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Research Article

Predictive Value of Circulating Renalase for Left Ventricular Hypertrophy in Non-Dialysis CKD Patients

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Abstract

Background: Chronic kidney disease (CKD) is a global health burden strongly associated with cardiovascular morbidity and mortality. Left ventricular hypertrophy (LVH), a hallmark of cardiac remodeling in CKD, is a major predictor of heart failure and sudden cardiac death. Current biomarkers fail to capture early remodeling risk adequately, underscoring the need for novel predictors. ***Objective***: To evaluate serum renalase levels in non-dialysis CKD patients (stages 3–5) and determine its predictive value for cardiac remodeling, particularly LVH. ***Methods***: A cross-sectional study was conducted, including 89 CKD patients, 40 heart failure patients, and 37 healthy controls. Demographic, clinical, biochemical, and echocardiographic data were collected. Serum renalase was measured using ELISA. Logistic regression models and receiver operating characteristic (ROC) analyses were applied to assess the independent predictive value of renalase for cardiac remodeling. ***Results***: CKD patients with cardiac remodeling had significantly higher renalase levels compared to those without (36.31ng/mL *vs*. 33.05ng/mL, p=0.009). ROC analysis yielded an AUC of 0.656, with a cutoff value of >37.64 ng/mL (sensitivity, 47.5%; specificity, 83.3%). Logistic regression confirmed renalase as an independent predictor of remodeling (adjusted OR: 1.105, 95% CI=1.036–1.178, p=0.002), alongside uncontrolled hypertension (OR=3.462, p=0.014). ***Conclusions***: Serum renalase is independently associated with LVH in non-dialysis CKD patients and demonstrates moderate discriminative ability with high specificity. These findings highlight renalase as a promising biomarker for early cardiac risk stratification in CKD, warranting further longitudinal validation and standardization of measurement protocols.

Keywords: Biomarkers; Hypertrophy; Kidney diseases; Left ventricle; Renalase; Ventricular remodeling.

القيمة التنبؤية للرينياليز في المصل لضمور البطين الأيسر لدى مرضى الكلى المزمن غير الخاضعين للغسيل الكلوي

الخلاصة

الخلفية: مرض الكلى المزمن (CKD) هو عبء صحي عالمي مرتبط بشكل كبير بأمراض القلب والأوعية الدموية والوفيات. تضخم البطين الأيسر (LVH)، وهو علامة مميزة لإعادة تشكيل القلب في مرض الكلى المزمن، يعد مؤشرا رئيسيا لفشل القلب والموت المفاجئ في القلب (LVH). المؤشرات الحيوية الحالية تفشل في التقاط مخاطر إعادة التشكيل المبكرة بشكل كاف، مما يؤكد الحاجة إلى متنبئات جديدة. **الهدف**: تقييم مستويات إنزيم الرينياليز في المصل لدى مرضى الكلى المزمن (المراحل 3–5) وتحديد قيمته التنبؤية لإعادة تشكيل القلب، وخاصة LVH. **الطرائق**: أجريت دراسة مقطعية شملت 89 مريضا بمرض الكلى المزمن، و40 مريضا بفشل قلبي، و37 ضابطا صحيا. تم جمع بيانات ديموغرافية وسريرية وكيميائية حيوية وتخطيط صدى القلب. تم قياس إنزيم الرينياليز في المصل باستخدام ELISA. تم تطبيق نماذج الانحدار اللوجستي وتحليلات ROC لتقييم القيمة التنبؤية المستقلة لإنزال الرينالاس في إعادة تشكيل القلب. **النتائج**: كان لدى مرضى الكلى المزمن الذين خضعوا لإعادة تشكيل القلب مستويات أعلى بشكل ملحوظ من الكلى مقارنة بمن لم يكونوا (p=0.009). أظهر تحليل ROC قيمة AUC بمقدار 0.656، مع قيمة حط <37.64 نانوغرام/مل (الحساسية، 47.5٪؛ النوعية، 83.3٪). أكد الانحدار اللوجستي أن الرينالاز هو متنبئ مستقل لإعادة التشكيل (معدل p=0.002، CI=1.036–1.178 ،95٪ :OR: 1.105)، إلى جانب ارتفاع ضغط الدم غير المسيطر عليه (p=0.014). **الاستنتاجات**: يرتبط إنزيم الرينياليز المصلي بشكل مستقل ب LVH لدى مرضى الكلى المزمن غير الخاضعين لغسيل الكلى ويظهر قدرة تمييزية متوسطة مع خصوصية عالية. تسلط هذه النتائج الضوء على وجود الرينالاز كمؤشر حيوي واعدة لتصنيف المخاطر القلبية المبكرة في مرض الكلى المزمن، مما يستدعي المزيد من التحقق الطولي وتوحيد بروتوكولات القياس.

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INTRODUCTION

Chronic kidney disease (CKD) is a global health concern, affecting 10–15% of the adult population and accounting for substantial morbidity and mortality worldwide [1]. Among the complications of CKD, cardiovascular disease (CVD) remains the predominant cause of death, with an estimated 40–50% of patients with advanced CKD succumbing to cardiovascular events rather than progressing to end-stage renal disease (ESRD) [2]. The prevalence and severity of CVD in CKD increase with disease progression, manifesting even in early stages and further intensifying in those with diminished renal function [3]. This persistent elevation in cardiovascular risk is only partially explained by traditional risk factors such as hypertension, diabetes, and dyslipidemia and is

compounded by non-traditional CKD-associated factors, including chronic inflammation, endothelial dysfunction, mineral bone disorder, oxidative stress, and the accumulation of uremic toxins [2]. A key cardiac manifestation of CKD is pathological remodeling, characterized principally by left ventricular hypertrophy (LVH) and myocardial fibrosis, collectively termed "uremic cardiomyopathy" [2,3]. LVH is recognized as both a prevalent structural abnormality and a potent prognostic marker in CKD, predicting progression to heart failure (HF), arrhythmias, and sudden cardiac death [2, 3]. Recent cardiac imaging studies underscore the frequency and severity of LVH and other remodeling indices in CKD populations, with LVH prevalence reaching up to 80% in Stage 3–5 CKD, including those not yet requiring dialysis [3-5]. Importantly, the presence of LVH confers an independent increase in both cardiovascular and all-cause mortality, yet established risk prediction tools and conventional biomarkers often fail to capture the full spectrum of risk in this complex population [3]. Traditional risk stratification in CKD relies on measures such as estimated glomerular filtration rate (eGFR), albuminuria, and established cardiac biomarkers (e.g., NT-proBNP, troponins), but these exhibit significant limitations. Both the KDIGO 2024 and prior guidelines recognize the pressing need for novel biomarkers that can provide sensitive, specific, and pathophysiologically grounded risk stratification of cardiovascular complications in non-dialysis CKD [6]. Renalase (RNLS), a secreted flavin adenine dinucleotide (FAD)-dependent enzyme and cytokine, was first identified in 2005 as a kidney- and heart-derived protein with potential roles in blood pressure regulation and cardiac protection [7]. Originally posited to degrade circulating catecholamines, subsequent research has substantially expanded the functional repertoire of renalase to include novel enzymatic (α-NAD(P)H oxidase/anomerase) and non-enzymatic, cytokine-like signaling functions—particularly the activation of pro-survival and anti-inflammatory pathways via the PMCA4b receptor and MAPK signaling network [7]. Crucially, renalase is highly expressed not only in the kidney but also in cardiac tissue, where it responds to stress signals such as hypoxia and inflammation and exhibits regulatory mechanisms involving transcription factors (STAT3, SP1, and HIF-1α) and microRNAs [7]. Recent mechanistic studies reveal that renalase expression is dynamically modulated in response to renal injury, CKD progression, and myocardial stress, positioning it at the intersection of renal and cardiac pathophysiology [8]. The alteration of circulating renalase levels in CKD and cardiovascular disease has become a subject of intense investigation. Notably, studies in animal models and human cohorts have documented that renalase deficiency or impaired signaling accelerates both renal and cardiac injury [9,10]. Conversely, exogenous or cardiac-specific overexpression of renalase produces significant anti-hypertrophic and anti-fibrotic effects in models of CKD-induced cardiac remodeling [11, 12]. This expanding body of evidence suggests that renalase plays a key role in modulating cardiac structure and function, particularly in the context of uremic cardiomyopathy. Within the last five years, a growing number of clinical and translational studies have proposed serum/plasma renalase as a potentially powerful biomarker for renal dysfunction, CKD progression, and cardiovascular complications, including LVH [8,13]. In non-dialysis CKD patients (stages 3–5), both cross-sectional and longitudinal data support an association between elevations in serum renalase levels and severity of renal impairment, as well as with the presence and burden of LVH, coronary artery disease, and adverse outcomes such as hospitalization and mortality [8,13]. Notably, logistic regression analyses and receiver operating characteristic (ROC) curve approaches have demonstrated that renalase exhibits independent and sometimes superior predictive value for adverse cardiac remodeling when compared to traditional metrics (e.g., eGFR, BP, albuminuria, or standard cardiac biomarkers) [13]. Recent evidence documented that higher serum renalase at baseline in pre-dialysis CKD predicts not only progression of CKD but also hospitalizations and all-cause mortality, with effects robust to adjustment for age, comorbidity, diabetes, and hypertension. Furthermore, experimental and clinical studies converge in demonstrating that elevated renalase levels correlate with cardiac structural changes and the spectrum of cardiac remodeling (hypertrophy and fibrosis) independently of other risk factors [13]. This sets renalase apart as not only a marker of renal dysfunction but also as a pathophysiologically relevant signal for early, subclinical cardiac injury in CKD. Despite its clear promise, renalase has not yet been integrated into routine clinical risk stratification instruments, in part due to methodological variability across assays, the complexity of its circulating forms (free vs. total), and unresolved mechanistic questions regarding its context-specific elevations [8]. This study addresses important gaps in the current understanding of biomarker-based risk assessment in CKD. Specifically, it provides a direct evaluation of serum renalase levels as a predictor of LVH in non-dialysis CKD patients (stages 3–5), a subgroup with substantial unmet needs in cardiovascular risk stratification. By applying robust statistical approaches, including logistic regression and receiver operating characteristic (ROC) analysis, the study establishes the independent predictive value of renalase. It quantifies its diagnostic performance through discrimination metrics such as area under the curve, sensitivity, and specificity. In addition, the work situates renalase within the broader context of recent advances in biomarker research, CKD epidemiology, and evolving clinical guidelines, highlighting its translational potential for early intervention and individualized patient management. By focusing on a non-dialysis CKD population, the study demonstrates the potential of

renalase not only as a marker of renal dysfunction but also as a predictor of cardiovascular remodeling before the onset of end-stage renal disease. This dual role positions renalase as a promising tool for earlier and more precise identification of patients at risk of cardiac complications, thereby offering a framework for improved risk stratification and targeted therapeutic strategies.

METHODS

Study design and settings

A cross-sectional observational study was conducted at private clinics specializing in nephrology, cardiology, and internal medicine located in Thi-Qar Governorate, Iraq. The data collection and analysis phase spanned from October 2024 to April 2025. It targeted three groups: the primary group included patients with CKD stages 3 to 5 who are non-dialysis-dependent, with all stages classified according to KDIGO guidelines [14]. The estimated glomerular filtration rate (eGFR) for each participant was calculated based on data from the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN), using the CKD-EPI Creatinine Equation (online calculator) after at least two consecutive doctor visits [15]. The second group consisted of participants diagnosed with heart failure (HFpEF, HFmrEF, and HFrEF) according to the European Society of Cardiology (ESC) guidelines and confirmed through transthoracic echocardiography (TTE) [16]. The third group includes healthy controls.

Sample size calculation

The sample size for the CKD group was calculated using G-Power software version 3.1, aiming for 95% power to detect a moderate to large effect size at a 5% significance level. The event-per-variable ratio was approximately 8.4, with predictors well specified. A total of 89 participants with CKD were included. Additionally, 40 participants diagnosed with heart failure (HF) and 37 healthy volunteers were enrolled; all underwent identical procedures and measurements as the clinical groups.

Inclusion criteria

For CKD patients aged between 18 and 75 years, both sexes, with a diagnosis of stable CKD stages 3 to 5 lasting more than 3 months, and eGFR below 60 mL/min. For HF patients, those diagnosed with heart failure for more than 6 months. Both sexes are eligible. Age between 40 and 75 years old.

Exclusion criteria

For CKD patients, unstable clinical conditions or significant comorbidities, including recent renal surgery within the past 6 months, kidney transplantation, coronary artery bypass grafting (CABG), vascular surgery, unstable angina, malignancies, immune disorders, ongoing immunosuppressive therapy, chronic antibiotic use, or renal replacement therapy. Recent diagnosis of CKD within the past 3 months. Confirmed infection with HIV, hepatitis viruses, or tuberculosis. Substance abuse involving drugs or alcohol. Incomplete clinical or laboratory data. Cognitive impairment prevents completing questionnaires. Pregnancy or lactation. Inability to provide informed consent. For HF patients, the exclusion criteria include unstable cardiac conditions, including recent (within the past month) episodes of arrhythmia, acute coronary syndrome, or acute decompensated heart failure. Presence of coexisting infections, CKD, immune-mediated diseases, or malignancies. Inability to provide informed consent.

Demographic and clinical data

This study employed structured clinical interviews in conjunction with the collection of demographic and clinical data. Data included patients' names, ages, sexes, BMI, BSA, and blood pressure measurements, which were obtained in a seated position after a 5-minute rest using a calibrated sphygmomanometer on the upper right arm. Hypertension (HT) was diagnosed according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, with classification into controlled and uncontrolled subgroups based on blood pressure readings [17]. Patients with diabetes mellitus were classified according to the American Diabetes Association (ADA) criteria and further divided into controlled and uncontrolled diabetes mellitus (DM) subgroups, based on treatment type and disease duration [18,19]. All data were documented using Microsoft Excel version 16.

Laboratory analysis

Blood samples were collected from all patients (approximately 6 mL) of venous blood, drawn from the elbow. For each patient, 1 mL of serum was stored in Eppendorf tubes at -40°C for approximately 2 months until renalase analysis was performed. Quantitative sandwich enzyme-linked immunoassay, following the manufacturer's instructions (Shanghai YL Biotech Co., Ltd., Bionet, 96 tests, China). Samples were examined using a microplate reader (Stat Fax 4200, Awareness Technology Inc., USA) to measure absorbance at 450 nm. A standard curve was constructed to determine concentration based on the given known absorbance values from the standards. Kit with a sensitivity of 0.51 ng/mL. The second part of the blood serum is used for measuring serum urea and creatinine; lipid profile (including total cholesterol, LDL, HDL, and triglycerides); serum calcium; hemoglobin; vitamin D3 (with levels categorized as optimal (> 30 ng/mL),

insufficient (15-30 ng/mL), and deficient (< 15 ng/mL) [20]; and HbA1c.

Echocardiography

Transthoracic Echocardiography (TTE) study for all participants, utilizing the 3D Auto LV quantification application, a powerful combination of Philips and TOMTEC innovations with advanced automation (computer workstations, Imaging Systems, Germany), by a trained specialist echocardiographer; data reported according to American Society of Echocardiography (ASE) and European Society of Cardiology (ESC) guidelines [16,21]. For measuring left ventricular mass (LVM) indexed to body surface area (BSA), an online Omni calculator was utilized. TTE data, including Left Ventricular End-Diastolic Diameter (LVEDD), Interventricular Septum Thickness (IVSD), and P-wave dispersion (PWD), as well as sex and BSA, were entered into the Omni calculator to obtain Left Ventricular Mass Index (LVMI) and Relative Wall Thickness (RWT), along with ejection fraction percentage, for all participants. Normal RWT is less than 0.45. Left ventricular (LV) geometry was categorized as normal (normal LVMI, normal RWT), concentric remodeling (normal LVMI, high RWT), eccentric LVH (high LVMI, normal RWT), or concentric LVH (high LVMI, high RWT). The reference range for LVH: LVMI > 115 g/m² in men and > 95 g/m² in women [22].

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. Written informed consent was obtained from all study participants before their inclusion. Patient confidentiality and data protection were maintained throughout the study. This research study has been reviewed and approved by the Research Ethics Committee of the College of Pharmacy, Mustansiriyah University (Approval number: 74, Reference number: 174, Date: June 3, 2024).

Statistical analysis

All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.3 (GraphPad Software, San Diego, CA, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), while non-normally distributed data are expressed as median with interquartile range (IQR). Categorical variables are summarized as frequencies and percentages. For group comparisons: One-way ANOVA with post hoc Tukey's test was applied to normally distributed continuous variables. The Kruskal–Wallis test with post hoc Dunn's test was used for non-normally distributed variables. A chi-square test or Fisher's exact test was employed for categorical variables, as appropriate. Associations between serum renalase levels and cardiac remodeling were evaluated using binary logistic regression analysis. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). To assess the robustness of renalase as an independent predictor, sequential adjustment models were constructed: Model 1 adjusted for demographic variables (age, sex, BMI). Model 2 additionally adjusted for comorbidities (hypertension, diabetes mellitus, dyslipidemia, and disease duration). Model 3 further adjusted for treatment control of hypertension and diabetes. The diagnostic performance of renalase for predicting cardiac remodeling was evaluated using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), optimal cutoff values, sensitivity, and specificity based on the Youden index. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

The study included 37 controls, 89 CKD patients, and 40 HF patients. Participants with CKD and HF were significantly older than controls ($p< 0.001$), with the majority of controls being < 45 years, while most CKD and HF patients were ≥ 45 years. Sex distribution was comparable across groups ($p= 0.561$). BMI was significantly higher in the HF group compared to the controls ($p= 0.030$), although the prevalence of obesity did not differ significantly ($p= 0.136$). Marital status showed a higher proportion of married individuals in CKD and HF groups ($p= 0.022$). Educational attainment was markedly lower in CKD and HF groups, with illiteracy most prevalent in HF patients (90.0%) compared to controls (54.1%) ($p< 0.001$). Blood pressure differed significantly: CKD patients had higher systolic BP than controls, while HF patients had lower diastolic BP compared to CKD ($p< 0.001$ and $p= 0.001$, respectively). Glycemic control was impaired in both CKD and HF groups, with higher HbA1c compared to controls ($p< 0.001$). Hemoglobin levels were lowest in patients with CKD, while those with HF had intermediate values ($p< 0.001$). Renal function markers (urea, creatinine, eGFR) showed profound impairment in CKD compared to both controls and HF (all $p< 0.001$). Vitamin D3 deficiency was strikingly more common in CKD (71.9%) and HF (17.5%) compared to controls (0%) ($p< 0.001$). Regarding lipids, LDL cholesterol was higher in CKD than HF ($p= 0.007$), while HDL cholesterol was significantly lower in CKD compared to controls ($p= 0.010$). Total cholesterol and triglycerides did not differ significantly among groups. Overall, CKD and HF groups demonstrated older age, lower education, higher cardiometabolic burden, anemia, vitamin D deficiency, and impaired renal function compared to controls. CKD patients showed the most severe biochemical

derangements, while HF patients exhibited intermediate abnormalities, particularly in BMI, glycemic control, and renal indices. These findings underscore the systemic metabolic and cardiovascular risk clustering in CKD and HF populations relative to healthy controls, as seen in Table 1.

Table 1: Baseline demographic, clinical, and biochemical characteristics of control, chronic kidney disease (CKD), and heart failure (HF) groups

Variables	Control	CKD	HF	*p*-value
Number	37	89	40	-
Age (year)ø	38.05±11.85	55.48±13.39*	60.68±10.17*	<0.001[a]
<45 yearsφ	27(73)	16(18.0)	3(7.5)	
45 – 65 yearsφ	9(24.3)	51 (57.3)	22(55)	<0.001[b]
>65 yearsφ	1(2.7)	22(24.7)	15(37.5)	
*Sex*φ				
Female	14(37.8)	39(43.8)	20(50)	0.561[b]
Male	23(62.2)	50(56.2)	20(50)	
BMI (kg/m^2)ø	25.75±5.05	26.83±4.8	28.48±3.24*	0.030[a]
Non-obeseφ	31(83.8)	69(77.5)	26 (65)	0.136[b]
Obeseφ	6(16.2)	20(22.5)	14(35)	
*Marital status*φ				
Married	31(83.8)	83(93.3)	40(100)	0.022[c]
Single	6(16.2)	6(6.7)	0(0.0)	
*Education levels*φ				
Illiterate	20(54.1)	56 (62.9)	36(90)	<0.001[c]
Primary/secondary	2(5.4)	27(30.3)	4(10)	
College or higher	15(40.5)	6(6.7)	0(0.0)	
*Education status*φ				
Low	17(45.9)	64(71.9)	33(82.5)	<0.001[c]
Middle	9(24.3)	22(24.7)	7(17.5)	
High	11(29.7)	3(3.4)	0(0.0)	
Active smoker	8(21.6)	1(1.1)	4(10)	<0.001[b]
BSA (m^2)ø	1.91±0.25	1.85±0.24	1.95±0.17	0.054[a]
SBP (mmHg)ø	128.97±2.96	149.51±26.07*	132.15±22.71#	<0.001[a]
DBP (mmHg)ø	84.03±11	88.08±15.82	77.95± 2.57#	0.001[a]
HbA1c (%)ø	4.88±0.35	6.78±2.12*	7.09± 2.22*	<0.001[a]
Hemoglubin (mg/dL)ø	13.61±1.47	9.29±2.20*	12.73±0.88*#	<0.001[a]
Serum calcium (mg/dL)	7.95±0.52	8.32±0.73*	8.0±0.69	0.006[a]
Vitamin D3 levels (ng/mL)ə	28(21.6-34.5)	9.1(6.9-16.5)*	20.1(16.7-27)#	<0.001[d]
Deficientφ	0(0.0)	64(71.9)	7(17.5)	
Insufficientφ	23(62.2)	21(23.6)	27(67.5)	<0.001[b]
Optimalφ	14(37.8)	4(4.5)	6(15)	
Urea (mg/dL)ə	38(34.5-41)	102(77-136.5)*	47.5(44-60.8)*#	<0.001[d]
Creatinine (mg/dL)ə	0.8(0.7-0.9)	2.8(2.4-5.6) *	0.9(0.8-1.3)#	<0.001[d]
eGFR (mL/min)ə	121(103.5-132.5)	19(10.5-27) *	74.5(66.3-97.8)*#	<0.001[d]
Total cholesterol (mg/dL)	163(140.5-171.5)	155(119.5-175)	155.5(143.0-193.8)	0.224[d]
Serum LDL (mg/dL)	65(60.0-77)	73(64.5-86.5)	66.5(52.3-79.5)#	0.007[d]
Serum HDL (mg/dL)	55(46.0-63.5)	48(42-53) *	50(45.3-58.8)	0.010[d]
Serum triglycerides (mg/dL)	160(125-183)	134(102-198.5)	129(110-177.3)	0.305[d]

Data presentation: ø indicates mean±standard deviation, φ indicates number (percentage), ə indicates Median (interquartile range). * Indicate $p<0.05$ compared to the control group, # Indicate $p<0.05$ between HF and CKD groups. [a] One-way ANOVA with *post-hoc* Tukey test, [b] Chi-square test, [c] Fisher-Freeman-Halton exact test, [d] Kruskal-Wallis test with *post hoc* Dunn test.

Among the 89 CKD and 40 HF patients, hypertension was highly prevalent in both groups (94.4% vs. 100%, $p= 0.323$), and diabetes mellitus was more frequent in HF patients (82.5%) compared to CKD (66.3%), though not statistically significant ($p= 0.060$). Nearly all patients were on antihypertensive therapy, but uncontrolled hypertension was significantly more common in CKD (69.0%) than HF (45.0%) ($p= 0.010$). Patterns of antihypertensive use differed: beta-blockers were prescribed more frequently in HF (75.0% vs. 48.3%, $p= 0.005$), while calcium channel blockers (34.8% vs. 0%, $p< 0.001$) and centrally acting agents (15.7% vs. 0%, $p= 0.008$) were used exclusively in CKD. Neprilysin inhibitors were markedly more common in HF (32.5% vs. 2.2%, $p< 0.001$). The use of antidiabetic medications was similar between groups ($p= 0.651$), but SGLT2 inhibitors were significantly more frequent in HF (52.5% vs. 28.1%, $p= 0.007$). Insulin use was higher in CKD (42.7% *vs*. 25.0%), though this did not reach statistical significance ($p= 0.054$). The median disease duration was short in both groups (1 year, IQR 0–2 in CKD vs. 1–2 years in HF, $p= 0.347$), with most patients having a disease history of < 2 years (77.5% in CKD *vs*. 90.0% in HF, $p= 0.092$). Both CKD and HF patients exhibited a high burden of hypertension and diabetes, but their therapeutic profiles diverged. CKD patients were more likely to have uncontrolled hypertension and to receive calcium channel blockers or centrally acting agents. In contrast, HF patients were more frequently treated with beta-blockers, neprilysin inhibitors, and SGLT2 inhibitors. These differences reflect disease-specific management strategies and highlight the distinct therapeutic priorities in CKD versus HF populations, as seen in Table 2.

Table 2: Comorbidities, antihypertensive and antidiabetic medication use, and disease duration in chronic kidney disease (CKD) and heart failure (HF) patients

Variables	CKD	HF	*p*-value
Number	89	40	-
Comorbid disease			
Hypertension	84(94.4)	40(100)	0.323[a]
DM	59(66.3)	33(82.5)	0.060[a]
Patients receiving anti-hypertension treatment	85(95.5)	38(95)	0.900[a]
Uncontrolled hypertension	58(69)	18(45)	0.010[a]
Anti-hypertensive medications			
ACI/ARB	49(55.1)	29(72.5)	0.061[a]
Beta-blockers	43(48.3)	30(75)	0.005[a]
Calcium channel blockers	31(34.8)	0(0.0)	<0.001[b]
Centrally acting	14(15.7)	0(0.0)	0.008[b]
Vasodilator	8(9.0)	0(0.0)	0.057[b]
Diuretics	22(24.7)	5(12.5)	0.115[a]
Neprilysin inhibitor	2(2.2)	13(32.5)	<0.001[a]
Anti-dyslipidemic medications	22(24.7)	15(37.5)	0.138[a]
Antidiabetic medications	61(68.5)	29(72.5)	0.651[a]
Sulfonylurea	5(5.6)	2(5.0)	0.999[a]
Biguanide	7(7.9)	0(0.0)	0.098[b]
DPP4I	3(3.4)	4(10)	0.202[a]
SGL2I	25(28.1)	21(52.5)	0.007[a]
Insulin	38(42.7)	10(25)	0.054[a]
Disease duration (year)	1.0(0–2)	1.0(1–2)	0.347[c]
≤2 years	69(77.5)	36(90)	0.092[a]
>2 years	20(22.5)	4(10)	
Cardiac remodeling	59(66.3)	37(92.5)	<0.001[a]

NI: neprilysin inhibitor, DPP4I: dipeptidyl peptidase-4 inhibitor. Results are expressed as frequency (percentage), and median (interquartile range). [a] indicates chi-square test, [b] indicates Fisher's exact test, [c] indicates Mann-Whitney U test.

Compared to controls, both CKD and HF patients showed significantly higher left ventricular mass indices (LVMI) (median 108.5 and 115.2 g/m² vs. 67.9 g/m², $p< 0.001$), indicating the presence of left ventricular hypertrophy. Relative wall thickness (RWT) was also increased in CKD (0.4 [0.4–0.5]) compared to controls (0.4 [0.3–0.4], $p< 0.001$), while HF patients exhibited a broader distribution (0.4 [0.3–0.5]), which significantly differed from CKD ($p< 0.001$). Ejection fraction (EF) was preserved in controls (66.0%) and mildly reduced in CKD (62.0%), but was markedly impaired in HF (35.0%), with significant differences across all groups ($p< 0.001$). Serum renalase levels were higher in HF patients (41.6 ng/mL) compared to controls (28.4 ng/mL, $p= 0.021$), while CKD patients displayed intermediate values (35.5 ng/mL), as seen in Figure 1. Both CKD and HF groups demonstrated structural cardiac remodeling (increased LVMI and RWT) relative to controls, but only HF patients exhibited severe systolic dysfunction (reduced EF). Elevated renalase levels in HF suggest a potential compensatory or maladaptive response to heightened cardiovascular stress. These findings highlight the progressive interplay between renal dysfunction, cardiac remodeling, and neurohormonal activation across CKD and HF populations, as seen in Figure 1. In patients with chronic kidney disease, serum renalase levels were significantly higher among those with cardiac remodeling compared to those without [36.31 ng/mL (IQR: 30.96–41.99) vs. 33.05 ng/mL (IQR: 29.04–37.49), $p= 0.009$]. Receiver operating characteristic (ROC) curve analysis demonstrated a modest discriminative capacity of renalase for predicting cardiac remodeling, with an area under the curve (AUC) of 0.656.

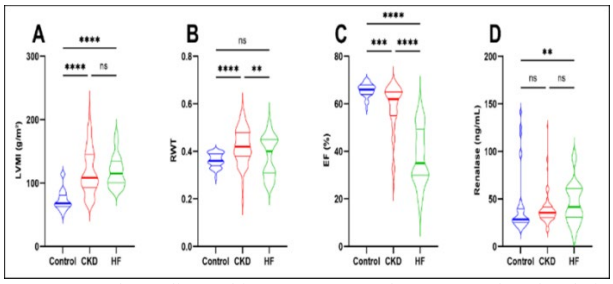

Figure 1: Echocardiographic parameters and serum renalase levels in control, chronic kidney disease (CKD), and heart failure (HF) groups. **A**) LVMI, **B**) RWT, **C**) EF, and **D**) renalase.

The optimal cutoff value of >37.64 ng/mL yielded a sensitivity of 47.46% and a specificity of 83.33%, indicating that while elevated renalase levels are associated with cardiac remodeling, the marker demonstrates higher specificity than sensitivity in this cohort, as seen in Table 3 and Figure 2. Logistic regression analysis was performed to identify predictors of cardiac remodeling in patients with chronic kidney disease.

Table 3:Assessment of the levels and diagnostic utility of renalase as a predictor of cardiac remodeling in CKD patients

Renalase (ng/mL)		AUC	*p*-value	Cut off	SN	SP
No CR	CR					
33.05 (29.04-37.49)	36.31 (30.96-41.99)	0.656	0.009	>37.64	47.46	83.33

CR: cardiac remodeling, AUC: area under the curve, SN: sensitivity, SP: specificity.

Among the examined variables, uncontrolled hypertension emerged as a significant independent predictor, with an odds ratio (OR) of 3.462 (95% CI: 1.292–9.277, p= 0.014). Renalase levels were also independently associated with cardiac remodeling, showing an OR of 1.066 (95% CI: 1.008–1.127, p= 0.024).

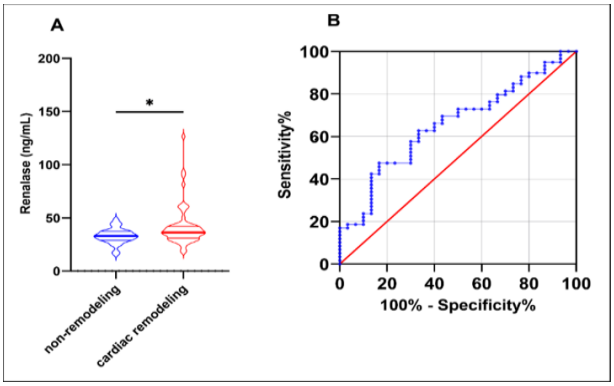

Figure 2: **A**) Violin plot of renalase levels in CKD patients; **B**) ROC curve of renalase as a predictor of cardiac remodeling in CKD patients.

Other factors, including sex, age, body mass index, diabetes mellitus, dyslipidemia, diabetic control, and estimated glomerular filtration rate (eGFR), did not reach statistical significance. Notably, hypertension (OR: 8.923, 95% CI: 0.950–83.784, p= 0.055) and disease duration (OR: 1.356, 95% CI: 0.993–1.850, p= 0.055) demonstrated borderline associations with cardiac remodeling, as seen in Table 4.

Table 4: Logistic regression analysis of the predictors of cardiac remodeling in CKD patients

Variables	β	OR (95%CI)	*p*-value
Sex (female)	-0.788	0.455 (0.186-1.112)	0.084
Age	0.021	1.021 (0.988-1.055)	0.219
BMI	-0.049	0.952 (0.868-1.044)	0.295
Hypertension	2.189	8.923 (0.950-83.784)	0.055
Uncontrolled hypertension	1.242	3.462 (1.292-9.277)	0.014
DM	0.636	1.889 (0.756-4.721)	0.173
Disease duration	0.304	1.356 (0.993-1.850)	0.055
eGFR	-0.007	0.993 (0.955-1.033)	0.740
Dyslipidemia	-0.441	0.643 (0.266-1.557)	0.328
Diabetic control	0.087	1.090 (0.606-1.962)	0.773
Renalase	0.064	1.066 (1.008-1.127)	0.024

To further evaluate the robustness of renalase as a predictor of cardiac remodeling, sequential logistic regression models were constructed. In the unadjusted model, renalase was significantly associated with cardiac remodeling (OR: 1.066, 95% CI: 1.008–1.127, p= 0.024). This association remained significant after adjustment for demographic variables (Model 1: OR: 1.061, 95% CI: 1.005–1.121, p= 0.033), and after additional adjustment for comorbidities, including hypertension, diabetes mellitus, dyslipidemia, and disease duration (Model 2: OR: 1.068, 95% CI: 1.007–1.132, p= 0.029). Importantly, in the fully adjusted model that incorporated treatment control for hypertension and diabetes (Model 3), renalase demonstrated an even stronger association with cardiac remodeling (OR: 1.105, 95% CI: 1.036–1.178, p= 0.002). These findings indicate that renalase is an independent and consistent predictor of cardiac remodeling across multiple adjustment models, as seen in Table 5.

Table 5: Sequential multivariable logistic regression models demonstrating renalase as an independent predictor of cardiac remodeling in CKD patients

Model	β	OR (95%CI)	*p*-value
Unadjusted	0.064	1.066 (1.008-1.127)	0.024
Model 1[a]	0.059	1.061 (1.005-1.121)	0.033
Model 2[b]	0.065	1.068 (1.007-1.132)	0.029
Model 3[c]	0.100	1.105 (1.036-1.178)	0.002

[a] Adjusted for demographic (age, sex, and BMI); [b] Adjusted for model 1 variables and diseases (hypertension, DM, dyslipidemia, and disease duration); [c] Adjusted for models 1 and 2 variables and treatment control (hypertension and DM).

DISCUSSION

The present study reinforces the epidemiological observation that left ventricular hypertrophy (LVH) is a pervasive and prognostically significant consequence of CKD, with prevalence and severity increasing progressively from stage 3 through 5 in non-dialyzed populations [2, 3, 5]. This aligns with recent large-scale imaging cohorts and clinical registry data, which indicate that nearly half of CKD stage 3–5 patients without dialysis exhibit LVH on echocardiography or cardiac MRI, independent of preceding or concurrent hypertension, diabetes, or overt heart failure [2,4]. Mechanistically, pathological cardiac remodeling in CKD—including LVH and myocardial fibrosis—results from a multifactorial interplay of pressure and volume overload, neurohormonal activation (RAAS, sympathetic overactivity), metabolic disturbances, chronic inflammation, and the toxic sequelae of accumulating uremic solutes [2,8]. Notably, uremic toxins, persistent inflammation, oxidative stress, and aberrant signaling through the RAAS and sympathetic pathways induce maladaptive changes in cardiomyocyte growth and extracellular matrix remodeling, culminating in concentric or, in advanced cases, eccentric LVH with increased ventricular stiffness and an increased risk of arrhythmias [2]. Recent imaging biomarker studies have demonstrated that both hypertrophy and myocardial fibrosis can be detected early in CKD stages 2–4, even before clinical symptoms develop, supporting the need for improved early risk stratification [2,4]. In this study, we demonstrated that serum renalase levels are significantly elevated in patients with chronic kidney disease (CKD) who exhibit cardiac remodeling, particularly left ventricular hypertrophy (LVH). Compared with CKD patients without remodeling, those with remodeling had higher renalase concentrations (36.31 ng/mL vs. 33.05 ng/mL, p = 0.009), and receiver operating characteristic (ROC) analysis confirmed a modest but significant discriminative ability (AUC= 0.656). At a cutoff of >37.64 ng/mL, renalase achieved high specificity (83.3%) but moderate sensitivity (47.5%), suggesting that while not universally sensitive,

elevated renalase levels strongly indicate the presence of remodeling when detected. Logistic regression analysis further established renalase as an independent predictor of cardiac remodeling in CKD patients. In univariate models, renalase was significantly associated with remodeling (OR: 1.066, 95% CI: 1.008–1.127, p= 0.024). Importantly, this association persisted across sequential multivariable models adjusting for demographic factors, comorbidities, and treatment control. In the fully adjusted model, renalase retained a robust predictive value (OR: 1.105, 95% CI: 1.036–1.178, p= 0.002), underscoring its independence from traditional risk factors, including age, sex, BMI, diabetes, and eGFR. Alongside renalase, uncontrolled hypertension emerged as a strong predictor (OR: 3.462, 95% CI: 1.292–9.277, p= 0.014), highlighting the dual contribution of hemodynamic stress and biochemical signaling in driving cardiac remodeling. Recent prospective cohort and cross-sectional studies provide compelling data supporting renalase as a context-specific biomarker predicting both renal and cardiovascular outcomes, especially in non-dialysis CKD. In a five-year cohort of pre-dialysis CKD patients, serum renalase was independently associated with CKD progression, cardiovascular hospitalizations, and all-cause mortality, exceeding many conventional risk factors (e.g., hypertension, diabetes, Charlson score, eGFR) in adjusted models [8]. These findings mirror prior observations in CKD cohorts, transplant recipients, and cardiac populations, where elevated renalase tracks with lower GFR, higher cardiovascular risk, and poor survival [8]. Notably, recent ROC analysis reveals that serum renalase can predict left ventricular hypertrophy and cardiac remodeling with respectable sensitivity and specificity, yielding AUCs that are comparable to or superior to those of established biomarkers (e.g., natriuretic peptides, sST2, galectin-3, GDF-15) [13]. For example, in heart failure populations stratified by ejection fraction, renalase AUC for ischemia or adverse remodeling prediction approached 0.8–0.9, with higher discriminatory power in HFrEF and in the setting of advanced CKD [3,13]. Furthermore, elevated renalase has been shown to correlate with increased left ventricular mass, reduced ejection fraction, and myocardial fibrosis as measured by imaging and molecular profiling [2]. The consistency of these findings is bolstered by supportive mechanistic data from animal models, which show that genetic or pharmacological enhancement of renalase expression decreases cardiac hypertrophy and interstitial fibrosis. In contrast, knockout or deficiency models exhibit accelerated pathology, linking the biomarker signal to an underlying pathophysiology [23-25]. However, it is important to note that the relationship between serum renalase levels and disease risk is not always linear or unidirectional. Both extreme elevations and deficiencies in renalase have been associated with worse outcomes in various disease states (renal and extra-renal)—a pattern suggesting context-specific, potentially compensatory or maladaptive responses [26-28]. This emphasizes the necessity of clinical interpretation within a broader disease model and emphasizes the necessity of standardization in renalase assays for translational applications.

Clinical and Translational Implications

The determination that serum renalase is an independent and robust predictor of cardiac remodeling in non-dialysis CKD has significant translational implications. Early identification of subclinical cardiac remodeling—before the onset of heart failure or irreversible myocardial fibrosis—is vital for personalized management, targeted intervention, and effective secondary prevention in CKD populations [2,3]. Current clinical practice lacks reliable serum markers for predicting LVH and remodeling before overt heart failure develops. Our data suggests that renalase, particularly when combined with clinical variables such as blood pressure control, may help identify high-risk patients who could benefit from intensified cardiovascular monitoring or early therapeutic interventions. The relatively high specificity of renalase at the identified cutoff supports its utility as a confirmatory marker, while its integration into multiple-marker panels may enhance sensitivity.

Strengths and Limitations

A key strength of this study is the use of robust statistical modeling, including multivariable logistic regression and ROC analysis, to establish the independent predictive role of renalase. The inclusion of a non-dialysis CKD cohort also highlights the biomarker's relevance in earlier disease stages, where intervention may have the most significant impact. Several limitations should be acknowledged when interpreting these findings. First, the cross-sectional design precludes causal inference, and the modest sample size may limit the generalizability of results to broader CKD populations. Second, although renalase emerged as an independent predictor of cardiac remodeling, its moderate AUC indicates that it should be considered as part of a multiple-marker strategy rather than a standalone diagnostic tool. Third, the study population was restricted to non-dialysis CKD stages 3–5, limiting extrapolation to earlier CKD, dialysis, transplant, or non-CKD cardiovascular cohorts. Finally, while our findings support a strong association between renalase and cardiac remodeling, these relationships remain correlative; interventional and longitudinal studies are required to establish causality and clarify the therapeutic potential of targeting the renalase pathway.

Conclusion

This study's demonstration that serum renalase is an independent and robust predictor of left ventricular

hypertrophy in non-dialysis CKD stages 3–5 establishes renalase as a clinically and biologically novel biomarker at the intersection of renal and cardiac disease. Going beyond conventional metrics, renalase captures both the systemic and tissue-specific perturbations that underlie uremic cardiomyopathy and LVH, offering a pathway for early risk stratification and personalized intervention. Further research to standardize measurement, define context-specific thresholds, and integrate renalase into clinical practice may transform the management of cardiovascular risk in CKD populations, shifting the paradigm toward proactive monitoring and individualized treatment.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

All datasets generated during and/or analysed during the current study are available in the Zenodo repository, https://doi.org/10.5281/zenodo.17501774. The authors have full access to the study data in electronic files.

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