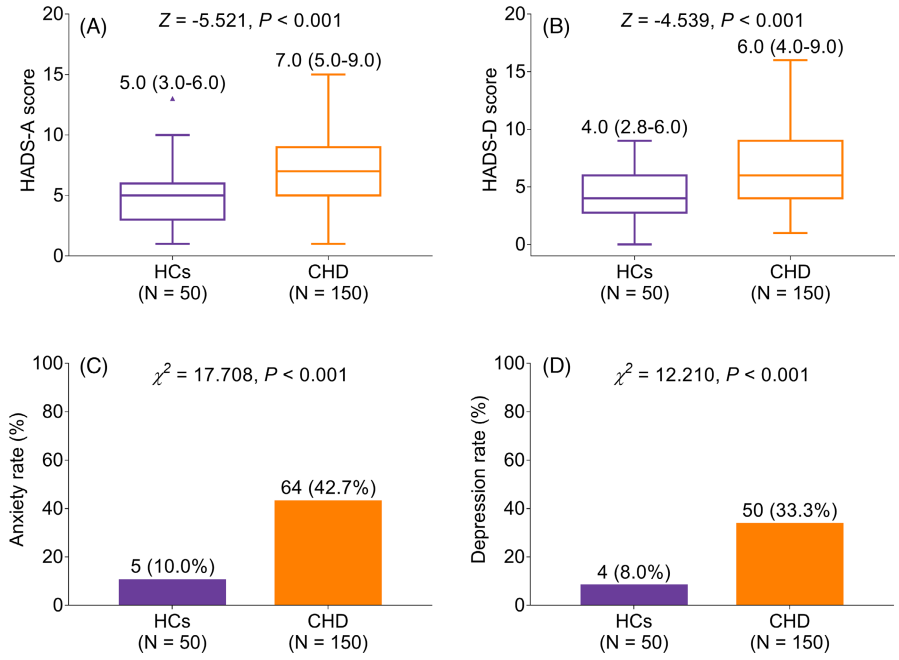


FIGURE 2 CHD patients presented with psychological issues. Comparison of HADS-A score (A), HADS-D score (B), anxiety rate (C), and depression rate (D) between CHD patients and controls

3.3 | Correlation of inflammatory cytokines with Gensini score in CHD patients

TNF-α (r_s = 0.524, $p < 0.001$), IL-1β (r_s = 0.433, $p < 0.001$), and IL-6 (r_s = 0.264, p = 0.001) were positively, while IL-10 (r_s = −0.266, p = 0.001) was negatively related to Gensini score in CHD patients (Table S1).

3.4 | Correlation of inflammatory cytokines with anxiety and depression in CHD patients

TNF-α (r_s = 0.243, p = 0.003), IL-1β (r_s = 0.186, p = 0.023), and IL-17A (r_s = 0.292, $p < 0.001$) were positively related to HADS-A score (Table 2). Meanwhile, TNF-α (r_s = 0.201, p = 0.014) and IL-17A (r_s = 0.189, p = 0.020) were positively, while IL-10 (r_s = −0.162, p = 0.047) was negatively associated with HADS-D score.

Furthermore, CHD patients were classified into anxiety patients and non-anxiety patients; depression patients and non-depression patients based on HADS score. Then comparison analyses displayed that TNF-α (p = 0.016) and IL-17A (p = 0.023) were elevated in anxiety patients compared to non-anxiety patients, while IL-1β (p = 0.230), IL-6 (p = 0.642), and IL-10 (p = 0.955) were of no difference between these two groups (Figure 3A-E). Meanwhile, TNF-α (p = 0.007) and IL-17A (p = 0.019) were also increased in depression patients compared to non-depression patients, while other cytokines were similar between these two groups (all $p > 0.05$) (Figure 3F-J).

3.5 | Correlation of inflammatory cytokines with anxiety and depression in HCs

There was no correlation of TNF-α, IL-1β, IL-6, IL-10, or IL-17A with anxiety in HCs (all $p > 0.05$) (Table S2). Moreover, TNF-α, IL-1β, IL-6, IL-10, or IL-17A did not relate to depression in HCs either (all $p > 0.05$) (Table S3).

TABLE 2 Correlation of inflammatory cytokines with HADS score in CHD patients

	HADS-A score		HADS-D score	
Items	r_s	p value	r_s	p value
TNF-α	0.243	0.003	0.201	0.014
IL-1β	0.186	0.023	0.056	0.497
IL-6	0.099	0.228	0.095	0.248
IL-10	−0.115	0.160	−0.162	0.047
IL-17A	0.292	<0.001	0.189	0.020

Abbreviations: CHD, coronary heart disease; HADS, Hospital Anxiety and Depression Scale; IL-1β, interleukin 1 beta; IL-6, interleukin 6; IL-10, interleukin 10; IL-17A, interleukin 17A; TNF-α, tumor necrosis factor alpha.

3.6 | Correlation of inflammatory cytokines, anxiety and depression with accumulating MACE in CHD patients

The median duration of follow-up was 21.0 months with a range of 3.0–41.0 months. During the follow-up, MACE occurred in 10 (6.7%) CHD patients. Only TNF-α high was related to elevated accumulating MACE rate (p = 0.041), while no correlation of IL-1β high (p = 0.128), IL-6 high (p = 0.191), IL-10 high (p = 0.235), or IL-17A high (p = 0.089) with accumulating MACE rate was observed (Figure 4A-E). Furthermore, neither anxiety (p = 0.173) nor depression (p = 0.068) was correlated with accumulating MACE rate (Figure 5A,B). Further subgroup analyses displayed that only IL-10 high was related to low accumulating MACE rate in CHD patients with anxiety (p = 0.025) (Figure S1A-T).

Univariate and multivariate Cox's regression model analysis was conducted to determine the potential factors relating to the occurrence of MACE in CHD patients. Then, it was discovered that only CRP was independently related to the occurrence of MACE in CHD patients (hazard ratio (HR): 1.152, p = 0.008) (Table 3).

4 | DISCUSSION

Inflammatory cytokines are previously reported to be overexpressed in cerebro-cardiovascular disease patients.[22] For instance, TNF-α and IL-17 are elevated in CHD patients and AIS patients, respectively.[23,24] In line with previous studies, it was observed that pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-17A were elevated in CHD patients compared to HCs since pro-inflammatory cytokines heavily participated in atherosclerotic plaque formation and CHD pathogenesis, thus led to CHD occurrence.[7,8] Meanwhile, it was noticed that HADS scores were raised in CHD patients compared to HCs, which could be explained as that CHD patients presented with more concomitants (such as hypertension, hyperlipidemia, etc.) compared to HCs, which exacerbated the concern about their disease condition and resulted in anxiety and depression.[25]

Inflammatory cytokines play a critical role in the occurrence and development of psychological disorders. For instance, inflammatory cytokines alter the intracellular metabolic processes (including kynurenine and glutamine etc.) to promote the oxidative stress and neural apoptosis, then further causing anxiety and depression.[26,27] Moreover, inflammatory cytokines are able to degrade the signal integrity of neurotransmitters in cortical and hippocampal regions of the brain, causing the imbalance of neurotransmitters (such as GABA and glutamate, etc.) and psychological disorder.[13] Furthermore, certain neurotransmitters (such as dopamine and 5-hydroxytryptamine) may also serve as inflammatory mediators and suppress neuroinflammation, which further mediates the occurrence of psychological disorders.[10,28,29]

Inflammatory cytokines are correlated with the occurrence and severity of psychological disorders in cerebro-cardiovascular disease patients. For instance, several studies report that the

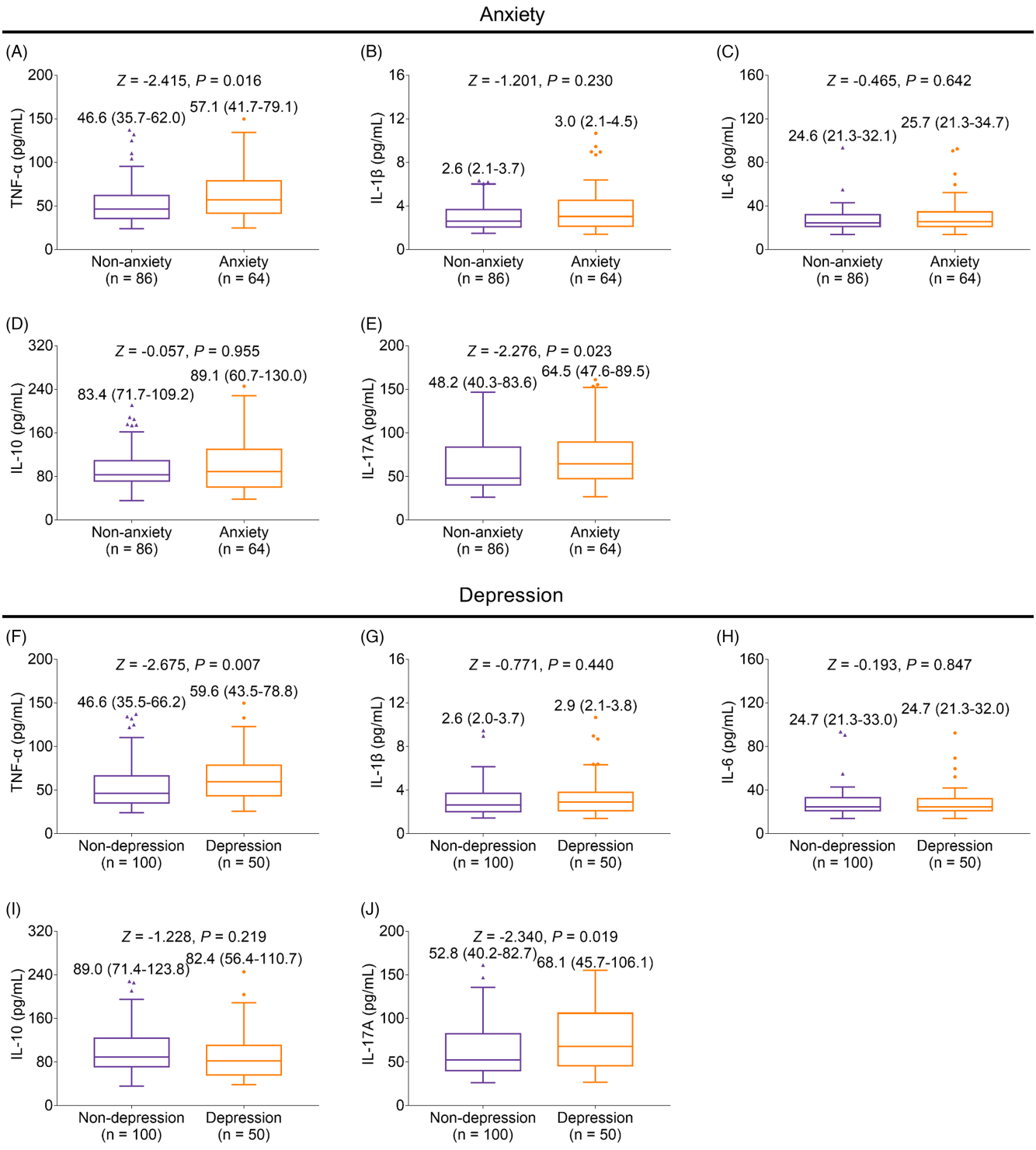


FIGURE 3 TNF-α and IL-17A were upregulated in CHD patients with anxiety and depression. Comparison of TNF-α (A), IL-1β (B), IL-6 (C), IL-10 (D), and IL-17A (E) between anxiety and non-anxiety patients. Comparison of TNF-α (F), IL-1β (G), IL-6 (H), IL-10 (I), and IL-17A (J) between depression and non-depression patients

expression of TNF-α and IL-6 are increased in AIS patients with depression compared to those without depression.[17-19] Also, high TNF-α and IL-6 are independently correlated with elevated post-stroke depression risk in AIS patients.[18,19] Moreover, overexpressed TNF-α, IL-6, and IL-17 are related to severer depression symptoms in AIS patients and acute coronary syndrome patients.[19,30] In the current study, it was discovered that TNF-α and IL-17A were elevated in CHD patients with anxiety and depression, also these two inflammatory cytokines were related to a higher HADS score in CHD patients, which could be explained as that (a) overexpressed TNF-α enhanced macrophage activation, polarization, and endoplasmic reticulum stress, which resulted in neural apoptosis and

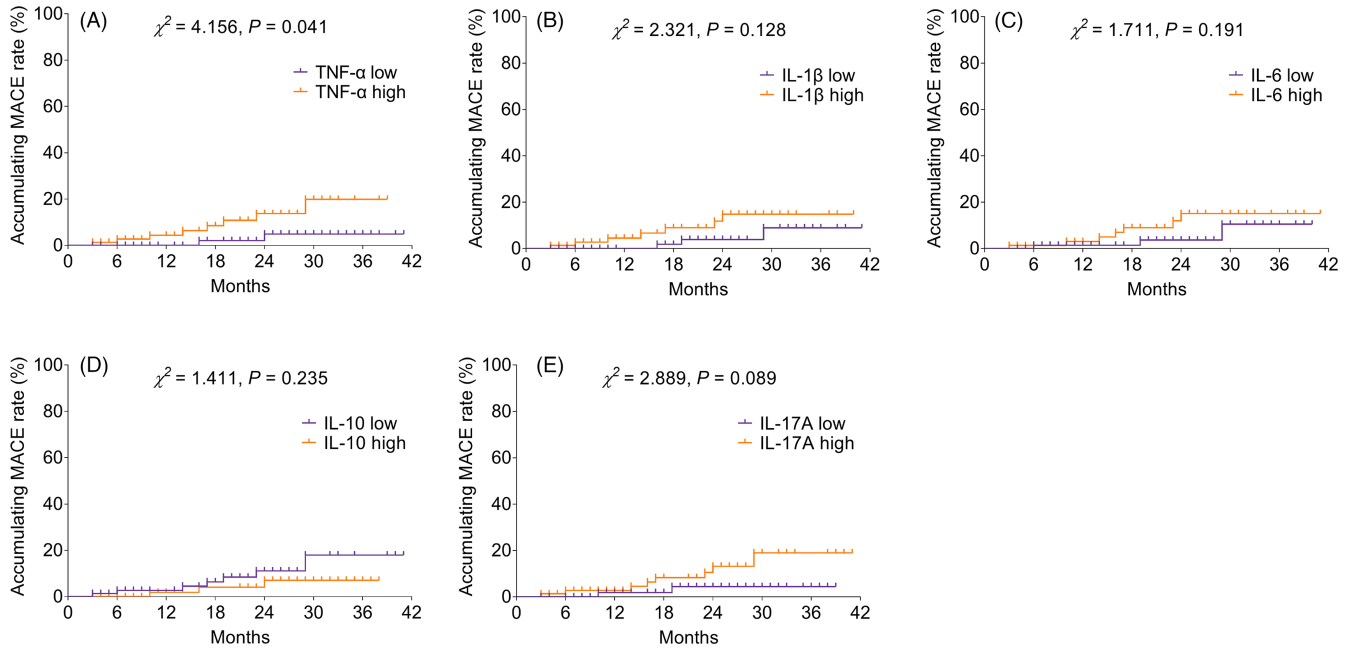
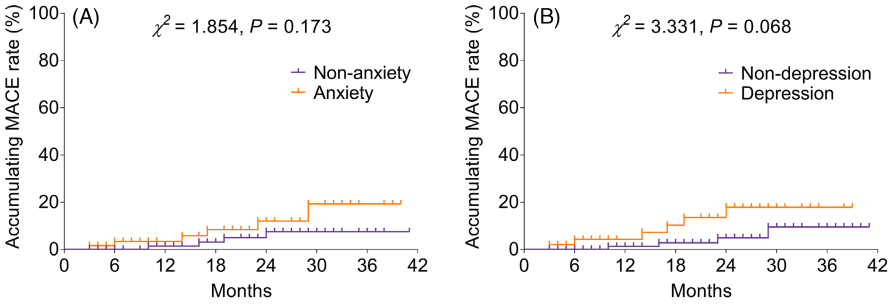


FIGURE 4 TNF-α high was related to elevated accumulating MACE rate. Correlation of TNF-α high (A), IL-1β high (B), IL-6 high (C), IL-10 high (D), and IL-17A high (E) with accumulating MACE rate in CHD patients

FIGURE 5 Psychological status did not correlate with accumulating MACE rate. Correlation of anxiety (A) and depression (B) with accumulating MACE rate in CHD patients. CE rate in CHD patients



caused psychological disorders in CHD patients.[31,32] (b) T helper (Th)-17 cells were related to the occurrence and severity of anxiety and depression, thus the positive association of IL-17A (secreted by Th17 cells) with anxiety, depression, and their severity in CHD patients was observed.[33] (c).

Limited studies report the association of inflammatory cytokines with cardiovascular-related outcomes in cerebro-cardiovascular disease patients since most previous studies are cross-sectional studies with the absence of the follow-up period.[17-19] In the current study, MACE events were recorded, and accumulating MACE rate was analyzed in CHD patients to investigate the association of inflammatory cytokines with MACE rates of CHD patients. Interestingly, only TNF-α high was related to elevated MACE rate in CHD patients, which could be explained as that TNF-α was strongly involved in CHD progression by regulating endothelial dysfunction, lipid metabolism, and atherosclerotic plaque formation.[7,8] Thus, upregulation of TNF-α was related to an unfavorable prognosis in CHD patients. Also, in the present study, it was discovered that the occurrence of anxiety and depression seemed to be associated with elevated MACE rates in CHD patients (without statistical significance). The possible reasons were: (a) anxiety and depression status might change during the disease course, also multiple factors might contribute to the outcomes of CHD patients, thus there was no correlation of baseline anxiety and depression with MACE rate in CHD patients. (b) a few MACE events were recorded in the current study causing low statistical power, then it was observed that depression or anxiety was not related to the MACE rate in CHD patients.

There were some limitations in the current study. For instance, detection of inflammatory cytokines and assessment of anxiety/depression at multiple time points was needed in the following studies to observe the longitudinal change in inflammatory cytokines in CHD patients with psychological issues. Moreover, the unmatched number of CHD patients and HCs in the present study might cause low statistical power, and further study could improve this aspect. Besides, further studies with a longer follow-up period were needed

TABLE 3 Factors related to the occurrence of MACE in CHD patients by Cox's proportional hazards regression analysis

Items	*P* value	HR	95% CI	
			Lower	Upper
Univariate Cox's regression analysis				
TNF-α (high vs. low)	0.062	4.376	0.928	20.632
IL-1β (high vs. low)	0.144	2.746	0.708	10.646
IL-6 (high vs. low)	0.205	2.401	0.620	9.305
IL-10 (high vs. low)	0.247	0.449	0.115	1.743
IL-17A (high vs. low)	0.111	3.529	0.748	16.655
Anxiety (yes vs. no)	0.186	2.348	0.662	8.327
Depression (yes vs. no)	0.083	3.062	0.864	10.854
Age (≥60 years vs. <60 years)	0.098	0.319	0.082	1.236
Gender (male vs. female)	0.922	1.080	0.229	5.096
Hypertension (yes vs. no)	0.644	1.442	0.306	6.792
Hyperlipidemia (yes vs. no)	0.290	2.079	0.537	8.055
DM (yes vs. no)	0.341	0.366	0.046	2.896
Smoke (yes vs. no)	0.807	1.168	0.337	4.047
FBG	0.317	0.734	0.401	1.345
Scr	0.838	1.004	0.970	1.039
SUA	0.063	1.008	1.000	1.016
TG	0.739	1.138	0.532	2.436
TC	0.648	1.122	0.684	1.840
LDL-C	0.494	1.195	0.716	1.994
HDL-C	0.352	0.271	0.017	4.235
CRP	**0.008**	1.152	1.037	1.279
Gensini score	0.139	1.018	0.994	1.042
Multivariate Cox's regression analysis (Step forward)				
CRP	**0.008**	1.152	1.037	1.279

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IL-10, interleukin-10; IL-17A, interleukin-17A; IL-1β, interleukin-1beta; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-alpha.

Bold values indicates statistical significance of $p < 0.05$.

to observe the correlation of inflammatory cytokines with survival in CHD patients who experienced anxiety and depression.

In conclusion, TNF-α and IL-17A are correlated with anxiety and depression, while only TNF-α high is related to elevated accumulating MACE rate in CHD patients.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article, as no datasets were generated or analyzed during the current study.

ORCID

Yan Zhang https://orcid.org/0000-0003-2784-3801

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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