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Federal Fluminense University, Brazil

*CORRESPONDENCE

Cui-Fen Hu
✉ hucifensuda@126.com
Cheng-Xing Shen
✉ shenchienx2@hotmail.com

[†]These authors have contributed equally to this work

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Expression levels of thymosin $\alpha 1$ in acute myocardial infarction patients and its correlation to cardiac function

Liang Liu^{1†}, Zhen-Fa Zhou^{1,2†}, Xian Jin¹, Yu Chen^{1,3}, Cui-Fen Hu^{4*} and Cheng-Xing Shen^{1*}

¹Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, ²Department of Cardiovascular Medicine, Fuzhou First Hospital Affiliated with Fujian Medical University, Fuzhou, China, ³State Key Laboratory of Molecular Engineering of Polymers, Fudan University, Shanghai, China, ⁴Department of Ultrasound in Medicine, Minhang Hospital, Fudan University, Shanghai, China

Background: Early prediction of heart failure (HF) after acute myocardial infarction (AMI) remains a clinical challenge. There is a lack of studies investigating Thymosin $\alpha 1$ expression levels in AMI patients and its relationship with cardiac function post-AMI.

Methods: This retrospective analysis included patients with AMI from December 2019 to February 2022. The baseline data of two groups were collected. Thymosin $\alpha 1$ expression level of peripheral blood plasma in AMI patients was examined by ELISA. Logistic regression analysis was applied to evaluate risk factors in-hospital cardiac dysfunction after emergency PCI in AMI patients. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of the biomarker.

Results: A total of 307 hospitalized patients were enrolled in this study, divided into AMI group ($n = 274$) and non-AMI group ($n = 33$). The expression level of thymosin $\alpha 1$ in the AMI group was significantly higher than in the non-AMI group. The AMI patients were divided into two subgroups based on the EF values. The sample size was 64 (EF < 50%) and 210 (EF $\geq$ 50%), respectively. The expression of thymosin $\alpha 1$ in the EF $\geq$ 50% group was significantly higher than EF < 50% group. Spearman's correlation analysis demonstrated that thymosin $\alpha 1$ was positively correlated with the EF value. Logistic multivariate analysis suggested that thymosin $\alpha 1$, NT-proBNP, and creatine kinase were independent predictors of cardiac function after AMI. The AUC of thymosin $\alpha 1$, NT-proBNP, and creatine kinase was 0.614, 0.714, and 0.724, respectively.

Conclusion: Thymosin $\alpha 1$ may serve as a potential biomarker to predict cardiac function following AMI. This study may provide novel insights into the potential therapeutic targets for HF following AMI.

KEYWORDS

thymosin $\alpha 1$, cardiac function, acute myocardial infarction, biomarker, therapy

1 Introduction

Coronary heart disease remains one of the leading causes of morbidity and mortality worldwide (1). Acute myocardial infarction (AMI) is the most serious manifestation of coronary heart disease, which seriously threatens human health and increases social burden (2). With the advancement of contemporary medicine, especially the implementation of coronary intervention surgeries, many AMI patients can have their culprit vessels opened in

a timely and effective manner (3). As a result, the mortality rate has significantly decreased compared to the past (3). However, the complications of AMI cannot be ignored, as they seriously affect the patient's life and health as well as their quality of life. AMI is frequently associated with numerous complications, among which new-onset or chronic heart failure (HF) after discharge is a prevalent one (4). The emergence of HF after an MI can notably enhance the mortality rate and the risk of recurrent hospitalizations for this patient group (5). Therefore, the early and accurate detection of post-MI cardiac dysfunction through clinically effective laboratory indicators, and the subsequent administration of effective treatment, constitute the most efficacious strategies to mitigate the long-term adverse prognosis of this patient group.

Thymosins were initially purified from the calf thymus by Allan L. Goldstein in 1966 as a biologically active substance (6). Subsequent research has disclosed that numerous tissues in the human body can secrete thymosin (7). Due to the isoelectric point, thymosins are divided into isoforms α ($pI < 5$), β ($5 < pI < 7$), and γ ($pI > 7$) (7). T- $\beta 4$ is the most abundant β -thymosin (constituting approximately 70%–80%) and holds numerous biological effects, including cell proliferation and apoptosis, inflammatory responses, and fibrosis within the body (7–9). A significant number of studies have been conducted on the role of T- $\beta 4$ in myocardial fibrosis and cardiac function after AMI, suggesting its potential protective mechanisms in the myocardium following AMI (10, 11). Thymosin $\alpha 1$ is related to various biological effects in the body and mainly participates in immune regulation (12). It can promote the maturation and differentiation of T lymphocytes, stimulate the secretion of various lymphokines by mature T cells and NK cells, and augment the body's immune response and resistance to infection (7, 12). Moreover, it has an anti-inflammation protective effect to reduce the damage of central nervous system diseases (13). Given the regulation of thymosin $\alpha 1$ on the immune function of the body, in clinical practice, thymosin $\alpha 1$ is mainly used for the combined treatment of cancers (14), the treatment of hepatitis B virus (15), and the treatment of HIV patients (16). The inflammatory response following AMI plays a crucial role in the progression of myocardial injury. However, the role of Thymosin $\alpha 1$ post-AMI remains poorly understood. The potential of Thymosin $\alpha 1$ as a biomarker for myocardial injury and cardiac dysfunction following AMI is yet to be fully explored.

This study focuses on this issue. By comparing with the control group, the expression level of Thymosin $\alpha 1$ in the peripheral blood of patients with AMI and its relationship with early-onset HF after AMI are clarified. The goal is to identify a novel biomarker for the early clinical detection of HF following AMI, thereby facilitating early intervention and improving long-term outcomes for this patient population.

2 Materials and methods

2.1 Patients

From December 2019 to February 2022, a total of 307 patients were consecutively enrolled as the study subjects, including 274

patients with AMI as the case group, and 33 patients without AMI at enrollment and no prior history of AMI as the control group. All the AMI patients met the diagnostic criteria of the 2023 ESC Guidelines for the management of acute coronary syndromes (17). For AMI patients with confirmed ST-segment elevation myocardial infarction (STEMI), the infarct-related artery (IRA) should be opened within 12 h. For NSTEMI patients, the IRA will be opened within 2, 12, 24, and 72 h according to risk stratification. Moreover, all AMI patients will receive optimal drug therapy according to the guideline (17). The exclusion criteria for this study were as follows: (a) A previous history of AMI; (b) A history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI); (c) Severe hepatic/renal insufficiency or chronic obstructive pulmonary disease; (d) Disorders in the hematological, immune, or coagulation systems; (e) The presence of malignant tumors; (f) The existence of psychiatric disorders; (g) Incomplete clinical or laboratory data; (h) Any other circumstances that the researcher deems inappropriate to participate in this study. This study was approved by the Hospital Ethics Committee and the ethical number is 2021-KY-04(K)-(1). All the enrolled patients signed the informed consent form. The study was by the principles of the Declaration of Helsinki and was approved by the Hospital Ethics Committee.

2.2 Clinical or laboratory data

The baseline data of clinical records encompass age, gender, height, weight, systolic blood pressure, heart rate, etc. The past medical history of patients, including hypertension, diabetes, etc., was documented. Blood routine, biochemical markers, and coagulation indicators were all recorded as the fasting blood results in the early morning of patients. Markers of myocardial injury in AMI patients, including troponin, creatine kinase, N-terminal pro-B-type natriuretic peptide (NT-proBNP), etc., were all documented as the highest values during hospitalization. The LVEF assessment was performed within 7 days post-PCI for AMI patients and the Simpson method was used to measure LVEF.

2.3 Thymosin $\alpha 1$ examination by ELISA

Peripheral venous blood samples (5 ml) were collected from all subjects during the initial admission period prior to IRA revascularization. Subsequently, the venous blood was kept at room temperature for 30 min, and the serum was extracted after centrifugation at 1,000 g for 15 min using a centrifuge. The serum was stored at -80°C for subsequent use. The expression of serum thymosin $\alpha 1$ was determined using the enzyme-linked immunosorbent assay (ELISA) kit (Jing Mei Biotechnology, Jiangsu, China. No. JM-03731H1).

2.4 Statistical analysis

Continuous variables with a normal distribution were expressed as mean $\pm$ standard deviation (SD), and the

independent sample *t*-test was employed for intergroup comparison; data with a non-normal distribution were expressed as median [interquartile range (IQR)], and the Mann–Whitney *U*-test was utilized for comparison between groups. Categorical variables were depicted as percentages, and the χ^2 test or Fisher's exact test was applied for intergroup comparison.

All the significant variables identified in the intergroup comparison were enrolled in the logistic regression analysis, and the standard error and odd ratio (OR) were documented. The linear relationship between serum thymosin α 1 and EF value post-AMI was assessed using the Spearman correlation analysis. The predictive value of Thymosin α 1 for cardiac function following AMI was estimated by the receiver operating characteristic (ROC) curve. Statistical significance was considered as $P < 0.05$. All statistical analyses were performed using SPSS 26.0 statistical software.

3 Results

3.1 Comparison of baseline demographic and clinical data

A total of 307 patients were enrolled in this study, including 274 in the AMI group and 33 in the control group. Baseline data between the two groups, including gender, age, height, weight, BMI, systolic blood pressure, heart rate, smoking rate, drinking rate, prevalence of diabetes, and prevalence of hypertension, showed no statistically significant differences (Table 1).

3.2 Thymosin α 1 level was elevated in AMI patients with EF $\geq 50\%$

Compared with the control group, the expression level of thymosin α 1 was significantly elevated in AMI patients (Figure 1). The 2023 Focused Update of the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure utilizes the EF value as a crucial basis for chronic HF stratification. HF is classified into two types: HF with reduced ejection fraction (including EF between 41%

and 49%, known as HFmrEF, and EF $\leq 40\%$, known as HFrEF) and HF with preserved ejection fraction (EF $\geq 50\%$, known as HFpEF) (18). An EF of 50% is an important numerical cut-off for assessing cardiac function reduction. To further clarify the relationship between thymosin α 1 and cardiac function in patients with AMI, we categorized AMI patients into two groups based on postoperative echocardiography: one group with an EF $< 50\%$ and another group with an EF $\geq 50\%$. Initially, according to the design, the final number of enrolled patients with an EF $< 50\%$ was 64, while the number of patients with an EF $\geq 50\%$ was 210. Baseline data showed no statistically significant differences between the two groups in terms of gender, age, height, weight, systolic blood pressure, heart rate, smoking rate, drinking rate, prevalence of diabetes, and prevalence of hypertension, indicating that the two groups were comparable (Table 2). Furthermore, our study demonstrated that the expression levels of thymosin α 1 [2,913.28 (2,648.35–3,247.05) vs. 3,002.50 (2,846.48–3,497.68), $P = 0.006$] in peripheral blood were significantly higher in patients with an EF $\geq 50\%$ after AMI compared to those with an EF $< 50\%$ (Figure 2).

3.3 Thymosin α 1 level was positively correlated to EF value in AMI patients

To further elucidate the relationship between Thymosin α 1 level and cardiac function following AMI, a bivariate Spearman correlation analysis was conducted to assess the association between Thymosin α 1 level and EF value in all AMI patients. The results revealed that Thymosin α 1 level was positively correlated with EF value in patients post-AMI, with higher Thymosin α 1 level observed as EF value increased ($r = 0.219$, $P < 0.001$) (Figure 3).

3.4 Risk factors for EF value in AMI patients

To further investigate the risk factors of cardiac function in AMI patients after opening IRA, we divided AMI patients into two groups: the EF $< 50\%$ group and the EF $\geq 50\%$ group, with the specific number of samples in each group remaining the same as before. Firstly, a univariate comparison between the two groups of AMI patients in terms of blood routine, biochemistry, and coagulation was conducted. The results showed that the levels of white blood cell count, neutrophil cell count, and fasting blood glucose level in the EF $< 50\%$ group were significantly higher than those in the EF $\geq 50\%$ group. There were no statistically significant differences in other blood routine indicators, biochemical parameters such as liver and kidney function, blood lipid levels, and coagulation markers between the two groups (Table 3). Secondly, we collected myocardial injury markers of the two groups and compared them. The results indicated that the expression levels of troponin I, NT-proBNP, lactate dehydrogenase, creatine kinase, and creatine kinase isoenzyme in the group with poorer cardiac function post-AMI

TABLE 1 Comparison of clinical features between AMI group and control group.

Variable	AMI (<i>n</i> = 274)	Ccontrol (<i>n</i> = 33)	<i>P</i> -value
Male (<i>n</i> , %)	219 (79.9)	23 (69.7)	0.174
Age (Year)	65 (55–72)	66 (59–72)	0.817
Height (m)	1.70 (1.64–1.74)	1.70 (1.59–1.72)	0.220
Weight (kg)	70.0 (64.0–78.0)	67.0 (58.8–82.5)	0.250
BMI (kg/m ²)	24.68 (22.64–26.57)	24.22 (22.40–26.94)	0.596
SBP (mmHg)	126 (110–141)	132 (122–140)	0.290
HR (bpm)	80 (72–88)	78 (69–90)	0.367
Smoking (<i>n</i> , %)	165 (60.2)	21 (63.6)	0.704
Drinking (<i>n</i> , %)	73 (26.6)	7 (21.2)	0.502
Diabetes (<i>n</i> , %)	58 (21.2)	6 (18.2)	0.690
Hypertension (<i>n</i> , %)	148 (54.0)	22(66.7)	0.167

SBP, systolic blood pressure; HR, heart rate.

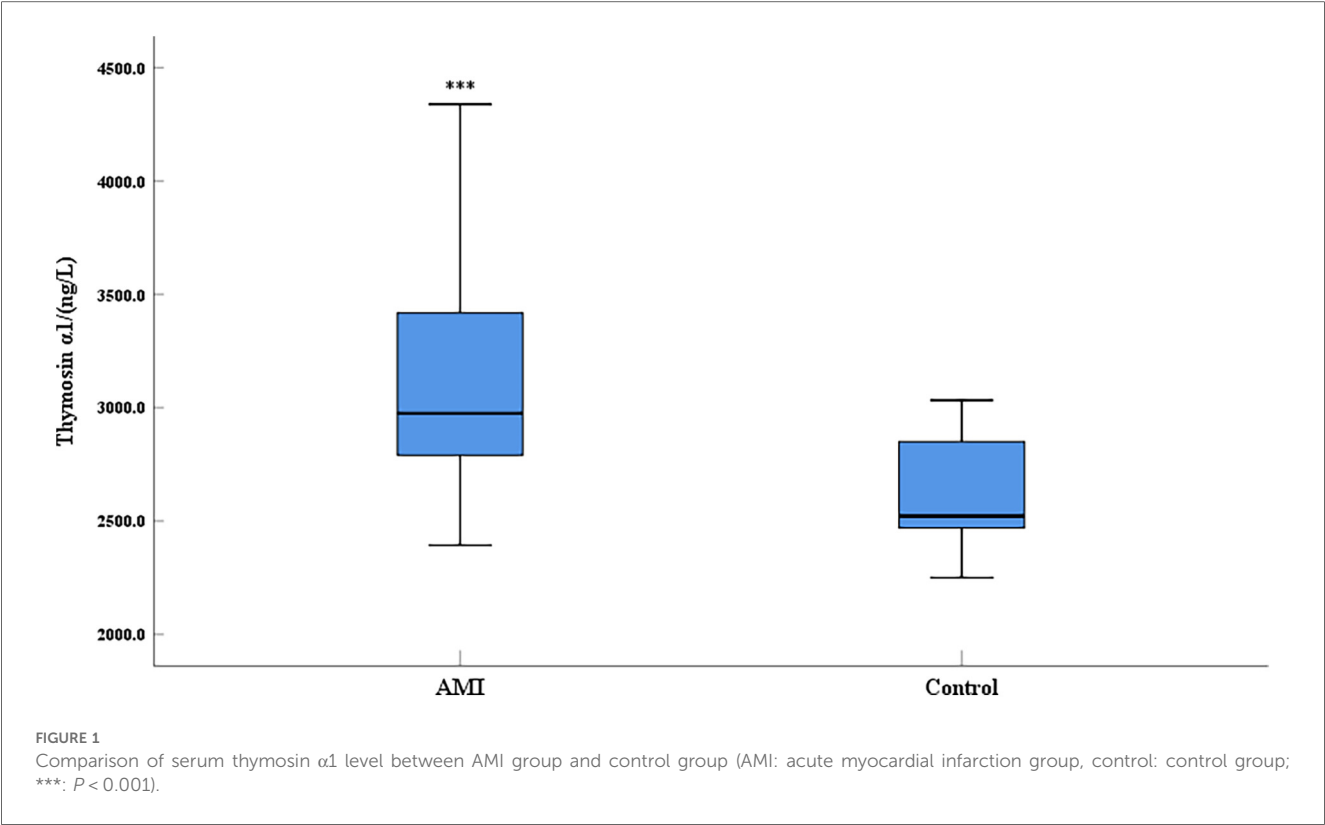


TABLE 2 Comparison of clinical features among different ejection fraction groups in AMI patients.

Variable	LVEF < 50% (<i>n</i> = 64)	LVEF ≥ 50% (<i>n</i> = 210)	<i>P</i> -value
Male (<i>n</i> , %)	52 (81.3)	154 (73.3)	0.199
Age (Year)	65.00 (60.00–72.75)	64.00 (54.00–72.00)	0.123
Height (m)	1.70 (1.65–1.75)	1.70 (1.63–1.74)	0.773
Weight (kg)	70.00 (60.00–75.00)	70.50 (65.00–80.00)	0.090
BMI (kg/m ²)	24.01 (21.97–25.93)	24.85 (23.14–26.90)	0.009
SBP (mmHg)	120 (106–136)	128 (112–141)	0.082
HR (bpm)	80 (71–94)	80 (73–86)	0.763
Smoking (<i>n</i> , %)	42 (65.6)	123 (58.6)	0.313
Drinking (<i>n</i> , %)	19 (29.7)	54 (25.7)	0.529
Diabetes (<i>n</i> , %)	13 (20.3)	45 (21.4)	0.848
Hypertension (<i>n</i> , %)	35 (54.7)	113(53.8)	0.902

SBP, systolic blood pressure; HR, heart rate.
Bold indicates statistical differences ($P < 0.05$).

(EF < 50%) were dramatically higher than those in the group with better cardiac function following AMI (EF ≥ 50%) (Table 4).

3.5 OR for AMI-related EF value using logistic regression analysis

Logistic regression analysis was conducted on all parameters including thymosin α 1 that were notably different by univariate analysis between the EF < 50% group and the EF ≥ 50% group. Risk factors with a remarkable difference in AMI-related EF value included Thymosin α 1 (OR = 1.000808, $P = 0.048$), NT-proBNP (OR = 0.999844, $P < 0.001$), and creatine kinase (OR = 0.999638, $P < 0.001$) (Table 5).

3.6 The ROC analysis of thymosin α 1 for predicting AMI-induced cardiac dysfunction

Thymosin α 1, NT-proBNP, and creatine kinase were analyzed using the ROC curve to evaluate their predictive value for EF decline caused by AMI. For predicting LVEF < 50% post-AMI, the area under the curve (AUC) of NT-proBNP was 0.714 (0.635–0.792, $P < 0.001$), with an optimal cutoff of 2,163 pg/ml, and the sensitivity and specificity were 60.9% and 73.4%, respectively (Figure 4). The AUC of creatine kinase was 0.724 (0.651–0.798, $P < 0.001$), with an optimal cutoff of 1,943 pg/ml, and the sensitivity and specificity were 78.6% and 65.7%, respectively (Figure 4). However, for predicting LVEF ≥ 50% in AMI patients during hospitalization, the AUC of Thymosin α 1 level was 0.614 (0.533–0.694, $P < 0.001$), with an optimal cutoff of 2,961.72 ng/L, and the sensitivity and specificity were 57.6% and 60.9%, respectively (Figure 5).

4 Discussion

This study primarily revealed a positive correlation between thymosin α 1 level and cardiac function following AMI. Specifically, higher expression levels of thymosin α 1 were associated with improved cardiac function after AMI. Additionally, the ROC curve analysis indicated that thymosin α 1 was an independent predictor of cardiac function (EF ≥ 50%) following AMI, with its sensitivity and specificity being 57.6% and 60.9%, respectively. Our team formerly reported the

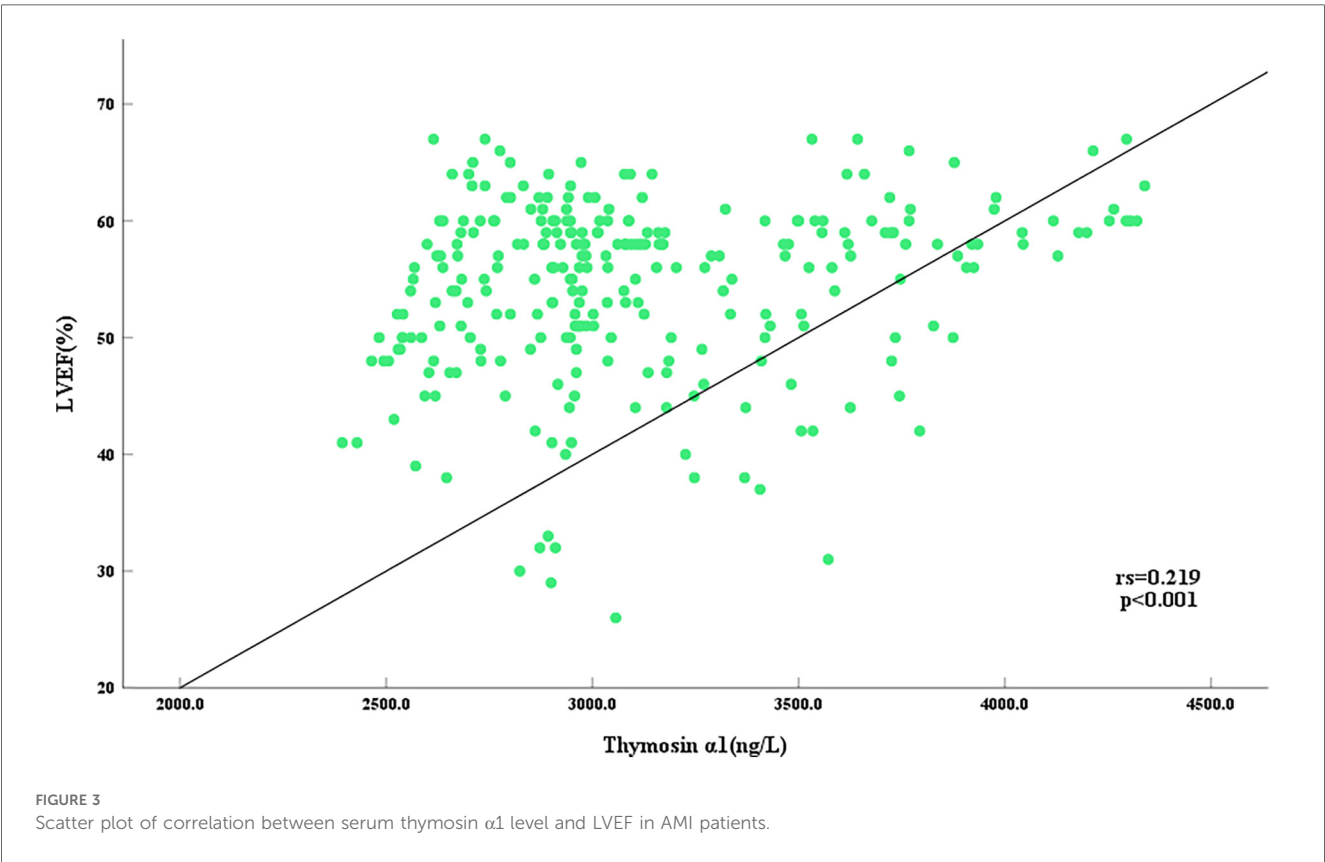
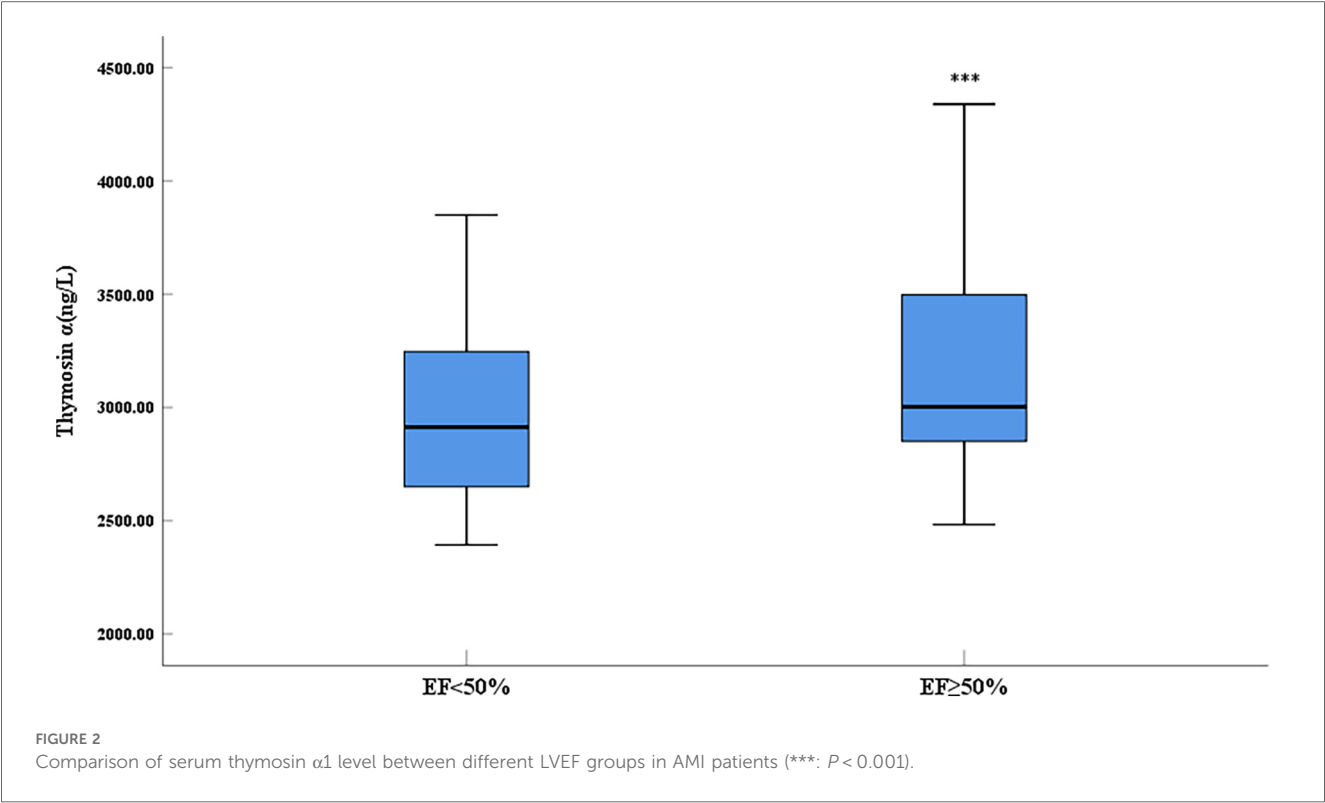


TABLE 3 Comparison of serum biochemical indexes among different ejection fraction groups in AMI patients.

Variable	LVEF < 50% (n = 64)	LVEF ≥ 50% (n = 210)	P-value
Hemoglobin (g/L)	141.0 (132.3–155.0)	146.0 (134.5–157.0)	0.190
Red blood cell (×10 ¹² /L)	4.64 (4.24–5.05)	4.71 (4.40–5.09)	0.414
Platelet (×10 ⁹ /L)	214.5 (182.8–256.0)	222.5 (187.0–262.3)	0.492
White blood cell (×10 ⁹ /L)	10.15 (8.65–12.68)	9.25 (7.68–11.03)	0.013
Neutrophil (%)	75.40 (61.50–83.60)	73.40 (62.63–81.13)	0.515
Lymphocyte (%)	18.40 (10.65–29.40)	18.15 (12.08–29.33)	0.530
Monocyte (%)	5.7 (4.3–7.2)	5.7 (4.5–7.2)	0.727
Neutrophil (×10 ⁹ /L)	7.7 (5.9–9.5)	6.5 (4.7–8.6)	0.019
Lymphocyte (×10 ⁹ /L)	1.6 (1.2–2.7)	1.8 (1.2–2.4)	0.870
Monocyte (×10 ⁹ /L)	0.6 (0.4–0.7)	0.5 (0.4–0.7)	0.131
Kalium (mmol/L)	3.7 (3.5–4.0)	3.8 (3.4–4.0)	0.696
Natrium (mmol/L)	138.0 (136.0–140.8)	139.0 (136.0–140.0)	0.818
Chlorinum (mmol/L)	103 (100–105)	102 (100–104)	0.468
Glucose (mmol/L)	7.06 (6.13–8.58)	6.45 (5.52–8.30)	0.001
Glycated hemoglobin (%)	6.0 (5.7–6.5)	6.0 (5.7–6.6)	0.670
Total Protein (g/L)	72 (68–77)	72 (69–76)	0.467
Albumin (g/L)	42.0 (40.0–43.3)	42.0 (40.0–44.0)	0.664
Alanine aminotransferase (U/L)	35.5 (24.3–54.5)	36.5 (27.0–46.3)	0.765
Creatinine (umol/L)	75.5 (60.0–94.8)	71.0 (62.0–81.0)	0.141
Urea nitrogen (mmol/L)	5.9 (4.9–7.8)	5.5 (4.8–6.7)	0.062
Uric acid (μmol/L)	373.0 (295.3–427.5)	353.0 (285.8–418.0)	0.107
Triglyceride (mmol/L)	1.085 (0.735–1.923)	1.380 (0.880–1.920)	0.095
Total cholesterol (mmol/L)	4.860 (4.093–5.605)	4.970 (4.280–5.720)	0.300
High-density lipoprotein (mmol/L)	1.07 (0.83–1.28)	1.02 (0.85–1.21)	0.463
Low-density lipoprotein (mmol/L)	3.09 (2.55–3.60)	3.18 (2.49–3.77)	0.180
Apolipoprotein A1 (g/L)	1.15 (0.97–1.28)	1.15 (1.04–1.28)	0.712
Apolipoprotein B (g/L)	0.91 (0.72–1.01)	0.95 (0.80–1.10)	0.106
Prothrombin time (s)	11.7 (10.5–11.9)	11.1 (10.5–11.9)	0.081
Apolipoprotein E (g/L)	3.76 (3.24–4.80)	3.76 (3.04–4.71)	0.710
Lipoprotein α (g/L)	23.35 (14.03–36.23)	16.40 (9.40–29.90)	0.077
International normalized ratio	1.02 (0.96–1.05)	0.96 (0.91–1.04)	0.081
Activated partial thromboplastin (s)	26.8 (23.9–29.6)	26.0 (22.9–28.5)	0.253
Thrombin time (s)	16.5 (15.9–17.4)	16.5 (15.8–17.2)	0.729
Fibrinogen (g/L)	2.699 (2.388–3.163)	2.636 (2.356–2.992)	0.172
D-dimer (mg/L)	0.39 (0.22–0.81)	0.32 (0.20–0.54)	0.095
C-reactive protein (g/L)	3.345(0.499–8.628)	1.110(0.499–6.820)	0.349

Bold indicates statistical differences ($P < 0.05$).

relationship between thymosin $\alpha 1$ and cardiac function after acute anterior ST-segment elevation myocardial infarction in the Chinese Journal of Interventional Radiology. Building upon this prior research, an expanded sample size and a broader range of AMI types were examined to draw more reliable conclusions. As far as we are aware, this study was the first to focus on thymosin $\alpha 1$ as a predictive marker for cardiac function following AMI, potentially offering a novel target for the early clinical detection and treatment of HF post-AMI.

A comparison was initially conducted between the control group and the AMI group, followed by a subgroup analysis based on whether the EF value from echocardiography during hospitalization post-AMI exceeded 50%. Myocardial ischemia, hypoxia, and even necrosis occur after AMI, leading to myocardial damage (19). Reperfusion injury of the myocardium after culprit vessel recanalization can further exacerbate myocardial damage (19). Therefore, during the early hospitalization period of AMI, some patients may begin to experience a decline in cardiac function, and the occurrence of HF is also possible (19). Clinically, the EF value from early echocardiography can be used to assess myocardial contractility and indirectly reflect cardiac function post-AMI. A lower EF value indicates worse cardiac function and a higher long-term risk of HF for AMI patients, which in turn suggests a poorer long-term prognosis (20, 21). Therefore, the subgroup analysis in this study based on the EF value during hospitalization post-AMI was justified. Our results indicate that in addition to thymosin $\alpha 1$, the traditional HF marker NT-proBNP and the myocardial injury marker creatine kinase were retained in the logistic multivariate analysis. NT-proBNP is a well-recognized marker of HF, with higher NT-proBNP values correlating with more severe HF. Previous studies have shown that BNP is associated with the larger size of myocardial infarction and the reduction of cardiac function, and is also related to the long-term adverse prognosis of AMI patients (22, 23). Our study concluded that there was a negative correlation between the expression level of NT-proBNP post-AMI and the EF value which was consistent with previous research. Furthermore, our study also identified the predictive value of creatine kinase for the reduction of cardiac function post-AMI. Creatine kinase is a traditional marker of myocardial damage area following AMI and is typically associated with the extent of myocardial damage post-AMI (24, 25), which explains

TABLE 4 Comparison of myocardial injury markers and serum thymosin $\alpha 1$ levels among different ejection fraction groups in AMI patients.

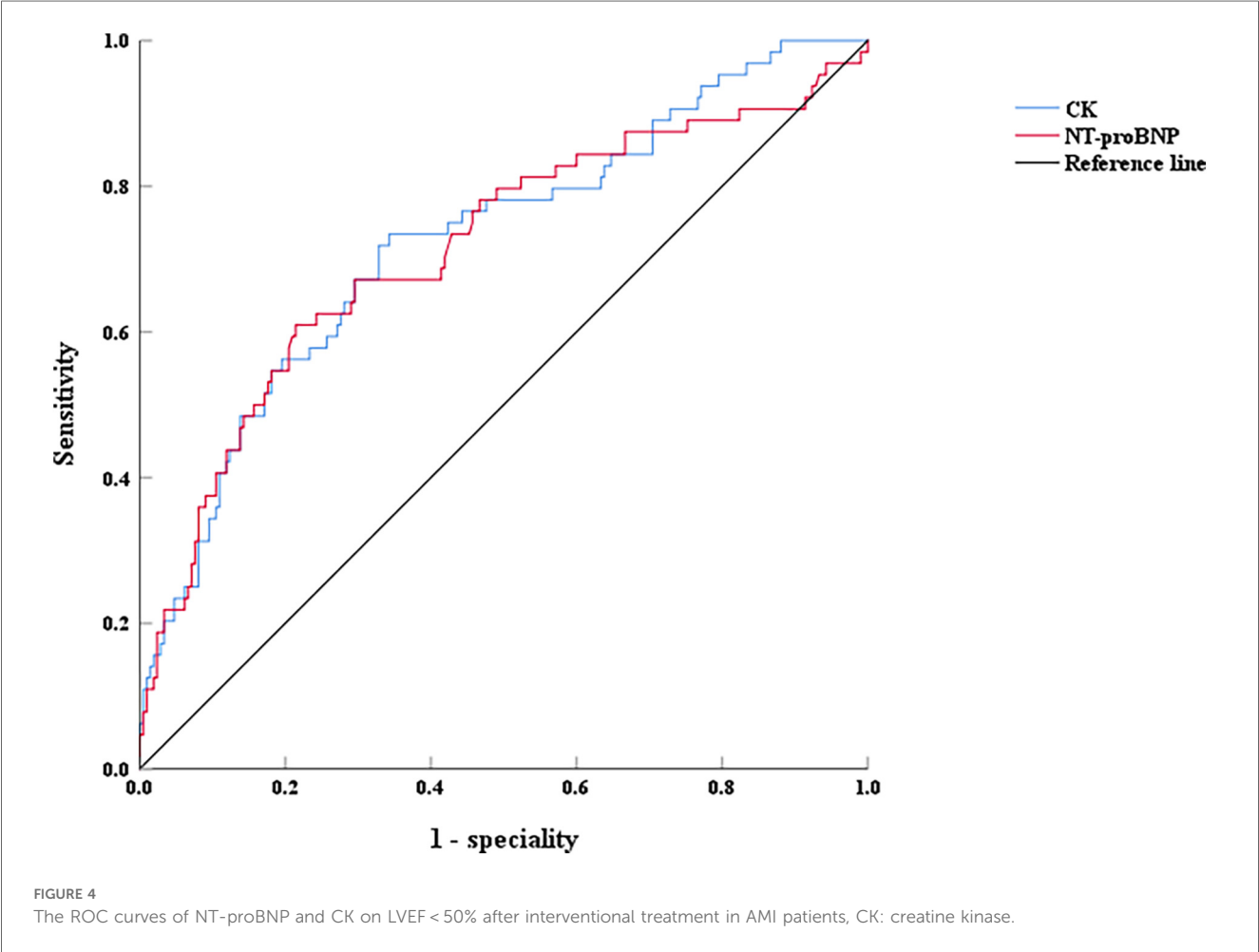
Variable	LVEF < 50% (n = 64)	LVEF ≥ 50% (n = 210)	P-value
Troponin I (μg/L)	158.86 (44.18–253.73)	46.67 (12.64–105.35)	<0.001
N-terminal pro-B-type natriuretic peptide (pg/ml)	2,943 (1,083–5,919)	972 (556–1,957)	<0.001
Aspartic aminotransferase (U/L)	129 (40–282)	92 (46–205)	0.155
Lactate dehydrogenase (U/L)	1,083 (679–1,858)	561 (373–810)	<0.001
Creatine kinase (U/L)	3,563 (1,668–5,353)	1,474 (630–2,717)	<0.001
Creatine kinase isoenzyme (U/L)	286.75 (133.50–413.13)	140.95 (63.75–239.08)	<0.001
Thymosin $\alpha 1$ (ng/L)	2,913.28 (2,648.35–3,247.05)	3,002.50 (2,846.48–3,497.68)	0.006

Bold indicates statistical differences ($P < 0.05$).

TABLE 5 Multivariate logistic regression analysis of LVEF $\geq 50\%$ after AMI.

Variable	B value	Wald χ^2	OR (95% CI)	P-value
Thymosin $\alpha 1$ (ng/L)	0.00081	3.899	1.000808 (1.000006–1.001611)	0.048
N-terminal pro-B-type natriuretic peptide (pg/ml)	−0.00016	13.250	0.999844 (0.999760–0.999928)	<0.001
Creatine kinase (U/L)	−0.00036	25.209	0.999638 (0.999496–0.999779)	<0.001

Bold indicates statistical differences ($P < 0.05$).



its predictive value for the reduction of cardiac function post-AMI. The retention of these traditional predictive markers of myocardial injury post-AMI for cardiac function in this study further underscores the reliability of the study’s conclusions.

Thymosin $\alpha 1$ is a bioactive peptide containing 28 amino acid residues, obtained by cleavage of prothymosin α (composed of 109 amino acid residues) with asparagine endopeptidase (26). It may be involved in cell cycle regulation and indirectly affect transcription and/or DNA replication processes (27). Thymosin $\alpha 1$ can bind to receptors on or near the membrane, triggering biological signal cascade reactions and participating in various physiological processes in the body, especially the regulation of immune responses (28). Currently, the inflammatory response plays a crucial role in the progression of AMI, which can lead to an increased infarct size and reduced cardiac function. Particularly, monocytes and macrophages significantly contribute

to the infarct size and remodeling after AMI. Previous studies have demonstrated that anti-inflammatory macrophages (M2-type macrophages) or cardiac repair macrophages *in situ* post-AMI can alleviate post-infarction myocardial inflammation by secreting anti-inflammatory cytokines, thereby reducing ventricular remodeling and ultimately improving cardiac function (29, 30). A study has shown that thymosin $\alpha 1$ can improve the efficacy of chemotherapy for breast cancer by reversing M2 polarization of efferocytosis-activated macrophages (31). In addition, the latest study indicated that both the exogenously provided and the adenovirus-produced thymosin $\alpha 1$ mediate the tumor-associated macrophages M2 polarization via CD8+ T cells, thereby enhancing the anti-tumor effect of adenovirus (32). Therefore, we could infer that the high expression of thymosin $\alpha 1$ post-AMI may promote the transformation of macrophages infiltrating the myocardium into anti-inflammatory (M2 type)

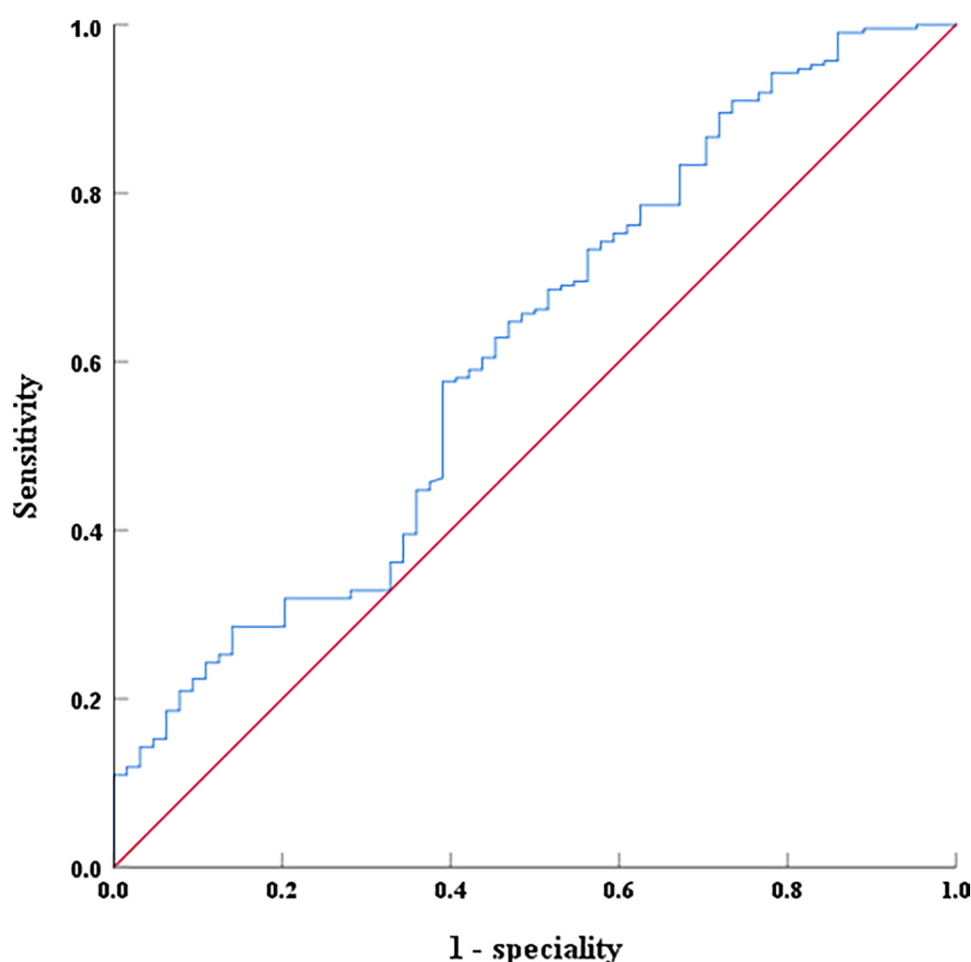


FIGURE 5
The ROC curves of serum thymosin $\alpha 1$ levels on LVEF $\geq 50\%$ after interventional treatment in AMI patients.

macrophages, thereby exerting a cardioprotective effect and improving cardiac function. This may explain the high expression of thymosin $\alpha 1$ observed in the group with better cardiac function following AMI in our study.

In addition to the association between monocytes/macrophages and cardiac function in AMI, recent studies have demonstrated that regulatory T cells (Tregs), acting as immune response modulators, can also exert cardioprotective effects after AMI and improve cardiac function by modulating the polarization of macrophages (33, 34). Previous studies have shown that in the treatment of cytomegalovirus infection, thymosin $\alpha 1$ could enhance the function of regulatory T cells (Tregs) and reduce Treg cell senescence (35). Furthermore, thymosin $\alpha 1$ could also promote the development and tolerance of Treg cells by regulating DC cells (36). In conclusion, it could be speculated that the up-regulation of thymosin $\alpha 1$ following AMI might reduce the myocardial inflammatory response by enhancing the function of Treg, thereby exerting a cardioprotective effect and improving cardiac function. However, the specific mechanisms underlying these effects require further investigation. To our knowledge, this was the

first report demonstrating that thymosin $\alpha 1$ expression was increased following AMI, with higher expression levels correlating with better cardiac function. Through this study, we have uncovered for the first time that thymosin $\alpha 1$ might serve as a protective factor against myocardial injury post-AMI. This finding could provide a novel target for clinically improving cardiac function following AMI and a new therapeutic strategy for reducing the incidence of HF post-AMI.

Although the sample size was increased compared with our previous study, it remained relatively small. The relatively small sample size of the control group and the larger sample size of the case group in our study may influence subsequent research outcomes, such as the moderate sensitivity and specificity of thymosin $\alpha 1$ (AUC = 0.614). Moreover, our study exclusively focuses on Chinese individuals. We plan to increase the total sample size, including additional control group samples and more diverse populations, to enable more comprehensive analysis. Secondly, the blood samples collected in this study were taken during patients' hospitalization. As myocardial infarction is a dynamic process, we will continue monitoring thymosin $\alpha 1$ levels after coronary artery revascularization to further validate

our research conclusions. Thirdly, we identified elevated thymosin $\alpha 1$ as a novel correlate of post-AMI cardiac function recovery. While its predictive power for thymosin $\alpha 1$ remains moderate (AUC = 0.614), this emerging biomarker warrants further investigation. Importantly, our data confirm the expected inverse relationships between LVEF and traditional markers, NT-proBNP (AUC = 0.714) and CK (AUC = 0.724), demonstrating methodological validity while contextualizing thymosin $\alpha 1$'s comparatively modest effect size. Subsequent investigations will incorporate serial thymosin $\alpha 1$ measurements at standardized pre-intervention and post-intervention timepoints to delineate its prognostic utility. And the specific protective mechanisms and underlying signaling pathways remain to be elucidated. Lastly, this was a retrospective study which resulted in deficiencies in the data collection process and possible selection bias. Future prospective multicenter studies should investigate thymosin $\alpha 1$ as a potential cardioprotective agent following AMI and elucidate its role in reducing HF incidence.

5 Conclusions

In conclusion, this study discovered that in comparison with the control group, the expression level of thymosin $\alpha 1$ in peripheral blood after AMI was notably elevated, and the better the cardiac function, the higher the expression level of thymosin $\alpha 1$. Thymosin $\alpha 1$ might be a biological indicator for the enhancement of cardiac function following AMI, and it could also be an important bioactive substance for the treatment of cardiac dysfunction after AMI. A prospective, randomized, and multicenter study should be devised to further validate the efficacy of thymosin $\alpha 1$ in improving cardiac function after AMI. Additionally, the two traditional biomarkers for cardiac function post-MI were still maintained in this study, indicating that these traditional predictive markers should not be disregarded.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LL: Investigation, Conceptualization, Funding acquisition, Writing – review & editing, Writing – original draft, Formal analysis, Methodology, Data curation, Resources. Z-FZ: Investigation, Writing – review & editing, Conceptualization, Writing – original draft, Data curation, Methodology, Formal analysis. XJ: Writing – review & editing, Writing – original draft, Visualization, Conceptualization, Validation. YC: Conceptualization, Data curation, Writing – review & editing, Writing – original draft. C-FH: Software, Writing – original draft, Writing – review & editing, Methodology, Formal analysis, Conceptualization. C-XS: Writing – review & editing, Conceptualization, Supervision, Writing – original draft, Validation, Visualization, Methodology, Formal analysis.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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