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RESEARCH ARTICLE

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Clinical value of long non-coding RNA KCNQ1OT1 in estimating the stenosis, lipid level, inflammation status, and prognostication in coronary heart disease patients

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Abstract

Objective: Long non-coding RNA KQT-like subfamily, member 1 opposite strand/antisense transcript 1 (KCNQ1OT1) could regulate lipid metabolism, vascular smooth muscle cell function, inflammation, and atherosclerosis. This study aimed to evaluate whether lncRNA KCNQ1OT1 could serve as a biomarker for reflecting coronary heart disease (CHD) patients' disease situation and prognosis.

Methods: LncRNA KCNQ1OT1 expression was determined in peripheral blood mononuclear cells from 267 CHD patients, 50 disease controls (DCs) (unexplained chest pain), and 50 healthy controls (HCs) by the RT-qPCR method. TNF-α, IL-17A, VCAM-1, and ICAM-1 were determined by the ELISA procedure in serum from CHD patients only. The mean (95% confidential interval) follow-up duration was 16.0 (15.3–16.8) months.

Results: LncRNA KCNQ1OT1 was highest in CHD patients, followed by DCs, and lowest in HCs ($p < 0.001$). LncRNA KCNQ1OT1 could distinguish the CHD patients from DCs (area under the curve [AUC]: 0.757) and from the HCs (AUC: 0.880). LncRNA KCNQ1OT1 was positively associated with triglyceride ($p = 0.026$), low-density lipoprotein cholesterol ($p = 0.023$), cardiac troponin I ($p = 0.023$), and C-reactive protein ($p = 0.001$). Besides, lncRNA KCNQ1OT1 was also positively linked with the Gensini score ($p = 0.008$). Furthermore, lncRNA KCNQ1OT1 was positively related to the TNF-α ($p < 0.001$), IL-17A ($p = 0.008$), and VCAM-1 ($p = 0.003$). LncRNA KCNQ1OT1 was elevated in CHD patients with MACE compared to those without MACE ($p = 0.006$); moreover, lncRNA KCNQ1OT1 high was associated with shorter MACE-free survival ($p = 0.018$).

Conclusion: Circulating lncRNA KCNQ1OT1 expression not only reflects the stenosis degree, blood lipid level, and inflammation status but also predicts the MACE risk, while a large-scale study is needed for verification.

KEYWORDS
blood lipid, coronary heart disease, inflammation, LncRNA KCNQ1OT1, major adverse cardiovascular event

1 | INTRODUCTION

Coronary heart disease (CHD) is viewed as one of the human health-threatening diseases with an estimated prevalence ranging from 6.0% to 6.2% according to the Behavioral Risk Factor Surveillance System (BRFSS) data in 2022; besides, the CHD causes the highest proportion of deaths.[1,2] The pathogenesis of CHD is complex, among which, atherosclerosis, plaque formation, excessive inflammatory cytokines production, abnormal lipids metabolism, etc. are currently acknowledged responsible for the incidence of CHD.[3–5] Therefore, the current treatment for CHD patients mainly focuses on improving the ischemia (such as nitroglycerin and percutaneous coronary intervention), anti-thrombogenesis (such as aspirin), lipid-lowering therapy (such as statins), etc.[6,7] Unfortunately, even though these intensive therapies are applied to CHD patients, a non-neglectable proportion of patients still might occur dismal outcomes such as myocardial infarction, heart failure, and even death.[8–11] Therefore, it is essential to find biomarkers that might reflect the disease risk and progression of CHD, which could help the cardiologist to stratify the patients and further improve the prognosis of CHD patients.

Long non-coding RNA (lncRNA) KQT-like subfamily, member 1 opposite strand/antisense transcript 1 (KCNQ1OT1) is localized in the nucleus, which is responsible for inhibiting the histone modifications.[12] Recent studies indicate that lncRNA KCNQ1OT1 is involved in regulating lipid metabolism, atherosclerosis, vascular smooth muscle cells' dysfunction, and inflammation, which implies that it might participate in the pathogenesis of CHD.[13,14] For instance, one study finds that lncRNA KCNQ1OT1 could promote lipid accumulation; besides, it also accelerates atherosclerosis via targeting the microRNA (miR)-452-3p/ histone deacetylase 3 (HDAC3)/ATP-binding cassette subfamily A member 1 (ABCA1) axis.[14] In another study, lncRNA KCNQ1OT1 could regulate the vascular smooth muscle cell apoptosis through miR-196a-5p/Forkhead box class O proteins 1 (FOXO1) axis.[15] Besides, lncRNA KCNQ1OT1 could promote inflammation by regulating the miR-147a/SRY-box transcription factor 6 (SOX6) axis in the diabetic nephropathy model.[13] Clinically, lncRNA KCNQ1OT1 could serve as a biomarker reflecting systemic inflammation, multiple organ dysfunction, and mortality risk in sepsis patients, and it is also reported to be overexpressed in CHD patients compared with healthy subjects.[16,17] Hence, we hypothesized that lncRNA KCNQ1OT1 could probably serve as a biomarker for CHD management.

Therefore, this study aimed to evaluate the dysregulation of lncRNA KCNQ1OT1, and its correlation with stenosis degree, lipids metabolism, inflammation status, and major adverse cardiovascular event (MACE) in CHD patients.

2 | METHODS

2.1 | Subjects

Between February 2019 and September 2021, a total of 267 first-episode coronary angiography (CAG)-confirmed CHD patients were enrolled in this prospective study. The following main inclusion criteria were applied: (1) diagnosed as first-episode CHD according to the CAG procedure; (2) age ≥18 years; (3) did not participate in other clinical studies; (4) willing to provide the peripheral blood for clinical study usage. Patients would be excluded if they met any of the following situations: (1) solid tumor or hematological malignancy patients; (2) pregnancy or childbearing women; (3) following conditions that might affect the lncRNA KCNQ1OT1 expression including active infection and auto-immune diseases; (4) severe insufficient function in liver or kidney. During the same period, 50 unexplained chest pain (but not diagnosed as CHD) patients as disease controls (DCs) and 50 healthy subjects as health controls (HCs) were also enrolled. The age and sex ratio in DCs and HCs were controlled to match with CHD patients. The exclusion criteria for the DCs and HCs were the same as that for CHD patients. Ethics Committee approved this study. All CHD patients, DCs, and HCs signed the written informed consent.

2.2 | Data collection and samples acquisition

Demographic information, history of the disease, and biochemical indexes were collected in CHD patients. Besides, peripheral blood from all subjects was obtained. Within 24 h after the peripheral blood collection, peripheral blood mononuclear cells (PBMCs) from all subjects (including the CHD patients, DCs, and HCs) and serum from CHD patients only were separated under the density gradient centrifugation, which was applied for the subsequent detection. In detail, the peripheral blood sample was centrifuged at 382 *g* for 20 min, then the serum and PBMCs layers were extracted. Following by that, the PBS solution was added into PBMCs and re-centrifuged at 215 *g* for 10 min. Then, the isolated PBMCs and serums were stored.

2.3 | Enzyme-linked immunosorbent assay

In the serum of CHD patients, inflammatory cytokines (including tumor necrosis factor-α [TNF-α] and interleukin [IL]-17A) and adhesion molecules (including vascular cell adhesion molecule-1 [VCAM-1] and intercellular adhesion molecule-1 [ICAM-1]) levels were determined by the Enzyme-linked immunosorbent assay (ELISA) procedure. The commercial TNF-α (Cat. No. DTA00D, R&D), IL-17A (Cat. No. D1700; R&D), VCAM-1 (Cat. No. DVC00; R&D), and ICAM-1 (Cat. No. DCD540; R&D) ELISA kits were applied, correspondingly. All detailed procedures were carried out according to the instruction books.

2.4 | Reverse transcriptive-quantitative polymerase chain reaction (RT-qPCR) assay

LncRNA KCNQ1OT1 expression was determined in the PBMCs from all subjects (including the CHD patients, DCs, and HCs) by using an RT-qPCR assay. In detail, the total RNA was exacted

from the PBMCs using the PureZOL RNA isolation reagent (Bio-Rad). Then, by employing the RNA as a template, cDNA was synthesized using the iScript™ Reverse Transcription Supermix (Bio-Rad). Finally, the qPCR was carried out using PCR: SYBR® Green Realtime PCR Master Mix (Toyobo). The GAPDH was used as the housekeeping gene. The design of the primers of lncRNA KCNQ1OT1 was referred to in a previous study.[18] The $2^{-\Delta\Delta C_T}$ method was carried out for calculating the expression of lncRNA KCNQ1OT1.

2.5 | Follow-up

Coronary heart disease patients were regularly followed up to February 2022. During this period, the MACE was recorded, which included documented cardiovascular death, myocardial infarction, repeat revascularization, and hospitalization for any cardiovascular reason.[19] The MACE-free survival was calculated as the duration from the enrollment to the occurrence of MACE. The median follow-up duration was 16.3 months, and the mean (95% confidential interval) follow-up duration was 16.0 (15.3–16.8) months; besides, its range was 3.2–29.2 months.

2.6 | Statistics

Analysis was completed using SPSS v.24.0 (IBM Corp.). Graphing was performed using GraphPad Prism v.6.01 (GraphPad Software Inc.). Continuous variables conforming to normal distribution were presented as mean with standard deviation (SD) and those continuous variables conforming to abnormal distribution were presented as median with interquartile range (IQR). Categorical variables were displayed as a number with frequency. Comparisons between two groups were carried out by the Wilcoxon rank sum test; in addition, comparisons among three groups were carried out by the Kruskal–Wallis *H* test. The spearman correlation test was applied for determining the inter-correlation between two sets of variables. The receiver operation curve (ROC) was drawn to estimate the value of lncRNA KCNQ1OT1 in distinguishing different subjects. Kaplan–Meier (KM) curve and log-rank test were applied for presenting the MACE-free survival rate. $p < 0.05$ indicated significance.

3 | RESULTS

3.1 | CHD patients' characteristics

The mean age of CHD patients was 63.7 ± 10.2 years. There were 62 (23.2%) females and 205 (76.8%) males. One hundred eighty-nine (70.8%) and 108 (40.4%) patients had a history of hypertension and hyperlipidemia, separately. The median (IQR) TNF-α, IL-17A, VCAM-1, and ICAM-1 values were 54.3 (42.9–70.8) pg/ml, 65.9 (55.1–79.4) pg/ml, 643.1 (529.0–889.5) ng/ml, and 128.4 (96.1–174.0) ng/ml, respectively (Table 1).

3.2 | LncRNA KCNQ1OT1 among all subjects

Coronary heart disease patients had the highest lncRNA KCNQ1OT1 level; DCs had an intermediate lncRNA KCNQ1OT1 level; while the

TABLE 1 Clinical characteristics

Items	CHD patients (*N* = 267)
Age (years), mean ± SD	63.7 ± 10.2
Gender, No. (%)	
Female	62 (23.2)
Male	205 (76.8)
BMI (kg/m^2), mean ± SD	24.1 ± 3.1
History of drink, No. (%)	103 (38.6)
History of smoke, No. (%)	130 (48.7)
History of disease, No. (%)	
Hypertension	189 (70.8)
Hyperlipidemia	108 (40.4)
DM	57 (21.3)
CKD	32 (12.0)
Biochemical indexes, median (IQR)	
FBG (mmol/L)	5.9 (5.1–6.9)
Scr (μmol/L)	81.6 (72.7–90.2)
SUA (μmol/L)	354.0 (310.0–412.0)
TG (mmol/L)	1.8 (1.1–2.5)
TC (mmol/L)	4.7 (4.0–5.5)
LDL-C (mmol/L)	3.3 (2.6–4.1)
HDL-C (mmol/L)	1.0 (0.8–1.1)
cTnI (ng/ml)	2.3 (1.5–3.6)
CK-MB (ng/ml)	17.0 (9.4–31.6)
CRP (mg/L)	6.1 (4.4–9.2)
Gensini score, median (IQR)	30.0 (17.0–51.0)
Inflammatory cytokines, median (IQR)	
TNF-α (pg/ml)	54.3 (42.9–70.8)
IL-17A (pg/ml)	65.9 (55.1–79.4)
Adhesion molecules, median (IQR)	
VCAM-1 (ng/ml)	643.1 (529.0–889.5)
ICAM-1 (ng/ml)	128.4 (96.1–174.0)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; ICAM-1, intercellular adhesion molecule-1; IL-17A, interleukin-17A; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SD, standard deviation; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1.

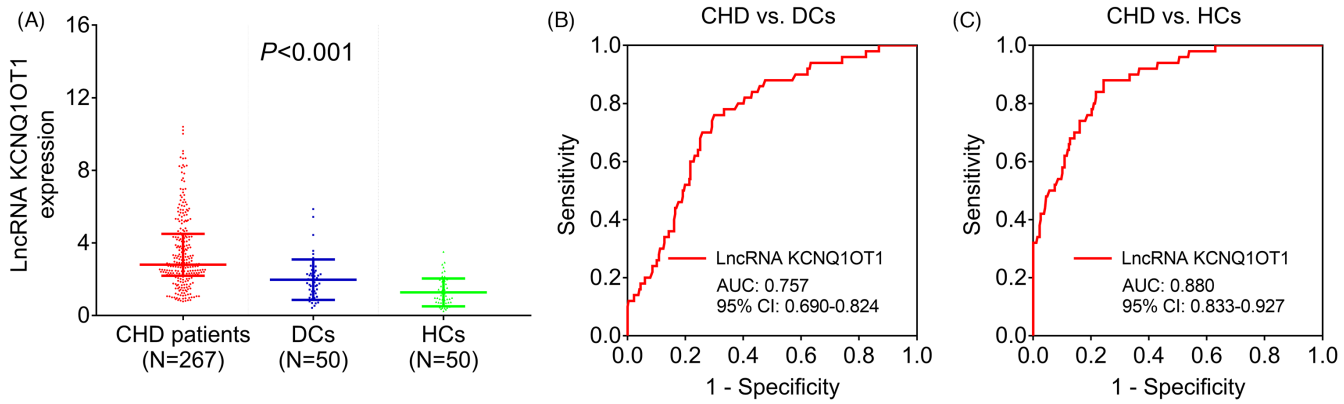

FIGURE 1 Aberrant lncRNA KCNQ1OT1 expression in CHD patients. Comparison of lncRNA KCNQ1OT1 expression among all subjects (A). The value of lncRNA KCNQ1OT1 in identifying CHD patients from DCs (B) and HCs (C)

HCs had the lowest lncRNA KCNQ1OT1 level ($p < 0.001$, Figure 1A). Then, the discovery from the ROC curve displayed lncRNA KCNQ1OT1 had a good value for identifying the CHD patients from DCs (area under the curve [AUC]: 0.757, 95% confidential interval [CI]: 0.690–0.824, Figure 1B) and HCs (AUC: 0.880, 95% CI: 0.833–0.927, Figure 1C).

3.3 | Correlation of lncRNA KCNQ1OT1 with CHD patients' clinical features

LncRNA KCNQ1OT1 did not correlate with any demographics (including age, gender, BMI, history of drink or smoke) or history of the disease (including the history of hypertension, hyperlipidemia, diabetes mellitus, or chronic kidney disease) (all $p > 0.05$) (Table 2). Besides, the lncRNA KCNQ1OT1 was positively associated with triglyceride (TG) (r_s: 0.136, $p = 0.026$), low-density lipoprotein cholesterol (LDL-C) (r_s: 0.139, $p = 0.023$), cardiac troponin I (cTnI) (r_s: 0.139, $p = 0.023$), and C-reactive protein (CRP) (r_s: 0.211, $p = 0.001$) but was not associated with other biochemical indexes (including fasting blood glucose, serum creatinine, serum uric acid, total cholesterol, and high-density lipoprotein cholesterol, etc., all $p > 0.05$) (Table 3).

3.4 | Association of lncRNA KCNQ1OT1 with CHD patients' stenosis degree, cytokines, and adhesion molecules

A positive association was found between the lncRNA KCNQ1OT1 and Gensini score (r_s: 0.161, $p = 0.008$, Figure 2). Apart from that, lncRNA KCNQ1OT1 was also positively related to the inflammation cytokines (including TNF-α [r_s: 0.212, $p < 0.001$, Figure 3A] and IL-17A [r_s: 0.163, $p = 0.008$, Figure 3B]) and VCAM-1 (r_s: 0.182, $p = 0.003$, Figure 3C), but not ICAM-1 (r_s: 0.118, $p = 0.055$, Figure 3D). Subgroup analysis disclosed that in patients with BMI ≥28 kg/m,^{2} the lncRNA KCNQ1OT1 was positively correlated with the Gensini score, while this correlation was not observed in patients with BMI <28 kg/m^2 (Figure S1A,B).

3.5 | Predictive value of lncRNA KCNQ1OT1 for the MACE risk in CHD patients

Coronary heart disease patients with MACE had an elevated level of lncRNA KCNQ1OT1 compared to those CHD patients without MACE ($p = 0.006$, Figure 4A); moreover, lncRNA KCNQ1OT1 disclosed a certain value in identifying the MACE patients from non-MACE patients (AUC: 0.670, 95% CI: 0.569–0.770, Figure 4B). After dividing the CHD patients into lncRNA KCNQ1OT1 high and low according to the median value of lncRNA KCNQ1OT1, the log-rank test revealed that lncRNA KCNQ1OT1 high was associated with shorter MACE-free survival ($p = 0.018$, Figure 4C). Furthermore, the multivariate Cox's regression analysis also disclosed that the lncRNA KCNQ1OT1 high was independently related to the shorter MACE-free survival (hazards ratio = 4.311, $p = 0.003$, Table S1).

4 | DISCUSSION

Only a few studies report the aberrant expression of lncRNA KCNQ1OT1 and its diagnostic value in cardiovascular disease. For instance, one study discloses that lncRNA KCNQ1OT1 is increased in coronary artery disease (CAD) patients, and it presents a good value in distinguishing CAD patients from non-CAD controls.[20] The current study also displayed that lncRNA KCNQ1OT1 had different expressions among CHD patients, DCs, and HCs; besides, it was highest in CHD patients; what's more, lncRNA KCNQ1OT1 could identify CHD patients from DCs and HCs. These findings could be explained as that the involvement of lncRNA KCNQ1OT1 in regulating the lipid metabolism and vascular smooth muscle cell apoptosis contributed to the incidence of CHD.[14,15] Apart from that, lncRNA KCNQ1OT1 could promote the inflammatory response and oxidative stress via regulating the miR-137/TNFA1P1 axis, which was responsible for atherosclerosis; therefore, lncRNA KCNQ1OT1 was associated with the elevated CHD risk.[20]

Previous studies have preliminary explored the role of lncRNA KCNQ1OT1 in regulating lipid accumulation, the function of the endothelial cell, and inflammation. For example, one study finds

TABLE 2 Correlation of lncRNA KCNQ1OT1 with demographics and history of the disease in CHD patients

Items	LncRNA KCNQ1OT1 expression median (IQR)	*p* Value
Age		
≥60 years	2.8 (2.2–4.5)	0.625
<60 years	2.8 (2.1–4.5)	
Gender, No. (%)		
Female	2.8 (2.0–4.5)	0.709
Male	2.8 (2.2–4.5)	
BMI		
≥28 kg/m^2	3.3 (2.3–5.1)	0.205
<28 kg/m^2	2.8 (2.1–4.4)	
History of drink		
Yes	2.8 (2.2–4.7)	0.703
No	2.8 (2.2–4.3)	
History of smoke		
Yes	2.8 (2.3–4.7)	0.345
No	2.8 (1.9–4.4)	
History of hypertension		
Yes	2.9 (2.2–4.7)	0.169
No	2.7 (1.9–4.2)	
History of hyperlipidemia		
Yes	3.1 (2.2–4.8)	0.231
No	2.7 (2.2–4.3)	
History of DM		
Yes	3.5 (2.2–5.2)	0.090
No	2.7 (2.2–4.3)	
History of CKD		
Yes	2.6 (2.2–5.7)	0.608
No	2.8 (2.1–4.4)	

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; IQR, interquartile range; LncRNA, long non-coding RNA.

TABLE 3 Correlation of lncRNA KCNQ1OT1 with biochemical indexes in CHD patients

Items	LncRNA KCNQ1OT1 expression	
	r_s Value	*p* Value
FBG	0.102	0.096
Scr	0.076	0.215
SUA	0.075	0.220
TG	0.136	0.026
TC	0.105	0.088
LDL-C	0.139	0.023
HDL-C	−0.092	0.134
cTnI	0.139	0.023
CK-MB	0.096	0.116
CRP	0.211	0.001

Abbreviations: CHD, coronary heart disease; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, cardiac troponin I; FBG, fasting blood 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.

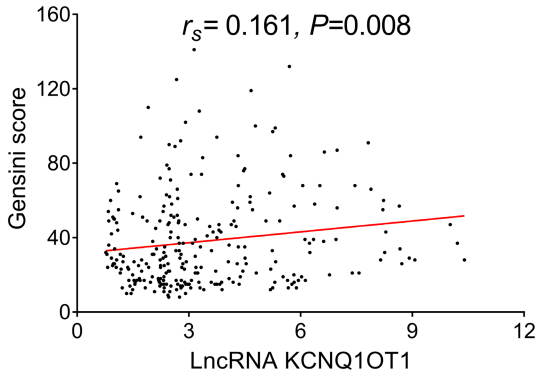

FIGURE 2 Correlation between lncRNA KCNQ1OT1 and Gensini score in CHD patients

that lncRNA KCNQ1OT1 could regulate the IκBα expression, then, suppress the proliferation of vascular smooth muscle cells.[21] Also, lncRNA KCNQ1OT1 could modulate the lipid metabolic disorder via sponging to miR-145-5p in an atherosclerosis mice model.[22] In another study, lncRNA KCNQ1OT1 could contribute to the inflammation flare via regulating the miR-130a-3p/ZNF791 axis.[23] However, the clinical value of lncRNA KCNQ1OT1 in reflecting the lipid concentration, endothelial cell situation, and inflammation status in CHD patients is still rarely reported. In our study, lncRNA KCNQ1OT1 positively correlated with lipid level (reflected by TG and LDL-C), endothelial cell dysfunction (reflected by VCAM-1), and the inflammation flare (reflected by the inflammation cytokines and CRP) in CHD patients. These findings could be explained as follows: as mentioned above, lncRNA KCNQ1OT1 was involved in accelerating lipid accumulation, facilitating endothelial cell apoptosis, and promoting inflammation; hence, lncRNA KCNQ1OT1 was positively linked with the TNF-α, IL-17A, CRP, TG, LDL-C, and VCAM-1. Apart from that, this study also revealed that lncRNA KCNQ1OT1 positively associated with the stenosis degree, which might be derived from that the lncRNA KCNQ1OT1 could facilitate atherosclerosis and plaque formation, which was responsible for the stenosis aggravating[22]; therefore, lncRNA KCNQ1OT1 positively correlated with the Gensini score. Furthermore, it was revealed that lncRNA KCNQ1OT1 was positively associated with cTnI. The possible reason might be that lncRNA KCNQ1OT1 could contribute to the apoptosis of cardiomyocytes via miR-130a-3p/ZNF791 axis, which further upregulated the cTnI expression in serum.[23]

Another finding in this study was that the lncRNA KCNQ1OT1 could predict the MACE risk in CHD patients, which had never been reported in the previous study. This phenomenon could be explained as that the lncRNA KCNQ1OT1 was involved in lipid metabolism and regulating inflammation as mentioned above; meanwhile, the latter biological processes were reported to be closely

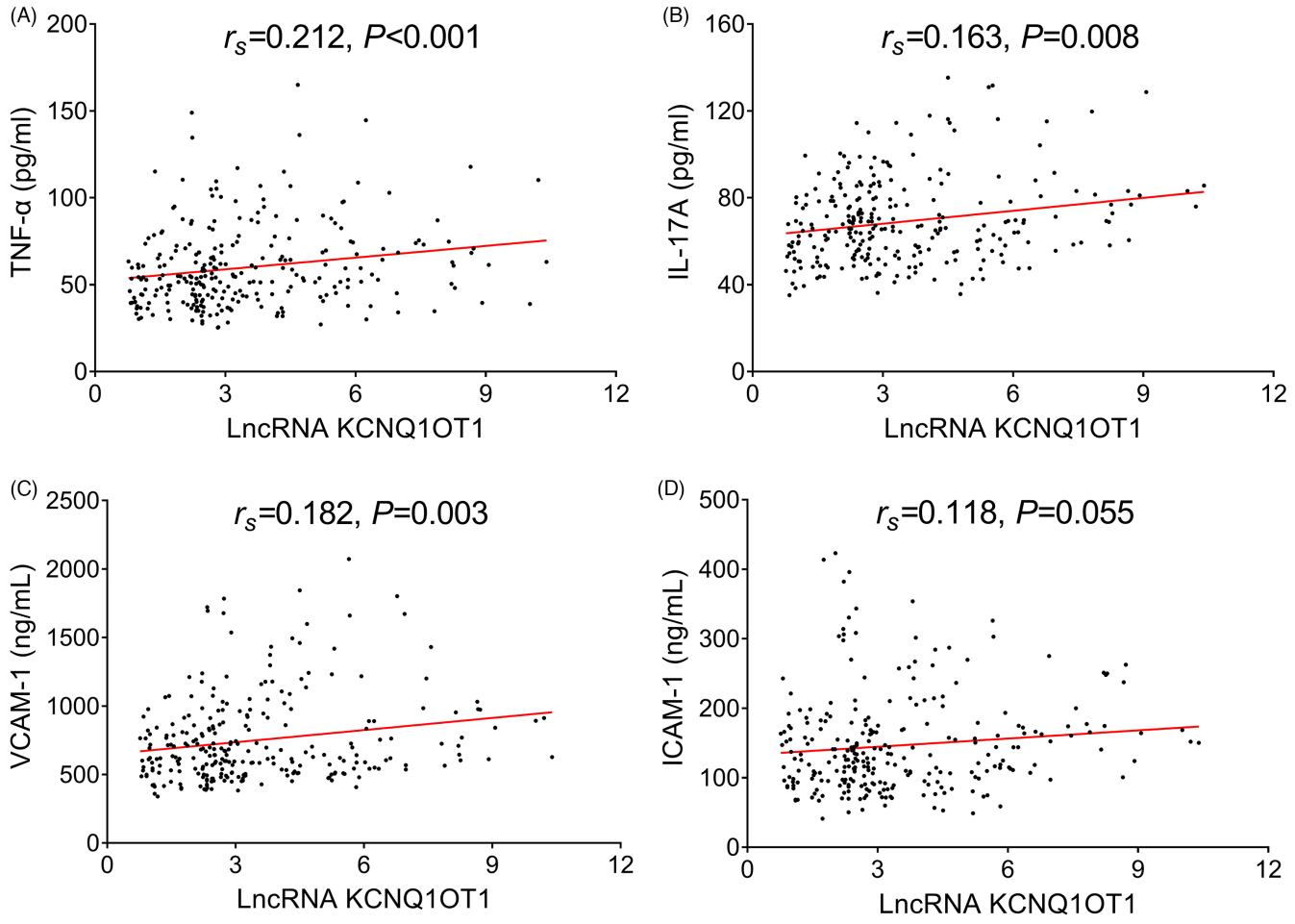

FIGURE 3 Correlation of lncRNA KCNQ1OT1 with cytokines in CHD patients. Association of lncRNA KCNQ1OT1 with TNF-α (A), IL-17A (B), VCAM-1 (C), and ICAM-1 (D)

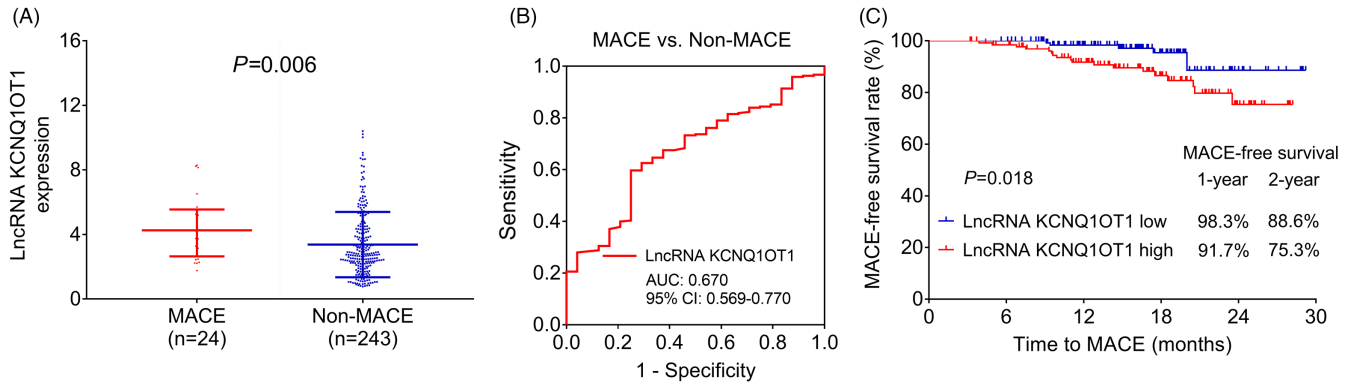

FIGURE 4 Value of lncRNA KCNQ1OT1 in identifying MACE risk in CHD patients. Comparison of lncRNA KCNQ1OT1 between CHD patients with and without MACE (A). The ability of lncRNA KCNQ1OT1 in identifying MACE patients from non-MACE patients (B); association of lncRNA KCNQ1OT1 high with MACE-free survival rate (C)

linked with the occurrence of MACE[24,25]; to summarize above, the lncRNA KCNQ1OT1 could serve as a biomarker in predicting the MACE risk.

Some limitations in this study were non-neglectable, such as (1) even though we proposed the potential explanations for the correlation of lncRNA KCNQ1OT1 with TNF-α, IL-17A, CRP, TG, LDL-C, and VCAM-1 in CHD patients, the detailed mechanism still needed to be explored in the in vitro and in vivo experiment; (2) Currently, CHD also frequently occurred in the young population, while the mean age of CHD patients in this study was 63.7 ± 10.2 years; therefore, the clinical value of lncRNA KCNQ1OT1 in young CHD patients should also be determined[26]; (3) the maximum follow-up duration was 29.2 months in this study, which was relatively short; thus, further longer follow-up should

be carried out to detect the long-term prognostic value of lncRNA KCNQ1OT1 for CHD management.

In conclusion, increased lncRNA KCNQ1OT1 expression in CHD patients could reflect their more severe disease status and MACE risk.

CONFLICT OF INTEREST

None.

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

All CHD patients, DCs, and HCs signed the written informed consent.

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REFERENCES

1. Patel J, Pallazola VA, Dudum R, et al. Assessment of coronary artery calcium scoring to guide statin therapy allocation according to risk-enhancing factors: the multi-ethnic study of atherosclerosis. *JAMA Cardiol*. 2021;6(10):1161-1170.
2. Lee YH, Fang J, Schieb L, Park S, Casper M, Gillespie C. Prevalence and trends of coronary heart disease in the United States, 2011 to 2018. *JAMA Cardiol*. 2022;7(4):459-462.
3. Fan X, Li A, Yan Z, et al. From iron metabolism to ferroptosis: pathologic changes in coronary heart disease. *Oxid Med Cell Longev*. 2022;2022:6291889.
4. Liu M, Wu Y. Role of mitophagy in coronary heart disease: targeting the mitochondrial dysfunction and inflammatory regulation. *Front Cardiovasc Med*. 2022;9:819454.
5. Wan Musa WZ, Abu Bakar NAF, Ahmad A, Naing NN. Association between fatty acids and coronary heart disease: a scoping review. *Med J Malaysia*. 2022;77(1):71-81.
6. Zhou H, Zhang S, Sun X, et al. Lipid management for coronary heart disease patients: an appraisal of updated international guidelines applying appraisal of guidelines for research and evaluation II-clinical practice guideline appraisal for lipid management in coronary heart disease. *J Thorac Dis*. 2019;11(8):3534-3546.
7. Han YL, Li Y. History and development of percutaneous coronary intervention for coronary heart disease in China. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2021;49(7):645-649.
8. Gayda M, Gremeaux V, Bherer L, et al. Cognitive function in patients with stable coronary heart disease: related cerebrovascular and cardiovascular responses. *PLoS One*. 2017;12(9):e0183791.
9. Waqar A, Lopez JJ. Neurological complications of coronary heart disease and their management. *Handb Clin Neurol*. 2021;177:57-63.
10. Olesen KKW, Steensig K, Madsen M, et al. Comparison of frequency of ischemic stroke in patients with versus without coronary heart disease and without atrial fibrillation. *Am J Cardiol*. 2019;123(1):153-158.
11. Leal J, Becker F, Lim LL, Holman RR, Gray AM. Health utilities in Chinese patients with coronary heart disease and impaired glucose tolerance (ACE): a longitudinal analysis of a randomized, double-blind, placebo-controlled trial. *J Diabetes*. 2022;14(7):455-464.
12. Redrup L, Branco MR, Perdeaux ER, et al. The long noncoding RNA Kcnq1ot1 organises a lineage-specific nuclear domain for epigenetic gene silencing. *Development*. 2009;136(4):525-530.
13. Xu Y, Zhan X. lncRNA KCNQ1OT1 regulated high glucose-induced proliferation, oxidative stress, extracellular matrix accumulation, and inflammation by miR-147a/SOX6 in diabetic nephropathy (DN). *Endocr J*. 2022;69(5):511-522.
14. Yu XH, Deng WY, Chen JJ, et al. LncRNA kcnq1ot1 promotes lipid accumulation and accelerates atherosclerosis via functioning as a ceRNA through the miR-452-3p/HDAC3/ABCA1 axis. *Cell Death Dis*. 2020;11(12):1043.
15. Li K, Cao H, Fan M, et al. LncRNA KCNQ1OT1 participates in ox-LDL-induced proliferation/apoptosis imbalance in vascular smooth muscle cells by regulating the MiR-196a-5p/FOXO1 Axis. *J Stroke Cerebrovasc Dis*. 2022;31(8):106622.
16. Wang Y, Jiao J, Wang D, Song J, Huang K. Effects of ticagrelor on proliferation, apoptosis, and inflammatory factors of human aortic vascular smooth muscle cells through lncRNA KCNQ1OT1. *Am J Transl Res*. 2021;13(12):13462-13470.
17. Jiao W, Zhou X, Wu J, Zhang X, Ding J. Potential of long non-coding RNA KCNQ1OT1 as a biomarker reflecting systemic inflammation, multiple organ dysfunction, and mortality risk in sepsis patients. *J Clin Lab Anal*. 2021;35(12):e24047.
18. Yang F, Qin Y, Wang Y, et al. LncRNA KCNQ1OT1 mediates pyroptosis in diabetic cardiomyopathy. *Cell Physiol Biochem*. 2018;50(4):1230-1244.
19. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA*. 2016;316(10):1051-1060.
20. Zhang Y, Zhang L, Wang Y, et al. KCNQ1OT1, HIF1A-AS2 and APOA1-AS are promising novel biomarkers for diagnosis of coronary artery disease. *Clin Exp Pharmacol Physiol*. 2019;46(7):635-642.
21. Ye B, Wu ZH, Tsui TY, et al. lncRNA KCNQ1OT1 suppresses the inflammation and proliferation of vascular smooth muscle cells through IkappaBa in intimal hyperplasia. *Mol Ther Nucleic Acids*. 2020;20:62-72.
22. Wang Y, Liu L, Li J. LncRNA KCNQ1OT1 depletion inhibits the malignant development of atherosclerosis by miR-145-5p. *Microvasc Res*. 2022;139:104236.
23. Xin H, Li C, Cai T, Cao J, Wang M. LncRNA KCNQ1OT1 contributes to hydrogen peroxide-induced apoptosis, inflammation, and oxidative stress of cardiomyocytes via miR-130a-3p/ZNF791 axis. *Cell Biol Int*. 2022;46(12):2018-2027.
24. Dregoesc MI, Tigu AB, Bekkering S, et al. Relation between plasma proteomics analysis and major adverse cardiovascular events in patients with stable coronary artery disease. *Front Cardiovasc Med*. 2022;9:731325.
25. Lee Y, Park S, Lee S, et al. Lipid profiles and risk of major adverse cardiovascular events in CKD and diabetes: a nationwide population-based study. *PLoS One*. 2020;15(4):e0231328.
26. Dzaye O, Razavi AC, Dardari ZA, et al. Modeling the recommended age for initiating coronary artery calcium testing among at-risk young adults. *J Am Coll Cardiol*. 2021;78(16):1573-1583.

SUPPORTING INFORMATION

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

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