

## Prevalence, Phenotypic Characteristics, and Predictors of Subclinical Cardiovascular Disease in Adults with Cardiovascular–Kidney–Metabolic Syndrome: An Analytical Cross-Sectional Study Using Cardiac Biomarkers and Echocardiography

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### Abstract

**Background:** Cardiovascular–kidney–metabolic (CKM) syndrome represents an interconnected spectrum of metabolic, renal, and cardiovascular abnormalities. Detection of subclinical cardiovascular involvement may enable identification of high-risk individuals before the development of overt cardiovascular disease.

**Objectives:** To determine the prevalence of subclinical cardiovascular disease among adults with CKM syndrome using cardiac biomarkers and echocardiographic parameters and to identify associated clinical, metabolic, renal, and cardiovascular predictors.

**Methods:** This single-centre, hospital-based, analytical cross-sectional study included 300 adults with CKM syndrome evaluated in the Departments of Cardiology, General Medicine, and Radiodiagnosis of a tertiary teaching healthcare facility in South India. Participants underwent clinical assessment, anthropometry, metabolic and renal profiling, hs-cTnT and NT-proBNP estimation, electrocardiography, and comprehensive transthoracic echocardiography. Multivariable logistic regression was used to determine independent predictors of subclinical cardiovascular disease.

**Results:** Subclinical cardiovascular disease was identified in 117 participants (39.0%). Cardiac biomarker elevation was present in 30.0%, while 19.3% demonstrated echocardiographic abnormalities. Left ventricular hypertrophy and diastolic dysfunction were present in 13.0% and 7.7%, respectively. Participants with subclinical disease were older ( $59.4 \pm 9.0$  vs  $48.9 \pm 9.4$  years), had higher prevalence of hypertension (80.3% vs 60.7%), diabetes (76.1% vs 49.2%), and CKD (52.1% vs 13.7%), and had higher hs-cTnT and NT-proBNP concentrations (all  $p < 0.001$ ). On multivariable analysis, age per 10-year increase (adjusted OR 3.43, 95% CI 2.36–4.97), diabetes duration  $\geq 10$  years (OR 6.01, 95% CI 1.65–21.91), and CKD (OR 5.01, 95% CI 2.46–10.20) independently predicted subclinical cardiovascular disease.

**Conclusion:** Subclinical cardiovascular disease was common among adults with CKM syndrome. Older age, prolonged diabetes duration, and CKD were independent predictors, supporting integrated biomarker and echocardiographic assessment in high-risk CKM populations.

**Keywords:** cardiovascular–kidney–metabolic syndrome, subclinical cardiovascular disease, high-sensitivity troponin T, NT-proBNP, echocardiography, chronic kidney disease.

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### Introduction

Cardiovascular–kidney–metabolic (CKM) syndrome represents the interconnected pathophysiological continuum linking excess or dysfunctional adiposity, metabolic abnormalities, chronic kidney disease (CKD), and cardiovascular disease (CVD). The CKM framework

conceptualizes progression from excess adiposity without additional metabolic abnormalities (stage 1), through metabolic risk factors and/or CKD (stage 2), to subclinical cardiovascular involvement (stage 3) and ultimately clinically manifest CVD (stage 4). Minhas et al., applying this framework to

nationally representative US data, reported that CKM stages 1–3 collectively affected 80.94% of adults aged 20–44 years and 85.95% of those aged 45–64 years, demonstrating that cardiovascular risk frequently accumulates long before overt disease becomes clinically apparent.[1] This interaction is particularly relevant in India because the population burden of metabolic risk factors is substantial. In the ICMR-INDIAB national study of 113,043 adults, Anjana et al. reported weighted prevalences of 11.4% for diabetes, 35.5% for hypertension, 28.6% for generalized obesity, 39.5% for abdominal obesity, and 81.2% for dyslipidaemia.[2] The coexistence of these disorders with renal dysfunction provides a biological substrate for myocardial hypertrophy, fibrosis, microvascular dysfunction, altered ventricular relaxation, and progressive cardiac injury even before symptoms of heart failure or ischemic heart disease develop.

Subclinical cardiac abnormalities are therefore increasingly recognized as an important intermediate phenotype. Antakly-Hanon et al. evaluated 200 patients with type 2 diabetes without overt CVD and identified increased left ventricular (LV) mass in 12%, increased relative wall thickness in 23%, left atrial enlargement in 13.6%, and impaired global longitudinal strain in 20.3%.[3] More recently, Gupta et al. studied 227 Indian patients undergoing echocardiography in routine clinical practice and identified stage B heart failure in 52.4%; reduced LV global longitudinal strain was present in 47%, increased left atrial volume index in 13%, and elevated E/e' ratio in 7%.[4] These findings emphasize that conventional preservation of LV ejection fraction does not exclude clinically relevant preclinical myocardial disease. Circulating cardiac biomarkers provide complementary evidence of myocardial injury and haemodynamic stress. In 1,510 participants with diabetes from the ARIC study, Gori et al. found that hs-cTnT  $\geq 14$  ng/L independently predicted incident cardiovascular events with a hazard ratio of 1.96, while NT-proBNP  $>125$  pg/mL conferred a hazard ratio of 1.61 over 13.1 years; incorporation of these biomarkers improved cardiovascular risk reclassification beyond conventional risk factors and diabetes-related complications.[5] Renal abnormalities further amplify this risk. In an individual-participant meta-analysis involving 637,315 individuals without previous CVD, Matsushita et al. demonstrated that both eGFR and albuminuria improved cardiovascular risk prediction, with albuminuria providing particularly meaningful incremental discrimination for heart failure.[6] Against this background, the present study aimed to determine the prevalence of subclinical cardiovascular disease among adults with cardiovascular–kidney–metabolic syndrome using echocardiographic parameters and cardiac

biomarkers, and to evaluate the clinical, metabolic, renal, and cardiovascular factors associated with subclinical cardiac involvement. It also sought to identify independent predictors of subclinical cardiovascular disease in this population.

## Materials and Methods

This was a single-centre, hospital-based, analytical, cross-sectional study conducted in the Departments of Cardiology, General Medicine and Radiodiagnosis of a tertiary teaching healthcare facility in South India over a period of two years (January 2024–December 2025). The study was approved by the Institutional Human Ethics Committee (IHEC). Each participant was provided with a Participant Information Sheet (PIS) translated into their local language. The information was also explained verbally to ensure clear understanding and voluntary agreement. Adults aged  $\geq 18$  years with CKM syndrome, defined by the presence of excess or dysfunctional adiposity, metabolic risk factors such as hypertension, hypertriglyceridemia, metabolic syndrome or type 2 diabetes mellitus, and/or chronic kidney disease, were eligible for inclusion, provided they had no previously diagnosed clinical cardiovascular disease and gave written informed consent. Patients with established coronary heart disease, previous myocardial infarction or coronary revascularisation, symptomatic heart failure, stroke or transient ischaemic attack, peripheral arterial disease, or atrial fibrillation were excluded. Patients with known cardiomyopathy, significant congenital or valvular heart disease, acute coronary syndrome or acute decompensated heart failure at presentation, severe acute systemic illness, pregnancy, or inability or unwillingness to provide informed consent were also excluded.

The sample size was calculated using the prevalence of subclinical cardiovascular disease reported by Fang et al., who observed a prevalence of 33.4% among adults with diabetes without a history of established cardiovascular disease.[7] Assuming an expected prevalence ( $p$ ) of 33.4%, a 95% confidence level ( $Z = 1.96$ ), and an absolute precision ( $d$ ) of 5.5%, the sample size was estimated using the formula  $n = Z^2 p(1-p)/d^2$ . After allowing approximately 5% for non-response, the minimum required sample was rounded off to 300 participants; enrolled using nonprobability sampling – purposive/convenience sampling technique. Sociodemographic and clinical details included age, sex, place of residence, smoking and alcohol-use, family history of premature cardiovascular disease, duration and treatment of hypertension and T2DM, history of dyslipidaemia and CKD, and current use of antihypertensive agents, glucose-lowering drugs, statins or other lipid-lowering therapy, renin–angiotensin system inhibitors, sodium–glucose cotransporter-2

inhibitors, and antiplatelet agents. A detailed cardiovascular history was obtained. Height was measured without footwear using a wall-mounted stadiometer to the nearest 0.1 cm, and body weight was measured in light clothing using a calibrated digital weighing scale to the nearest 0.1 kg; body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Waist circumference was measured using a non-stretchable tape in the standing position, midway between the lower margin of the last palpable rib and the superior border of the iliac crest, at the end of normal expiration without compressing the skin. For the Asian study population, excess adiposity was identified as BMI  $\geq 23$  kg/m<sup>2</sup> and/or waist circumference  $\geq 90$  cm in men or  $\geq 80$  cm in women. Resting blood pressure was measured with a validated and calibrated upper-arm sphygmomanometer using an appropriately sized cuff after the participant had remained seated quietly for at least 5 minutes with the back supported, feet flat on the floor and arm supported at heart level; participants were instructed to avoid smoking, caffeine and exercise for at least 30 minutes before measurement.[8] Two readings obtained at least 1 minute apart were recorded and their mean was used for analysis.

Following an overnight fast of at least 8 hours, venous blood samples were obtained for fasting plasma glucose, HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine and routine biochemical parameters. Diabetes mellitus was identified from a documented diagnosis or treatment and/or fasting plasma glucose  $\geq 126$  mg/dL or HbA1c  $\geq 6.5\%$ . Kidney function was assessed by estimating glomerular filtration rate from serum creatinine using a validated race-free CKD-EPI equation, and albuminuria was assessed using the urinary albumin-to-creatinine ratio (UACR), preferably from a first-morning spot urine specimen. CKD was identified by an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> and/or UACR  $\geq 30$  mg/g. CKM was categorized according to the 2023 American Heart Association framework, incorporating excess/dysfunctional adiposity, hypertension, hypertriglyceridaemia, metabolic syndrome, diabetes and CKD. [9] Cardiac biomarkers included high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). hs-cTnT was expressed in ng/L and NT-proBNP in pg/mL; for the primary analysis, elevated biomarkers were defined as hs-cTnT  $\geq 14$  ng/L and/or NT-proBNP  $\geq 125$  pg/mL.[7] A standard resting 12-lead electrocardiogram was recorded at a paper speed of 25 mm/s and calibration of 10 mm/mV. Transthoracic echocardiography was performed at rest with the participant in the left lateral decubitus position using standard parasternal long-axis,

parasternal short-axis and apical two- and four-chamber views, together with pulsed-wave, continuous-wave, colour and tissue Doppler imaging. Measurements were obtained in accordance with American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations and, wherever applicable, were averaged over three consecutive cardiac cycles. Left ventricular end-diastolic and end-systolic volumes were measured from apical four- and two-chamber views, and left ventricular ejection fraction (LVEF) was calculated using the biplane modified Simpson method. Interventricular septal thickness, posterior wall thickness and left ventricular internal diameter were measured at end-diastole; left ventricular mass was calculated using guideline-recommended linear measurements and indexed to body-surface area, with left ventricular hypertrophy defined as an LV mass index  $> 115$  g/m<sup>2</sup> in men or  $> 95$  g/m<sup>2</sup> in women. [10] Relative wall thickness was calculated as twice the posterior-wall thickness divided by the LV end-diastolic internal diameter, with a value  $> 0.42$  indicating increased relative wall thickness. Left atrial volume was determined using the biplane method and indexed to body-surface area, with a left atrial volume index  $> 34$  mL/m<sup>2</sup> considered abnormal. Diastolic function was evaluated from transmitral E- and A-wave velocities and E/A ratio, tissue-Doppler septal and lateral e' velocities, mean E/e' ratio, peak tricuspid-regurgitation velocity and indexed left atrial volume; according to the 2016 ASE/EACVI algorithm, septal e'  $< 7$  cm/s or lateral e'  $< 10$  cm/s, mean E/e'  $> 14$ , peak tricuspid-regurgitation velocity  $> 2.8$  m/s and left atrial volume index  $> 34$  mL/m<sup>2</sup> were considered abnormal, and diastolic dysfunction was classified on the basis of the number and concordance of abnormal variables.[11]

**Statistical analysis:** Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of histograms. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation and compared using the independent-samples t-test, whereas non-normally distributed variables were presented as median with interquartile range and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and analysed using the chi-square test or Fisher's exact test, as appropriate. Associations between cardiac biomarkers and clinical, renal, and echocardiographic parameters were assessed using Spearman's rank correlation coefficient. Univariable logistic regression was initially performed to identify factors associated with

subclinical cardiovascular disease, followed by multivariable logistic regression to determine independent predictors, with results expressed as odds ratios with 95% confidence intervals. A two-sided  $p$  value  $<0.05$  was considered statistically significant.

## Results

Overall, subclinical cardiovascular disease was identified in 117 of 300 participants, corresponding to a prevalence of 39.0%. Participants with subclinical cardiovascular disease were significantly older than those without subclinical disease ( $59.4 \pm 9.0$  vs  $48.9 \pm 9.4$  years,  $p<0.001$ ) and had a higher prevalence of hypertension (80.3% vs 60.7%,  $p<0.001$ ) and type 2 diabetes mellitus (76.1% vs 49.2%,  $p<0.001$ ). They also had a longer duration of diabetes ( $7.2 \pm 4.9$  vs  $5.3 \pm 3.2$  years,  $p=0.002$ ), higher systolic and diastolic blood pressures ( $137.0 \pm 15.6$  vs  $128.5 \pm 14.5$  mmHg,  $p<0.001$ ; and  $82.1 \pm 9.0$  vs  $79.9 \pm 8.4$  mmHg,  $p=0.029$ , respectively), and more frequent use of antihypertensive therapy and sodium–glucose cotransporter-2 inhibitors. Mean fasting plasma glucose and HbA1c were higher among participants with subclinical disease than among those without it ( $137.4 \pm 36.1$  vs  $118.8 \pm 34.1$  mg/dL and  $7.04 \pm 1.14\%$  vs  $6.36 \pm 1.19\%$ , respectively; both  $p<0.001$ ). Serum creatinine was higher, whereas eGFR was lower in the subclinical CVD group ( $0.96 \pm 0.15$  vs  $0.89 \pm 0.13$  mg/dL and  $78.9 \pm 12.8$  vs  $87.1 \pm 11.6$  mL/min/1.73 m<sup>2</sup>; both  $p<0.001$ ). Median UACR was also significantly greater [ $29.6$  (13.1–43.8) vs  $14.1$  (9.0–23.7) mg/g,  $p<0.001$ ], and chronic kidney disease was substantially more frequent (52.1% vs 13.7%,  $p<0.001$ ). Cardiac biomarker concentrations were markedly higher among participants with subclinical CVD, with median hs-cTnT of 11.6 versus 6.0 ng/L and median NT-proBNP of 115.9 versus 48.0 pg/mL (both  $p<0.001$ ). Cardiac biomarker elevation was present in 30.0% of the cohort, including hs-cTnT  $\geq 14$  ng/L in 17.7% and NT-proBNP  $\geq 125$  pg/mL in 18.0%. Echocardiographic abnormalities were detected in 19.3%, most commonly left ventricular hypertrophy (13.0%) and diastolic dysfunction (7.7%), while LVEF  $<50\%$  was uncommon (1.3%). With regard to phenotype, 19.7% had isolated biomarker abnormalities, 9.0% had isolated

echocardiographic abnormalities, and 10.3% demonstrated both. According to CKM staging, 6.0% of participants were classified as stage 1, 55.0% as stage 2 and 39.0% as stage 3. Electrocardiographic LVH was significantly more frequent among participants with subclinical cardiovascular disease than among those without it (23.9% vs 7.1%,  $p<0.001$ ), whereas nonspecific ST–T changes and conduction abnormalities did not differ significantly between the groups. On echocardiography, participants with subclinical CVD had a higher left ventricular mass index ( $94.8 \pm 14.9$  vs  $82.2 \pm 12.5$  g/m<sup>2</sup>), greater relative wall thickness ( $0.40 \pm 0.05$  vs  $0.37 \pm 0.05$ ), lower LVEF ( $59.4 \pm 4.7\%$  vs  $61.2 \pm 4.1\%$ ), lower septal and lateral  $e'$  velocities, and a higher mean  $E/e'$  ratio, left atrial volume index and peak tricuspid-regurgitation velocity (all  $p<0.001$ ). Echocardiographic LVH and diastolic dysfunction were present in 33.3% and 19.7% of participants with subclinical CVD, respectively, while 49.6% had at least one predefined echocardiographic abnormality. hs-cTnT showed a moderate positive correlation with age ( $\rho=0.548$ ,  $p<0.001$ ) and weaker positive correlations with UACR, LV mass index, mean  $E/e'$  ratio and left atrial volume index, while it correlated inversely with eGFR ( $\rho=-0.290$ ,  $p<0.001$ ). NT-proBNP similarly correlated positively with age ( $\rho=0.490$ ,  $p<0.001$ ), UACR, LV mass index and left atrial volume index, and inversely with eGFR ( $\rho=-0.292$ ,  $p<0.001$ ) and LVEF ( $\rho=-0.176$ ,  $p=0.002$ ). On univariable logistic regression, older age, hypertension, type 2 diabetes mellitus, diabetes duration  $\geq 10$  years, systolic blood pressure  $\geq 140$  mmHg, HbA1c  $\geq 7\%$ , and chronic kidney disease were significantly associated with subclinical cardiovascular disease. After multivariable adjustment, age, prolonged diabetes duration and CKD remained independent predictors. Each 10-year increase in age was associated with more than threefold higher odds of subclinical CVD (adjusted OR 3.43, 95% CI 2.36–4.97;  $p<0.001$ ), while diabetes duration  $\geq 10$  years was associated with approximately sixfold higher odds (adjusted OR 6.01, 95% CI 1.65–21.91;  $p=0.007$ ). Chronic kidney disease remained a strong independent predictor, with a fivefold increase in odds (adjusted OR 5.01, 95% CI 2.46–10.20;  $p<0.001$ ).

**Table 1: Sociodemographic, clinical, anthropometric, and treatment characteristics according to subclinical cardiovascular disease status**

|                         | Overall (N=300) | Subclinical CVD (n=117) | No subclinical CVD (n=183) | p value  |
|-------------------------|-----------------|-------------------------|----------------------------|----------|
| Age, years              | $53.0 \pm 10.5$ | $59.4 \pm 9.0$          | $48.9 \pm 9.4$             | $<0.001$ |
| Male sex                | 166 (55.3%)     | 63 (53.8%)              | 103 (56.3%)                | 0.768    |
| Urban residence         | 184 (61.3%)     | 70 (59.8%)              | 114 (62.3%)                | 0.759    |
| BMI, kg/m <sup>2</sup>  | $27.9 \pm 3.4$  | $27.7 \pm 3.6$          | $28.0 \pm 3.2$             | 0.457    |
| Waist circumference, cm | $103.1 \pm 6.8$ | $102.8 \pm 7.1$         | $103.2 \pm 6.6$            | 0.665    |

|                                  |              |              |              |        |
|----------------------------------|--------------|--------------|--------------|--------|
| Hypertension                     | 205 (68.3%)  | 94 (80.3%)   | 111 (60.7%)  | <0.001 |
| Duration of hypertension, years* | 7.2 ± 4.6    | 7.7 ± 4.2    | 6.7 ± 5.0    | 0.129  |
| Type 2 diabetes mellitus         | 179 (59.7%)  | 89 (76.1%)   | 90 (49.2%)   | <0.001 |
| Duration of diabetes, years†     | 6.3 ± 4.2    | 7.2 ± 4.9    | 5.3 ± 3.2    | 0.002  |
| Dyslipidaemia                    | 183 (61.0%)  | 73 (62.4%)   | 110 (60.1%)  | 0.784  |
| Current smoking                  | 81 (27.0%)   | 33 (28.2%)   | 48 (26.2%)   | 0.808  |
| Current alcohol use              | 79 (26.3%)   | 29 (24.8%)   | 50 (27.3%)   | 0.725  |
| Family history of premature CVD  | 50 (16.7%)   | 19 (16.2%)   | 31 (16.9%)   | 1.000  |
| Systolic blood pressure, mmHg    | 131.8 ± 15.5 | 137.0 ± 15.6 | 128.5 ± 14.5 | <0.001 |
| Diastolic blood pressure, mmHg   | 80.7 ± 8.7   | 82.1 ± 9.0   | 79.9 ± 8.4   | 0.029  |
| Any antihypertensive treatment   | 185 (61.7%)  | 86 (73.5%)   | 99 (54.1%)   | 0.001  |
| RAS inhibitor use                | 164 (54.7%)  | 67 (57.3%)   | 97 (53.0%)   | 0.546  |
| Statin use                       | 164 (54.7%)  | 68 (58.1%)   | 96 (52.5%)   | 0.400  |
| SGLT2 inhibitor use              | 61 (20.3%)   | 34 (29.1%)   | 27 (14.8%)   | 0.004  |
| Antiplatelet use                 | 33 (11.0%)   | 17 (14.5%)   | 16 (8.7%)    | 0.170  |

\*Calculated among participants with hypertension.  
†Calculated among participants with diabetes.

**Table 2: Metabolic, renal, and cardiac biomarker profile according to subclinical cardiovascular disease status**

|                                  | Overall (N=300)     | Subclinical CVD (n=117) | No subclinical CVD (n=183) | p value |
|----------------------------------|---------------------|-------------------------|----------------------------|---------|
| Fasting plasma glucose, mg/dL    | 126.1 ± 36.0        | 137.4 ± 36.1            | 118.8 ± 34.1               | <0.001  |
| HbA1c, %                         | 6.63 ± 1.22         | 7.04 ± 1.14             | 6.36 ± 1.19                | <0.001  |
| Total cholesterol, mg/dL         | 186.9 ± 29.1        | 183.4 ± 28.8            | 189.2 ± 29.2               | 0.093   |
| Triglycerides, mg/dL             | 164.9 (135.8–206.7) | 161.7 (134.1–206.2)     | 166.4 (136.4–207.8)        | 0.774   |
| HDL cholesterol, mg/dL           | 41.1 ± 8.6          | 40.5 ± 8.6              | 41.5 ± 8.6                 | 0.333   |
| LDL cholesterol, mg/dL           | 111.4 ± 26.0        | 108.2 ± 25.3            | 113.5 ± 26.3               | 0.079   |
| Serum creatinine, mg/dL          | 0.92 ± 0.15         | 0.96 ± 0.15             | 0.89 ± 0.13                | <0.001  |
| eGFR, mL/min/1.73 m <sup>2</sup> | 83.9 ± 12.7         | 78.9 ± 12.8             | 87.1 ± 11.6                | <0.001  |
| UACR, mg/g                       | 18.1 (10.1–31.2)    | 29.6 (13.1–43.8)        | 14.1 (9.0–23.7)            | <0.001  |
| Chronic kidney disease           | 86 (28.7%)          | 61 (52.1%)              | 25 (13.7%)                 | <0.001  |
| hs-cTnT, ng/L                    | 7.5 (4.7–11.5)      | 11.6 (7.7–16.9)         | 6.0 (4.3–8.8)              | <0.001  |
| NT-proBNP, pg/mL                 | 63.0 (39.7–103.4)   | 115.9 (67.3–156.3)      | 48.0 (34.9–70.2)           | <0.001  |
| hs-cTnT ≥14 ng/L                 | 53 (17.7%)          | 53 (45.3%)              | 0 (0.0%)                   | <0.001  |
| NT-proBNP ≥125 pg/mL             | 54 (18.0%)          | 54 (46.2%)              | 0 (0.0%)                   | <0.001  |

**Table 3: Prevalence and phenotypic distribution of subclinical cardiovascular disease and CKM stage**

|                                                    | n (%)       |
|----------------------------------------------------|-------------|
| Subclinical cardiovascular disease                 | 117 (39.0%) |
| No subclinical cardiovascular disease              | 183 (61.0%) |
| Any cardiac biomarker elevation                    | 90 (30.0%)  |
| hs-cTnT ≥14 ng/L                                   | 53 (17.7%)  |
| NT-proBNP ≥125 pg/mL                               | 54 (18.0%)  |
| Any echocardiographic abnormality                  | 58 (19.3%)  |
| Left ventricular hypertrophy                       | 39 (13.0%)  |
| Diastolic dysfunction                              | 23 (7.7%)   |
| LVEF <50%                                          | 4 (1.3%)    |
| Biomarker abnormality only                         | 59 (19.7%)  |
| Echocardiographic abnormality only                 | 27 (9.0%)   |
| Both biomarker and echocardiographic abnormalities | 31 (10.3%)  |
| CKM stage 1                                        | 18 (6.0%)   |
| CKM stage 2                                        | 165 (55.0%) |
| CKM stage 3                                        | 117 (39.0%) |

**Table 4: Electrocardiographic and echocardiographic findings according to subclinical cardiovascular disease status**

|                                             | Overall (N=300) | Subclinical CVD (n=117) | No subclinical CVD (n=183) | p value |
|---------------------------------------------|-----------------|-------------------------|----------------------------|---------|
| ECG evidence of LVH                         | 41 (13.7%)      | 28 (23.9%)              | 13 (7.1%)                  | <0.001  |
| Nonspecific ST-T abnormality                | 30 (10.0%)      | 13 (11.1%)              | 17 (9.3%)                  | 0.752   |
| Conduction abnormality                      | 9 (3.0%)        | 5 (4.3%)                | 4 (2.2%)                   | 0.319   |
| LV mass index, g/m <sup>2</sup>             | 87.1 ± 14.8     | 94.8 ± 14.9             | 82.2 ± 12.5                | <0.001  |
| Relative wall thickness                     | 0.38 ± 0.05     | 0.40 ± 0.05             | 0.37 ± 0.05                | <0.001  |
| LVEF, %                                     | 60.5 ± 4.4      | 59.4 ± 4.7              | 61.2 ± 4.1                 | <0.001  |
| Septal e', cm/s                             | 7.4 ± 1.3       | 6.9 ± 1.2               | 7.8 ± 1.3                  | <0.001  |
| Lateral e', cm/s                            | 10.1 ± 1.6      | 9.5 ± 1.6               | 10.4 ± 1.5                 | <0.001  |
| Mean E/e' ratio                             | 11.4 ± 2.4      | 12.2 ± 2.3              | 10.8 ± 2.3                 | <0.001  |
| Left atrial volume index, mL/m <sup>2</sup> | 32.2 ± 5.8      | 34.2 ± 5.1              | 31.0 ± 5.8                 | <0.001  |
| Peak TR velocity, m/s                       | 2.49 ± 0.21     | 2.56 ± 0.22             | 2.44 ± 0.20                | <0.001  |
| Echocardiographic LVH                       | 39 (13.0%)      | 39 (33.3%)              | 0 (0.0%)                   | —       |
| Diastolic dysfunction                       | 23 (7.7%)       | 23 (19.7%)              | 0 (0.0%)                   | —       |
| LVEF <50%                                   | 4 (1.3%)        | 4 (3.4%)                | 0 (0.0%)                   | —       |
| Any echocardiographic abnormality           | 58 (19.3%)      | 58 (49.6%)              | 0 (0.0%)                   | —       |

**Table 5: Spearman correlations of cardiac biomarkers with clinical, renal, and echocardiographic variables**

|                          | hs-cTnT ρ | p value | NT-proBNP ρ | p value |
|--------------------------|-----------|---------|-------------|---------|
| Age                      | 0.548     | <0.001  | 0.490       | <0.001  |
| eGFR                     | -0.290    | <0.001  | -0.292      | <0.001  |
| UACR                     | 0.264     | <0.001  | 0.276       | <0.001  |
| LV mass index            | 0.230     | <0.001  | 0.217       | <0.001  |
| Mean E/e' ratio          | 0.274     | <0.001  | 0.174       | 0.003   |
| Left atrial volume index | 0.287     | <0.001  | 0.210       | <0.001  |
| LVEF                     | -0.095    | 0.099   | -0.176      | 0.002   |

**Table 6: Univariable and multivariable logistic regression for predictors of subclinical cardiovascular disease**

|                              | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|------------------------------|------------------------|---------|----------------------|---------|
| Age, per 10-year increase    | 3.24 (2.39–4.40)       | <0.001  | 3.43 (2.36–4.97)     | <0.001  |
| Male sex                     | 0.91 (0.57–1.44)       | 0.679   | 0.97 (0.52–1.82)     | 0.926   |
| BMI, per 1 kg/m <sup>2</sup> | 0.97 (0.91–1.04)       | 0.443   | 0.96 (0.87–1.06)     | 0.454   |
| Hypertension                 | 2.65 (1.54–4.57)       | <0.001  | 1.50 (0.72–3.11)     | 0.274   |
| Type 2 diabetes mellitus     | 3.28 (1.96–5.49)       | <0.001  | 1.62 (0.70–3.77)     | 0.262   |
| Diabetes duration ≥10 years  | 6.90 (2.50–19.05)      | <0.001  | 6.01 (1.65–21.91)    | 0.007   |
| Systolic BP ≥140 mmHg        | 3.16 (1.88–5.29)       | <0.001  | 1.58 (0.79–3.18)     | 0.196   |
| HbA1c ≥7%                    | 2.67 (1.65–4.31)       | <0.001  | 1.23 (0.55–2.77)     | 0.609   |
| Chronic kidney disease       | 6.88 (3.95–12.01)      | <0.001  | 5.01 (2.46–10.20)    | <0.001  |
| Current smoking              | 1.10 (0.66–1.86)       | 0.707   | 1.37 (0.69–2.73)     | 0.368   |
| Dyslipidemia                 | 1.10 (0.68–1.77)       | 0.692   | 1.07 (0.57–2.01)     | 0.825   |

## Discussion

The present study identified subclinical cardiovascular disease in 39.0% of adults with CKM syndrome, indicating a substantial burden of clinically silent myocardial injury or structural/functional abnormality. Fang et al. evaluated 10,304 US adults without overt CVD and found biomarker-defined subclinical CVD in 33.4% of adults with diabetes compared with 16.1% of those without diabetes, using hs-cTnT ≥14 ng/L and/or NT-proBNP ≥125 pg/mL. [7]

Aggarwal et al. reported CKM stage 3 in only 5.4% of the general US adult population; [12] however, their NHANES analysis lacked cardiac biomarkers and echocardiography, which could underestimate advanced CKM.

The higher prevalence in the present hospital-based cohort is therefore consistent with enrichment for hypertension, diabetes and CKD and systematic assessment with both biomarkers and echocardiography. Age was one of the strongest determinants of subclinical CVD. Participants with

subclinical disease were approximately 10 years older, and each 10-year increase independently increased the odds 3.43-fold. Aggarwal et al. similarly showed advanced CKM in 55.3% of adults aged  $\geq 65$  years, compared with 10.7% at 45–64 years and 2.1% at 20–44 years. [12] This supports cumulative vascular, myocardial and renal injury with ageing as an important driver of progression to demonstrable cardiovascular involvement. Although Aggarwal et al. observed advanced CKM more often in men than women (16.9% vs 12.4%), sex was not independently associated with disease in the present cohort. [12]

Hypertension and diabetes were substantially more frequent in participants with subclinical CVD, accompanied by higher blood pressure, fasting glucose and HbA1c. However, hypertension, diabetes status, systolic blood pressure  $\geq 140$  mmHg and HbA1c  $\geq 7\%$  were no longer independently significant after multivariable adjustment, whereas diabetes duration  $\geq 10$  years remained strongly associated with disease (adjusted OR 6.01). Hamo et al., in 9,052 ARIC participants without heart failure or coronary disease, found that hs-cTnT  $\geq 14$  ng/L increased from 12% in diabetes of  $< 5$  years' duration to 31% with diabetes  $\geq 15$  years; diabetes duration  $\geq 15$  years was associated with a 9.29-fold adjusted relative risk of elevated hs-cTnT compared with no diabetes. [13] Fang et al. likewise reported greater hs-cTnT elevation with longer diabetes duration and poorer glycaemic control. [7] Kidney disease showed an especially strong relationship with subclinical CVD. CKD was present in 52.1% of affected participants compared with 13.7% of those without subclinical CVD and remained independently associated after adjustment (OR 5.01). Lower eGFR, higher UACR and inverse correlations of both cardiac biomarkers with eGFR further support the cardiorenal component of CKM syndrome. Mishra et al. studied 3,232 CRIC participants with CKD but no clinical heart failure and reported a median NT-proBNP of 126.6 pg/mL; the highest NT-proBNP quartile was associated with 2.7-fold higher odds of LVH and 2.0-fold higher odds of diastolic dysfunction. [14] Bansal et al. additionally found that the highest hs-cTnT quartile was associated with incident heart failure with an HR of 4.77, while the highest NT-proBNP quintile carried an HR of 9.57. [15] These data indicate that biomarker elevation in CKD reflects clinically meaningful myocardial stress and injury, rather than renal impairment alone.

Biomarker abnormalities were more common than echocardiographic abnormalities: 30.0% had elevated hs-cTnT and/or NT-proBNP, whereas 19.3% had a predefined echocardiographic abnormality. Isolated biomarker positivity occurred in 19.7%, compared with 9.0% with isolated

imaging abnormalities, suggesting that biochemical evidence may precede detectable conventional structural disease in some patients. Fang et al. found that, among adults with diabetes, elevated hs-cTnT and NT-proBNP were independently associated with all-cause mortality, with adjusted HRs of 1.77 and 1.78, respectively; elevated NT-proBNP was also associated with cardiovascular mortality (HR 2.46). [7] The echocardiographic phenotype was dominated by LV remodelling and diastolic abnormalities rather than reduced systolic function. Participants with subclinical CVD had higher LV mass index, relative wall thickness, E/e' ratio and left atrial volume index, together with lower septal and lateral e' velocities. Within the subclinical-CVD group, LVH was present in 33.3% and diastolic dysfunction in 19.7%, whereas LVEF  $< 50\%$  occurred in only 3.4%. This pattern is consistent with a pre-heart-failure phenotype in which hypertrophy, impaired relaxation and elevated filling pressure can occur despite preserved LVEF. Ndumele et al. incorporated elevated cardiac biomarkers and abnormal cardiac structure or function in asymptomatic individuals into the AHA definition of CKM stage 3. [9]

The biomarker–echocardiography correlations further support a continuum of subclinical myocardial injury. hs-cTnT correlated positively with LV mass index, E/e' and left atrial volume index, while NT-proBNP showed similar relationships and an inverse association with LVEF. Kang et al., in 2,017 participants with predialysis CKD in the KNOW-CKD cohort, found that elevated hs-cTnT was independently associated with LVH and diastolic dysfunction; hs-cTnT yielded areas under the ROC curve of 0.689 for LVH and 0.744 for diastolic dysfunction. [16] BMI, waist circumference, dyslipidaemia, smoking and conventional lipid fractions did not independently distinguish participants with subclinical CVD. Within an already high-risk CKM population, this suggests that cumulative exposure and end-organ involvement – particularly age, prolonged diabetes and CKD – were more closely related to stage 3 disease than static adiposity or lipid measurements. This pattern accords with the AHA CKM framework proposed by Ndumele et al., in which excess/dysfunctional adiposity characterizes stage 1, metabolic risk factors and CKD characterize stage 2, and objective subclinical cardiovascular injury defines stage 3. [9, 17, 18]

The present study had several limitations. Its single-centre, hospital-based design may have introduced referral and selection bias and may limit the generalizability of the findings to community-based populations or other healthcare settings. The cross-sectional analytical design permitted assessment of associations but did not establish temporal or causal relationships between CKM risk

factors and subclinical cardiovascular disease. Although subclinical cardiovascular involvement was evaluated using cardiac biomarkers and comprehensive echocardiography, more advanced modalities such as global longitudinal strain, cardiac magnetic resonance imaging, coronary artery calcium scoring, or coronary computed tomography angiography were not incorporated and could have identified additional occult disease. Cardiac biomarkers, particularly hs-cTnT and NT-proBNP, may also be influenced by age and renal dysfunction despite multivariable adjustment. Some clinical variables, including duration of hypertension and diabetes, medication exposure, smoking, and alcohol use, depended partly on participant recall or previous medical records and were therefore susceptible to information bias.

Finally, the study did not include longitudinal follow-up for incident cardiovascular events, heart failure, hospitalization, or mortality, and therefore the prognostic significance of the identified subclinical abnormalities could not be directly assessed.

### Conclusion

Subclinical cardiovascular disease was common among adults with cardiovascular–kidney–metabolic syndrome, affecting nearly two-fifths of the study population. Participants with subclinical disease exhibited a greater burden of hypertension, diabetes, impaired glycaemic control, renal dysfunction, elevated cardiac biomarkers, and adverse echocardiographic changes, particularly left ventricular hypertrophy and diastolic dysfunction. Older age, diabetes duration of  $\geq 10$  years, and chronic kidney disease emerged as independent predictors of subclinical cardiovascular involvement.

The findings highlight the importance of integrating cardiac biomarker assessment and echocardiography into the evaluation of high-risk CKM patients, as these tools may facilitate earlier recognition of preclinical myocardial injury and structural cardiac abnormalities before the onset of overt cardiovascular disease.

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