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ORIGINAL RESEARCH

Serum FGF23 and DPP4 Levels as Biomarkers for Coronary Artery Disease Severity in Type 2 Diabetic Patients with Coronary Heart Disease

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Objective: This study aimed to evaluate the relationship between serum fibroblast growth factor 23 (FGF23) and dipeptidyl peptidase 4 (DPP4) levels, and the severity and prognosis of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD).

Methods: A total of 113 patients with both T2DM and CHD (T2DM+CHD group) and 74 patients with T2DM without CHD (T2DM-only group) who underwent coronary angiography between January 2021 and June 2023 were enrolled. Based on Gensini scores, the T2DM+CHD group was further divided into three subgroups: mild (n=38), moderate (n=46), and severe (n=29) lesions. Serum levels of FGF23 and DPP4 were determined using enzyme-linked immunosorbent assay (ELISA). Correlation analysis and logistic regression were conducted to assess the association between biomarker levels and both disease severity and prognosis. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of these biomarkers.

Results: Serum levels of FGF23 and DPP4 were significantly higher in the T2DM+CHD group than in the T2DM-only group ($P<0.05$), and increased progressively with the severity of CAD ($P<0.05$). A positive correlation was observed between the levels of these biomarkers and CAD severity ($r=0.714$ for FGF23; $r=0.437$ for DPP4; $P<0.05$). Patients with poor prognosis exhibited increased left atrial diameter (LAD) and biomarker levels, along with reduced left ventricular ejection fraction (LVEF) ($P<0.05$). Multivariate analysis identified increased LAD, moderate-to-severe CAD, and elevated levels of FGF23/DPP4 as independent risk factors for poor prognosis, while higher LVEF served as a protective factor ($P<0.05$). Moreover, a combined predictive model using both FGF23 and DPP4 demonstrated superior diagnostic performance (AUC=0.921; $P<0.05$) compared to the use of each biomarker individually.

Conclusion: Elevated serum levels of FGF23 and DPP4 are significantly associated with both the severity and poor prognosis of CAD in patients with T2DM and CHD. These findings suggest that FGF23 and DPP4 may serve as valuable biomarkers for risk stratification and clinical decision-making in this patient population.

Keywords: diabetes mellitus, Coronary heart disease, coronary artery disease, prognosis, fibroblast growth factor 23, dipeptidyl peptidase-4

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by long-term abnormalities in glucose and lipid metabolism, which can lead to significant cardiovascular damage and an increased risk of developing cardiovascular diseases.[1] Coronary heart disease (CHD), an ischemic condition resulting from reduced coronary blood flow, is one of the most severe complications in T2DM patients and a leading cause of mortality.[2] T2DM patients with CHD tend to exhibit more severe vascular lesions; however, due to the often insidious onset of CHD, many patients miss the optimal treatment window, leading to poor clinical outcomes.[3] Currently, coronary angiography is considered the clinical "gold standard" for screening and diagnosing CHD. However, this method is invasive, expensive, and carries inherent risks, making it unsuitable for widespread screening.[4] Consequently, there is a pressing need to identify a more accessible and accurate method for assessing disease severity and prognosis. Fibroblast growth factor 23 (FGF23) is a hormone secreted by osteocytes that

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plays a crucial role in phosphate regulation. It enters the systemic circulation and affects multiple organs, including the kidneys and heart. Recent studies have demonstrated that elevated FGF23 levels are closely associated with cardiovascular remodeling.[5] Similarly, dipeptidyl peptidase-4 (DPP4) is a protease found on the surface of vascular endothelial cells, immune cells, and fibroblasts. Its substrates are involved in diverse physiological and pathological processes, such as nutrient metabolism, the maintenance of cardiovascular function, and immune-inflammatory responses.[6] Based on these findings, we hypothesize that serum levels of FGF23 and DPP4 may play a significant role in the progression of CHD in T2DM patients. However, to date, there have been no reports on using these biomarkers to predict the prognosis of patients with both T2DM and CHD. Therefore, the present study aims to analyze the relationship between serum FGF23 and DPP4 levels and the severity and prognosis of CHD in T2DM patients, with the goal of providing a reference for clinical treatment.

Materials and Methods

Materials

This retrospective study did not involve any disclosure of patient privacy and complies with relevant clinical ethical standards. Clinical data were collected from 113 patients with T2DM combined with CHD (T2DM + CHD group) and 74 patients with T2DM without CHD (T2DM-only group) who underwent coronary angiography at our hospital between September 2022 and June 2023. The patient recruitment process is illustrated in Figure 1. There were no statistically significant differences in age or gender between the two groups ($P > 0.05$). All participants were informed about the study objectives, and the study was approved by the hospital's ethics committee.

Inclusion criteria: (1) Patients with T2DM who met the clinical diagnostic criteria for T2DM.[7] Patients with CHD who met the clinical diagnostic criteria for CHD,[8] with the diagnosis confirmed by coronary angiography. Availability of complete clinical data. Exclusion criteria: (1) patients with malignant tumors or liver and kidney dysfunction; (2) patients

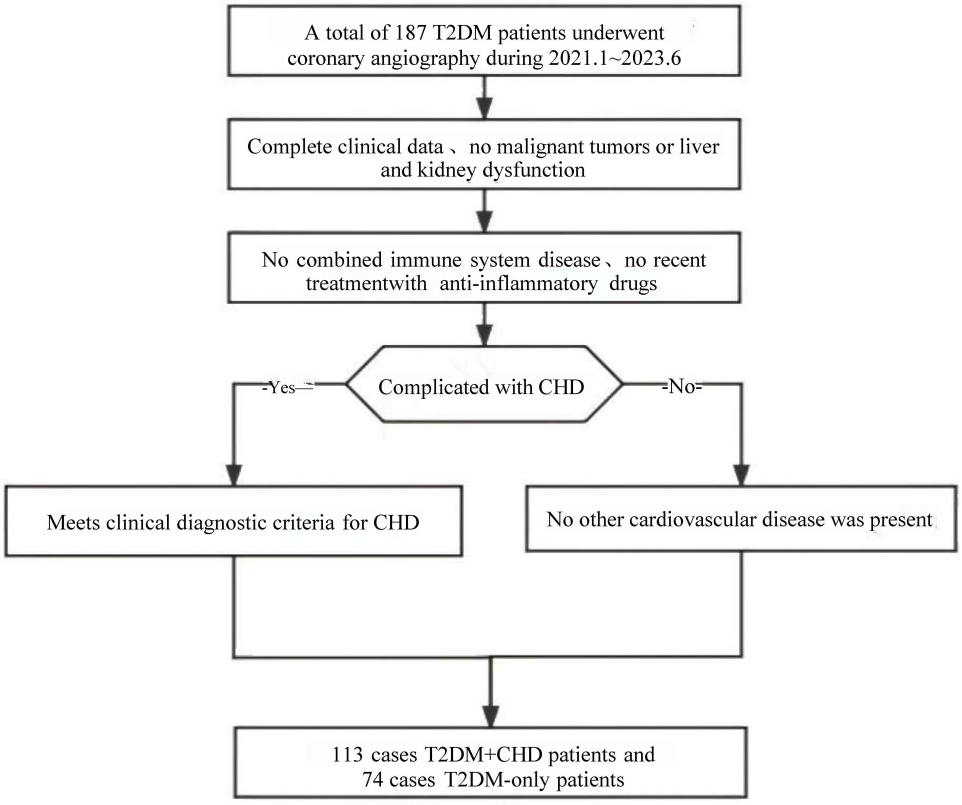

Figure 1 Flowchart of case collection.

with immune system diseases; (3) patients who recently received anti-inflammatory, anti-infective, or other medications that might affect the experimental results.

Research Methods

General Data Collection

The medical team collected comprehensive general information from the patient records, including age, gender, duration of T2DM, and histories of smoking, alcohol consumption, hypertension, and hyperlipidemia. In addition, laboratory data—including blood routine tests and biochemical indicators such as fasting blood glucose—were recorded. Echocardiographic measurements, specifically left atrial diameter (LAD) and left ventricular ejection fraction (LVEF), were also collected for further analysis.1.2.2 Serum FGF23 and DPP4 Level Detection

Residual serum samples from both T2DM-only patients and T2DM+CHD patients, collected at the time of hospital admission, were used for analysis. Serum FGF23 and DPP4 levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits from Shanghai Centon Bio-Technology Co., Ltd (product numbers QN-PS0319 and QY-PF9392, respectively). The assays were performed according to the manufacturer's instructions with a sample volume of 100 μL.

Coronary Artery Lesion Assessment

The extent of coronary artery lesions in patients with T2DM+CHD was assessed by two experienced physicians using the Gensini scoring system.[9] Among the 113 patients, 38 were classified as having mild lesions (Gensini score ≤20), 46 as having moderate lesions (20 < Gensini score ≤50), and 29 as having severe lesions (Gensini score >50).

Prognosis Follow-up

T2DM+CHD patients were followed for one year after discharge through online contact and outpatient visits, with the final follow-up conducted in July 2024 and a 100% follow-up rate. A poor prognosis was defined as rehospitalization or death resulting from adverse cardiovascular events during the follow-up period. Among the 113 patients, 41 experienced such events, yielding a poor prognosis incidence of 36.28%.

Statistical Analysis

SPSS 27.0 software was employed for statistical analysis. Quantitative data that followed a normal distribution, such as age and serum levels of FGF23 and DPP4, were expressed as mean ± standard deviation ($\bar{x}$±s), and group comparisons were performed using t-tests and F-tests. Categorical data, such as gender, were presented as n (%) and compared using χ^2-tests. Spearman correlation analysis was applied to evaluate the association between serum levels of FGF23 and DPP4 and the severity of coronary artery lesions in T2DM+CHD patients. Logistic regression analysis was used to identify factors influencing poor prognosis in these patients, and receiver operating characteristic (ROC) curve analysis, along with the area under the curve (AUC), was conducted to assess the clinical predictive value of serum FGF23 and DPP4 for poor prognosis. A P-value of <0.05 was considered statistically significant.

Results

Comparison of Serum FGF23 and DPP4 Levels Among the Two Groups

Serum FGF23 and DPP4 levels were significantly higher in the T2DM+CHD group compared to the T2DM-only group (P<0.05). See Table 1.

Comparison of Serum FGF23 and DPP4 Levels in T2DM+CHD Patients of Varying Coronary Artery Lesion Severity

Serum levels of FGF23 and DPP4 in T2DM+CHD patients increased significantly with the severity of coronary artery lesions (P < 0.05). See Table 2.

Table 1 Comparison of Serum FGF23 and DPP4 Levels in the Two Groups ($\bar{x}$±s)

Groups	n	FGF23 (ng/L)	DPP4 (ng/L)
T2DM-only group	74	247.84 ± 35.41	8.06 ± 2.57
T2DM+CHD group	113	362.64 ± 52.92	14.31 ± 5.02
t	–	16.403	9.889
P	–	0.000	0.000

Abbreviations: T2DM, Diabetes mellitus type 2; CHD, Coronary heart disease; FGF23, Fibroblast growth factor 23; DPP4, Dipeptidyl peptidase-4.

Table 2 Comparison of Serum FGF23 and DPP4 Levels in T2DM+CHD Patients with Different Degrees of Coronary Artery Lesions ($\bar{x}$± s)

Groups	n	FGF23 (ng/L)	DPP4 (ng/L)
Mild lesion group	38	300.68 ± 38.76	11.21 ± 3.16
Moderate lesion group	46	360.61 ± 47.15[a]	14.53 ± 4.90[a]
Severe lesion group	29	447.03 ± 68.79[ab]	18.02 ± 7.95[ab]
F	–	67.308	13.095
P	–	0.000	0.000

Notes: Compared with the mild lesion group, [a]P < 0.05; Compared with the moderate lesion group, [b]P < 0.05.
Abbreviations: FGF23, Fibroblast growth factor 23; DPP4, Dipeptidyl peptidase-4.

Correlation Analysis of Serum FGF23 and DPP4 Levels with Coronary Artery Lesion Severity in T2DM+CHD Patients

Spearman correlation analysis showed that serum levels of FGF23 and DPP4 in T2DM+CHD patients were positively correlated with the severity of coronary artery lesions (r = 0.714, 0.437, both P < 0.05).

Comparison of Serum FGF23 and DPP4 Levels in T2DM+CHD Patients of Different Prognoses

Serum levels of FGF23 and DPP4 in the poor prognosis group of T2DM+CHD patients were significantly higher than those in the good prognosis group (P < 0.05). See Table 3.

Comparison of General Data in T2DM+CHD Patients of Different Prognoses

There were no statistically significant differences in age, gender, duration of diabetes, smoking history, drinking history, hypertension history, or fasting blood glucose levels between T2DM+CHD patients with different prognoses (P > 0.05). However, compared to the good prognosis group, patients with poor prognosis exhibited a significantly lower left

Table 3 Comparison of Serum FGF23 and DPP4 Levels in T2DM+CHD Patients with Different Prognosis ($\bar{x}$±s)

Groups	n	FGF23 (ng/L)	DPP4 (ng/L)
Good prognosis group	72	334.03 ± 41.29	12.25 ± 3.26
Poor prognosis group	41	412.87 ± 63.28	17.92 ± 7.48
t	–	8.006	5.581
P	–	0.000	0.000

Abbreviations: FGF23, Fibroblast growth factor 23; DPP4, Dipeptidyl peptidase-4.

ventricular ejection fraction (LVEF), a larger left atrial diameter (LAD), and a higher proportion of moderate to severe coronary artery lesions ($P < 0.05$). See Table 4.

Analysis of Factors Influencing the Prognosis of T2DM+CHD Patients

A multivariate logistic regression model was established with poor prognosis (no = 0, yes = 1) as the dependent variable and the severity of coronary artery lesions (mild = 0, moderate to severe = 1), left atrial diameter (LAD), left ventricular ejection fraction (LVEF), and serum levels of FGF23 and DPP4 as independent variables. The analysis demonstrated that increased LAD, moderate to severe coronary artery lesions, and elevated serum levels of FGF23 and DPP4 were significant risk factors for poor prognosis in T2DM+CHD patients ($P < 0.05$), whereas a higher LVEF served as a protective factor ($P < 0.05$). See Table 5.

Analysis of the Predictive Value of Serum FGF23 and DPP4 Levels for Poor Prognosis in T2DM+CHD Patients

ROC curves were plotted for the prediction of poor prognosis in T2DM+CHD patients based on serum FGF23 and DPP4 levels.See Figure 2. The results showed that the AUCs for FGF23 and DPP4 predicting poor prognosis were 0.837 and 0.797, respectively, and the combined AUC for predicting poor prognosis was 0.921, which was significantly better than either marker alone (Zcombined-FGF23 = 2.055, P = 0.040; Zcombined-DPP4 = 2.442, P = 0.015). See Table 6.

Table 4 Comparison of General Data of T2DM+CHD Patients in Different Prognosis [($\bar{x}$±s) /n (%)]

Clinical Indicators	Good Prognosis Group (n=72)	Poor Prognosis Group (n=41)	χ^2/t	P
Age (years old)	57.43 ± 7.24	58.69 ± 8.03	0.855	0.395
Gender				
Male	42 (58.33)	26 (63.41)	0.281	0.596
Female	30 (41.67)	15 (36.59)		
T2DM course (year)	7.38 ± 1.79	7.75 ± 1.84	1.046	0.298
History of Smoking	29 (40.28)	24 (58.54)	3.497	0.061
History of drinking	27 (37.50)	20 (48.78)	1.368	0.242
History of hypertension	18 (25.00)	17 (41.46)	3.312	0.069
History of hyperlipidemia	17 (23.61)	14 (34.15)	1.456	0.227
Fasting plasma glucose (mmol/L)	7.73 ± 2.47	8.19 ± 2.56	0.939	0.350
LAD (mm)	33.27 ± 3.01	40.81 ± 3.12	12.635	0.000
LVEF (%)	63.17 ± 6.49	55.64 ± 5.61	6.220	0.000
Degrees of coronary artery lesions				
Mild lesion	33 (45.83)	5 (12.20)	22.234	0.000
Moderate lesion	30 (41.67)	16 (39.02)		
Severe lesion	9 (12.50)	20 (48.78)		

Abbreviations: T2DM, Diabetes mellitus type 2; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 5 Logistic Regression Analysis of Factors Affecting the Adverse Prognosis in T2DM +CHD Patients

Influencing factors	β	SE	Wald χ^2	P	OR	95%CI
LAD	0.512	0.197	6.745	0.009	1.668	1.134~2.454
LVEF	−0.524	0.164	10.218	0.001	0.592	0.429~0.816
Degrees of coronary artery lesions	0.573	0.169	11.505	0.001	1.774	1.274~2.471
FGF23	0.917	0.254	13.048	0.000	2.503	1.521~4.118
DPP4	0.726	0.208	12.186	0.000	2.067	1.385~3.107

Abbreviations: FGF23, Fibroblast growth factor 23; DPP4, Dipeptidyl peptidase-4; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

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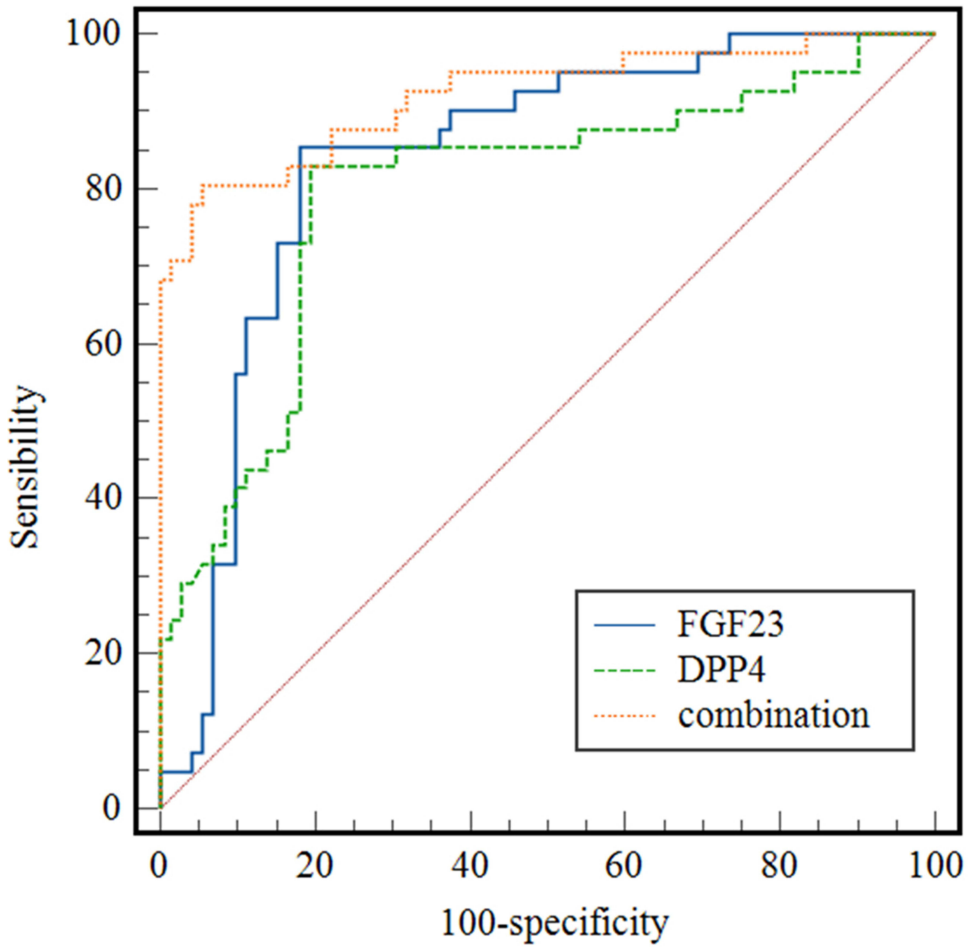

Figure 2 ROC curve of serum FGF23 and DPP4 predicting poor prognosis in T2DM with CHD patients.

Discussion

Long-term dysregulation of glucose and lipid metabolism, coupled with increased insulin resistance, renders T2DM patients highly susceptible to cardiovascular lesions, which can lead to coronary artery atherosclerosis, vascular rupture, and other cardiovascular diseases.[10] The presence of CHD is a leading cause of disability and mortality in T2DM patients. Therefore, identifying new biomarkers is crucial for improving outcomes in patients with T2DM and concomitant CHD.

Studies have shown that FGF23 can bind to related receptors, induce myocardial hypertrophy, affect the contractile function of myocardial cells, and increase the incidence of arrhythmia.[11] Moreover, some studies have reported that serum FGF23 levels are closely associated with the degree of coronary artery stenosis and lesion severity in patients with acute coronary syndrome, and that FGF23 serves as an independent risk factor for the onset of this condition.[12] Additionally, since endothelial dysfunction is a key clinical manifestation of coronary artery disease, research has found a significant correlation between serum FGF23 levels and endothelial function indicators in these patients.[13] Our study reached similar conclusions to those reported in previous research. Serum FGF23 levels in T2DM+CHD

Table 6 Value Analysis of Serum FGF23 and DPP4 in Predicting Poor Prognosis of T2DM+CHD Patients

Index	AUC	Cut-off Value	95%CI	Sensibility (%)	Specificity (%)	*Youden* Exponent
FGF23	0.837	369.48 ng/L	0.756~0.900	85.37	81.94	0.673
DPP4	0.797	16.08 ng/L	0.711~0.867	82.93	80.56	0.635
Combination	0.921	–	0.855~0.963	80.49	94.44	0.749

Abbreviations: T2DM, Diabetes mellitus type 2; CHD:Coronary heart disease; FGF23, Fibroblast growth factor 23; DPP4, Dipeptidyl peptidase-4.

patients were significantly elevated and increased progressively with the severity of coronary artery lesions, suggesting that FGF23 may play a role in both the occurrence and progression of coronary artery lesions in these patients. Therefore, it is speculated that elevated FGF23 levels may mediate endothelial damage and contribute to the progression of coronary artery lesions in T2DM+CHD patients.

DPP4 is a soluble protein widely present in the body, and research shows that DPP4 in the heart mainly originates from microvascular endothelial cells.[14] Numerous studies have demonstrated that DPP4 inhibitors can effectively improve endothelial function, reduce inflammation and oxidative stress, and exert beneficial effects on cardiovascular diseases such as coronary artery calcification and atherosclerosis.[15] Herman et al[16] found, through animal and in vitro experiments, that DPP4 protein expression was significantly elevated in the serum of atherosclerotic mice, and that inhibition of DPP4 expression reduced the accumulation of senescent cells and the secretion of coagulation factors, thereby enhancing plaque stability. Other studies have also reported that elevated serum DPP4 levels are detectable in patients with coronary artery disease, and that its expression correlates with inflammatory factor levels in the body.[17] Consistent with the above-mentioned studies, in this study, serum DPP4 levels were significantly elevated in T2DM +CHD patients, and levels were positively correlated with the severity of coronary artery lesions, suggesting that DPP4 level may be involved in the development and pathological progression of CHD in T2DM patients, likely related to its mediation of cardiovascular endothelial damage and inflammatory responses.

Numerous studies have demonstrated a strong association between FGF23, DPP4, and patient prognosis. For example, Kallmeyer et al[18] reported that high serum FGF23 levels were detected in acute coronary syndrome patients who experienced adverse cardiovascular events after discharge, highlighting its potential as a predictor of short-term adverse outcomes. Similarly, other research has shown that inhibiting DPP4 expression can significantly reduce both the mortality of T2DM-related cardiovascular diseases and the incidence of adverse events following percutaneous coronary intervention.[19] In our study, serum FGF23 and DPP4 levels were markedly higher in the poor prognosis group compared to the good prognosis group, and logistic regression analysis confirmed that elevated levels of these biomarkers are independent risk factors for poor prognosis in T2DM+CHD patients. These findings suggest that serum FGF23 and DPP4 are closely related to the occurrence of adverse outcomes in this patient population. ROC curve analysis further revealed that the combined use of serum FGF23 and DPP4 yielded an AUC of 0.921 for predicting poor prognosis in T2DM+CHD patients, surpassing the predictive value of either biomarker alone. When serum FGF23 levels exceed 369.48 ng/L or DPP4 levels exceed 16.08 ng/L, the risk of adverse outcomes increases significantly. These findings underscore the importance for clinicians to promptly adjust treatment strategies to proactively manage and reduce the risk of poor prognosis in these patients.

While our findings suggest that FGF23 and DPP4 are promising biomarkers for assessing CAD severity and predicting prognosis, our study is limited by a relatively small sample size and the absence of mechanistic investigations. Future research should involve larger cohorts and delve into the underlying molecular pathways.

Conclusion

Serum levels of FGF23 and DPP4 are significantly associated with both the severity of CAD and the prognosis in T2DM +CHD patients, highlighting their potential as non-invasive biomarkers. Further studies are warranted to elucidate their mechanistic roles and to validate these findings in larger, multi-center cohorts.

Data Sharing Statement

The original contributions presented in the study are included in the article.

Ethics Approval

This study, involving human participants, was conducted in accordance with the ethical standards of the Medical Ethics Committee of The Affiliated Shunde Hospital of Jinan University and the 1964 Helsinki Declaration. Informed consent was obtained from each patient or their guardian, as documented on the signed consent forms.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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