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Impact of coronary artery calcium on progression of diastolic dysfunction: a cohort study

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Abstract

Background The relationship between coronary artery calcium (CAC) and progression of diastolic dysfunction (DD) during longitudinal follow-up is uncertain. This study aimed to investigate the prevalence and progression of DD according to severity of CAC and understand their synergistic effect on mortality.

Methods This was a population-based cohort study. All 15,193 adults who underwent a health screening exam with simultaneous echocardiography and CAC scan were enrolled. Definite DD (≥ 3/4 abnormal parameters for DD [e', E/e', tricuspid regurgitation velocity, and left atrial volume index]) and definite or probable DD (≥ 2/4) were defined. All-cause mortality was assessed based on the CAC and DD.

Results Among the population, 7995 participants (52.6%) had CAC = 0; 4661 (30.7%) had 0 < CAC < 100; and 2537 (16.7%) had CAC ≥ 100. The prevalence ratios for definite (adjusted ratio: 1.72, 95% CI: 1.23–2.22) and definite or probable DD (adjusted ratio: 1.83, 95% CI: 1.31–2.36) were significantly higher in individuals with CAC ≥ 100 than in those with CAC = 0. There was significant linear association of CAC with E/e' (adjusted *p* for linearity = 0.001). Compared with CAC < 100 without definite DD, the adjusted HRs with 95% CI for mortality of CAC ≥ 100 without definite DD, CAC < 100 with definite DD, and CAC ≥ 100 with definite DD were 2.56 (95% CI: 1.67–3.94), 3.08 (95% CI: 1.28–7.39), and 3.91 (95% CI: 1.68–9.10). Among participants without DD at CAC measurement who had at least two echocardiographic measurements, the presence of significant CAC (≥ 100) was significantly associated with accelerated progression in definite DD over time (adjusted HR: 1.46, 95% CI: 1.13–1.88), with more rapid elevation of E/e' during follow-up (difference: 0.06, 95% CI: 0.02–0.10, $p = 0.003$).

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Conclusions In the general population, there was a significant relationship between CAC and prevalence of DD, and both subclinical parameters were associated with increased mortality. Moreover, CAC ≥ 100 significantly affects the progression of DD independently of other clinical factors.

Keywords Coronary artery calcium, Diastolic dysfunction, Mortality, Echocardiography, Heart failure

Background

Left ventricular (LV) diastolic dysfunction (DD) is associated with subclinical risk factors including advanced age, obesity, hypertension, diabetes, and atrial fibrillation [1–4], and cardiovascular mortality and major adverse cardiac events [5–7]. These results emphasize the importance of early preventive measures.

The coronary artery calcium (CAC) scan measured by computed tomography (CT) has been shown to be prognostic for atherosclerotic burden. The CAC is an independent risk factor for coronary artery disease irrespective of known risk factors as age, sex, race, or cardiovascular comorbidities [8–11]. Recently, there has been great interest in better understanding the relationship between DD and CAC as it relates to heart failure with preserved ejection fraction (HFpEF) [12–14]. However, there are limited data regarding the synergistic effects on mortality of DD and CAC in the general population. More importantly, the temporal relationship between CAC and progression of DD is poorly understood.

Therefore, our study aimed to evaluate the association of CAC score with prevalence of DD assessed at baseline echocardiography and to explore the combined effect of CAC and DD on mortality in the general population using a large cohort from a health screening examination program in Korea. We also sought to evaluate the incidence rates of progression of DD during follow-up according to the baseline CAC score in a longitudinal dataset.

Methods

Study population

We conducted a retrospective cohort analysis of men and women ≥ 18 years of age who had volunteered to undergo a comprehensive health screening examination with simultaneous echocardiography and CAC scan to assess their health status at the Samsung Medical Center Health Promotion Center, Republic of Korea, from January 2010 to December 2019 (N = 15,830). We excluded 1978 participants who had history of cardiovascular disease (N = 571) or LVEF < 50% at baseline (N = 31). Among the eligible participants (N = 15,228), we further excluded 35 who had missing data for lipid profile, blood pressure, and body mass index (BMI) at baseline. The final sample size was 15,193. The Institutional Review Board of Samsung Medical Center approved this study and waived the requirement for informed consent as we used only de-identified data routinely collected during health screening visits.

Measurement

Echocardiography

All echocardiography measurements were performed in health screening practice in accordance with guidelines using a commercially available system (Vivid7, GE Medical Systems, Horten, Norway; Vivid9, GE Medical Systems, Horten, Norway; SC2000, Siemens Medical Solution, Mountain View, CA, USA) [15]. The inter-ventricular septum thickness, posterior wall thickness, and LV dimensions in diastole and systole were measured from M-mode images, and the LV mass (g) was calculated using the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) equation [16]. LVEF was assessed using the biplane Simpson technique. In case it is not easy to measure the LVEF by the Simpson technique, M-mode or visual estimation was allowed. Left atrial volume was measured by the biplane method using dedicated apical 4- and 2-chamber views at the end-systolic frame to avoid foreshortening. The left atrial volume index (LAVI) was calculated as left atrial volume/body surface area (mL/m^2). Trans-mitral inflow velocities (E and A) were obtained by pulsed-wave Doppler analysis performed in the apical 4-chamber plane. Tissue Doppler imaging was used to obtain early (e′) and late (a′) atrial diastolic annular velocities in the apical 4-chamber view. Peak tricuspid regurgitation (TR) velocity was recorded using continuous Doppler.

Definitions of DD

DD was defined according to the 2016 ASE/EACVI recommendations [17]. Four main echocardiographic parameters were considered, and abnormal cutoffs were as follows: septal e′ < 7 cm/s, septal E/e′ > 15, LAVI > 34 mL/m^2, and TR velocity > 2.8 m/s. The presence of at least 3 of 4 abnormal DD parameters was mandatory to classify definite DD, even if some of the four diastolic parameters were missing. Similarly, the presence of at least 2 of 4 abnormal DD parameters was evaluated as a separate binary variable and defined as "definite or probable DD"

[4]. To define DD, parameters including septal e′, septal E/e′, LAVI, and TR velocity were generated using their respective cutoffs, and these parameters were also evaluated as continuous variables.

Coronary CT scans

Imaging data for the evaluation of CAC were acquired using Brilliance 40 (Philips Medical Systems), VCT LightSpeed 64 (GE Healthcare), or Discovery 750HD (GE Healthcare) multidetector CT scanners. The analysis of the scans was performed on Extended Brilliance Workspace (Philips Medical Systems) or Advantage (GE Healthcare) workstations. CAC scores were calculated as described by Agatston et al. [18]. Based on the clinical cutoff, we categorized CAC into CAC = 0, CAC > 0–CAC < 100, and CAC ≥ 100 [19].

Covariates

At each visit, demographic characteristics, smoking status, alcohol consumption, medical history, and medication use were collected through standardized, self-administered questionnaires. Smoking status was categorized into never, former, or current smoker. Alcohol consumption was categorized into none, light (< 10 g/day in women and < 20 g/day in men), moderate (10– < 40 g/day in women and 20– < 60 g/day in men), and heavy (≥ 40 g/day in women and ≥ 60 g/day in men) [20]. Height, weight, waist circumference, and sitting blood pressure were measured by trained nurses. BMI was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, a self-reported history of hypertension, or current use of anti-hypertensive medications. Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dL, a self-reported history of diabetes, or self-reported use of insulin or oral hypoglycemic medications.

Mortality

Mortality data were obtained from a health screening center registry through December 31, 2019, ascertained by the Korean Ministry of the Interior and Safety.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of participants by CAC category. To test for linear trends, we included the median value of each CAC category as a continuous variable in the regression models. If the p value from the test for linear trends (p for trends) was significant ($p < 0.05$), it indicated that the variables were associated with a linear trend according to CAC increased. To compare the parameters of echocardiography by CAC, we conducted multivariable linear regression models to control age, sex, BMI, smoking status, drinking status, diabetes, hypertension, hyperlipidemia, statin use, and aspirin use. To evaluate the association between CAC category and the prevalence of definite or probable DD, we calculated its prevalence and 95% confidence interval (CI) for definite or probable DD by CAC category. We also used log-binomial regression to estimate adjusted prevalence ratios and 95% CIs after adjusting for age, sex, BMI, smoking status, alcohol consumption, diabetes, hypertension, hyperlipidemia, statin use, and aspirin use.

To estimate the synergistic effects of CAC and DD on mortality, we generated 4 groups of CAC < 100 without definite DD, CAC < 100 with definite DD, CAC ≥ 100 without definite DD, and CAC ≥ 100 with definite DD. Participants were followed from the time of their first health screening exam until death or December 31, 2019, whichever came first. We used a proportional hazards model to assess the associations between the 4 groups at baseline and all-cause mortality.

Participants without definite or probable DD at baseline were followed for development of definite or probable DD using all available echocardiography until the last available echocardiography follow-up at the time of data extraction (31 December 2019). We also performed additional sensitivity analysis to evaluate the change of CAC on the incidence of definite DD. In this analysis, participants without DD at baseline and second visits who underwent serial CAC measurement and had at least three visits were included. We followed the development of definite DD from the second visit to the last available echocardiography follow-up at the time of data extraction (31 December 2019).

Since the development of DD occurred at an unknown time point between the visit of detection and the previous visit (interval censoring), we used a flexible parametric proportional hazards model to assess the association between the CAC status at baseline and the development of DD [21]. Since participants in our analyses had to have undergone at least 2 screening visits ($N = 5706$), we used inverse probability weights (IPWs) to correct for potential selection bias. The IPWs of study participants were reweighted so that participants who were similar to those lost to follow-up after the first echocardiography were assigned a higher weight. IPWs were obtained from a logistic regression model including all those screened with at least one echocardiography and with similar selection criteria to those used in this analysis ($N = 9487$).

We also compared the quantitative trajectories of e′ and E/e′ by CAC status at baseline using linear mixed models for longitudinal data with random intercepts and random slopes. We estimated the changes of e′ and E/e′ (with 95% CIs) relative to those of participants with CAC = 0.

All reported p values were two-sided, and the significance level was set to 0.05. All analyses were performed using STATA version 16 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics

The mean (standard deviation) age of study participants was 55.8 ± 8.6 years. The median CAC score at baseline was 0 (52.6% participants had a CAC score of 0). The prevalence of CAC by category was categorized as follows: 52.6% had a score of 0, 30.7% had a 0 < CAC < 100, and 16.7% had a CAC ≥ 100. The p value for trends for age, male sex, current smoking status, metabolically unhealthy status, and all other variables were found to be linearly associated with CAC (Table 1). In particular, there is an increased trend on N-terminal pro-B-type natriuretic peptide (NT-proBNP) with increasing CAC score (Table 1).

Table 1 Baseline characteristics of study participants by CAC group

Characteristic	CAC = 0 (*N* = 7995)	0 < CAC < 100 (*N* = 4661)	CAC ≥ 100 (*N* = 2537)
Age, years	52.9 ± 7.3	57.2 ± 8.2	62.1 ± 9.0
Sex, male	6041 (75.6)	3902 (83.7)	2227 (87.8)
BMI, kg/m^2	24.0 ± 2.8	24.7 ± 2.8	25.0 ± 2.8
Smoking			
Never	3067 (38.4)	1456 (31.2)	674 (26.6)
Ever	4572 (57.2)	2994 (64.2)	1727 (68.1)
Missing	356 (4.5)	211 (4.5)	136 (5.4)
Drinking status			
None	1759 (22)	998 (21.4)	562 (22.2)
Little	4380 (54.8)	2441 (52.4)	1257 (49.5)
Moderate	1007 (12.6)	685 (14.7)	358 (14.1)
Heavy	506 (6.3)	310 (6.7)	223 (8.8)
Missing	343 (4.3)	227 (4.9)	137 (5.4)
Comorbidities			
Diabetes	727 (9.1)	819 (17.6)	719 (28.3)
Hypertension	2392 (29.9)	2222 (47.7)	1580 (62.3)
Hyperlipidemia	4198 (52.5)	3101 (66.5)	1845 (72.7)
Atrial fibrillation	25 (0.3)	21 (0.5)	26 (1.0)
Cancer	463 (5.8)	373 (8.0)	252 (9.9)
Laboratory findings			
LVEF, %	64.6 ± 5.5	64.9 ± 5.6	65.2 ± 5.6
NT-proBNP, pg/mL (*N* = 8308)	30.6 ± 45.2	33.9 ± 58.5	55.8 ± 135.9
Total cholesterol, mg/dL	193.8 ± 34.3	192.5 ± 36.9	179.8 ± 37.4
LDL-C, mg/dL	125.6 ± 31.6	125.2 ± 33.6	112.8 ± 33.7
HDL-C, mg/dL	56.6 ± 15.0	54.2 ± 14.0	53.9 ± 14.1
hsCRP, mg/dL	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
Lipoprotein (a), mg/dL	18.6 ± 17.7	19.3 ± 19.4	21.1 ± 22.6
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.3
Medication			
Statin	891 (11.1)	1078 (23.1)	880 (34.7)
Aspirin	442 (5.5)	712 (15.3)	80 (3.2)
Antihypertensive agents	1495 (18.7)	1753 (37.6)	1413 (55.7)
Antidiabetic agents	464 (5.8)	545 (11.7)	553 (21.8)

The values are presented as the mean ± SD or number (%), respectively, for continuous or categorical variables

All p for trends comparing baseline characteristics of the three groups were < 0.05

Abbreviations: *BMI* Body mass index, *CAC* Coronary artery calcium, *HDL-C* High-density lipoprotein cholesterol, *hsCRP* high-sensitivity C-reactive protein, *IQR* Interquartile range, *LDL-C* Low-density lipoprotein cholesterol, *LVEF* Left ventricular ejection fraction, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *SD* Standard deviation

Associations between CAC and baseline echocardiographic parameters

In terms of the parameters of echocardiography, the CAC was linearly associated with lower septal e′, higher E/e′, LV mass, and TR velocity among the groups (Additional file 1: Table S1). On the other hand, CAC showed no linear association with E velocity. When performing association analysis between CAC as a continuous variable and E/e′, there was a linear correlation between CAC and E/e′ (p = 0.001, Fig. 1). At baseline, the prevalence of definite and probable DD was 2.6%, and 12.2%, respectively.

The prevalence ratio for definite DD was 1.34 (95% CI: 0.98–1.69) and 1.72 (95% CI: 1.23–2.22) in the groups of 0 < CAC < 100 and CAC ≥ 100 compared to the CAC = 0 group, respectively (Table 2). The prevalence ratio for definite or probable DD when comparing the groups of 0 < CAC < 100 and CAC ≥ 100 with the CAC = 0 group was 1.31 (95% CI: 1.15, 1.47) and 1.83 (95% CI: 1.31–2.36), respectively (Table 2). When we divided CAC ≥ 100 into 100 ≤ CAC < 400 and CAC ≥ 400, CAC ≥ 400 was strongest associated with both definite DD and definite or probable DD (Table 2). Higher CAC score was positively associated with the prevalence of definite and probable DD regardless of age (Additional file 1: Fig. S1).

Effects of CAC and DD on mortality

From baseline to date at vital status confirmation (median follow-up was 5.1 years, maximum 9.5 years), 117 individuals died. CAC and DD were independently associated with increased mortality (Additional file 1: Table S2). The CAC ≥ 100 with definite DD group at baseline showed the highest cumulative mortality rate among 4 groups (Fig. 2). Compared with CAC < 100 without definite DD, the adjusted HRs (95% CIs) for all-cause mortality of CAC ≥ 100 without definite DD and CAC < 100 with definite DD were 2.56 (95% CI: 1.67–3.94) and 3.08 (95% CI: 1.28–7.39), respectively. The

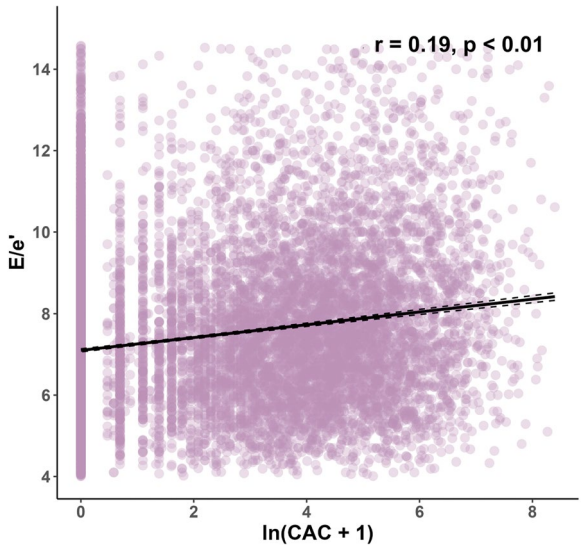

Fig. 1 Associations between CAC and E/e'. The linear *p* value for CAC with E/e' was 0.001. Abbreviations: CAC, coronary artery calcium; LVEF, left ventricular ejection fraction

Table 2 Prevalence ratio for incidence of diastolic dysfunction by CAC score

CAC score	Number of DD cases (%)	Adjusted prevalence ratio (95% CI)[a]	*p* value
Definite DD	407 (2.6)		
CAC = 0	108 (1.4)	Reference	
0 < CAC < 100	145 (3.1)	1.34 (0.98, 1.69)	0.053
CAC ≥ 100	154 (6.1)	1.72 (1.23, 2.22)	< 0.01
100 ≤ CAC < 400	90 (5.1)	1.62 (1.11, 2.14)	< 0.01
CAC ≥ 400	64 (8.3)	2.34 (1.49, 3.20)	< 0.01
Definite or probable DD	1857 (12.2)		
CAC = 0	555 (6.9)	Reference	
0 < CAC < 100	654 (14.0)	1.31 (1.15, 1.47)	< 0.01
CAC ≥ 100	648 (25.5)	1.83 (1.31, 2.36)	< 0.01
100 ≤ CAC < 400	388 (22.0)	1.60 (1.36, 1.85)	< 0.01
CAC ≥ 400	260 (33.6)	2.25 (1.85, 2.65)	< 0.01

Abbreviations: BMI Body mass index, *CAC* Coronary artery calcium, *CI* Confidence interval, *DD* Diastolic dysfunction

[a] Adjusted for age, sex, BMI category, smoking status (never, ever, or missing), drinking status, diabetes, hypertension, hyperlipidemia, atrial fibrillation, history of cancer, aspirin use, and statin use at baseline

risk of mortality was highest in patients with CAC ≥ 100 and definite DD (adjusted HR: 3.91, 95% CI: 1.68–9.10, Table 3). When comparing the outcomes between CAC ≥ 100 without definite DD and CAC < 100 with definite DD, there was no significant difference in the risk of mortality (adjusted HR: 1.20, 95% CI: 0.50–2.86, $p = 0.68$).

Association between CAC and progression of DD

Among the participants, those without definite or probable DD at the time of CAC measurement who had at least two available echocardiographic measurements were 4703 and 5540, respectively. The average duration of follow-up was 4.1 years (maximum 9.9 years; average number of visits per participant was 4.5). During the follow-up period, the annual average incidence rates of definite DD in participants with CAC = 0, 0 < CAC < 100, and CAC ≥ 100 at baseline were 0.48, 0.95, and 2.34, respectively (Fig. 3A). The multivariable adjusted hazard ratios (HRs) of definite DD (95% CI) for comparing participants with CAC = 0 to those with 0 < CAC < 100 and CAC ≥ 100 were 1.32 (95% CI: 0.90–1.95) and 1.95 (95% CI: 1.16–3.26), respectively (Table 4). The annual average incidence rates of definite or probable DD in participants with CAC = 0, 0 < CAC < 100, and CAC ≥ 100 were 1.82, 3.08, and 5.23, respectively (Fig. 3B). The multivariable adjusted HRs of definite or probable DD (95% CI) comparing participants with CAC = 0 to those with 0 < CAC < 100 and CAC ≥ 100 were 1.17 (95% CI: 0.96–1.44) and 1.46 (95% CI: 1.13–1.88), respectively (Table 4).

Among participants without definite or probable DD, the 0 < CAC < 100 (difference: 0.03, 95% CI: 0.00–0.06, $p = 0.042$) and CAC ≥ 100 (difference: 0.06; 95% CI: 0.02–0.10, $p = 0.003$) groups showed faster increasing trends of E/e' compared to the CAC = 0 group (Fig. 4).

Among the study participants, there were 2059 participants without DD at baseline and second visits who underwent serial CAC measurements and had at least three visits. Among these populations, median change of CAC between first and second visit was 14 (interquartile range from 0 to 65). During the median 2 years between the first and second CAC measurements (interquartile range from 1.2 to 3.2 years), there were 351 (33.1%), 552 (52.1%), and 156 (14.7%) patients with decreased or no change, increased > 0– < 100, and increased CAC ≥ 100 group, respectively. The participants who had increased CAC 100 or above had 2.6 times (95% CI: 1.16–5.83) higher risk of incidence of definite DD compared to the CAC decreased or no change group (Additional file 1: Table S3).

Discussion

The current study investigated the relationship between CAC score and prevalence of DD, their effects on mortality, and the progression of DD over time according to CAC score in a general population using a large longitudinal cohort from a health screening examination

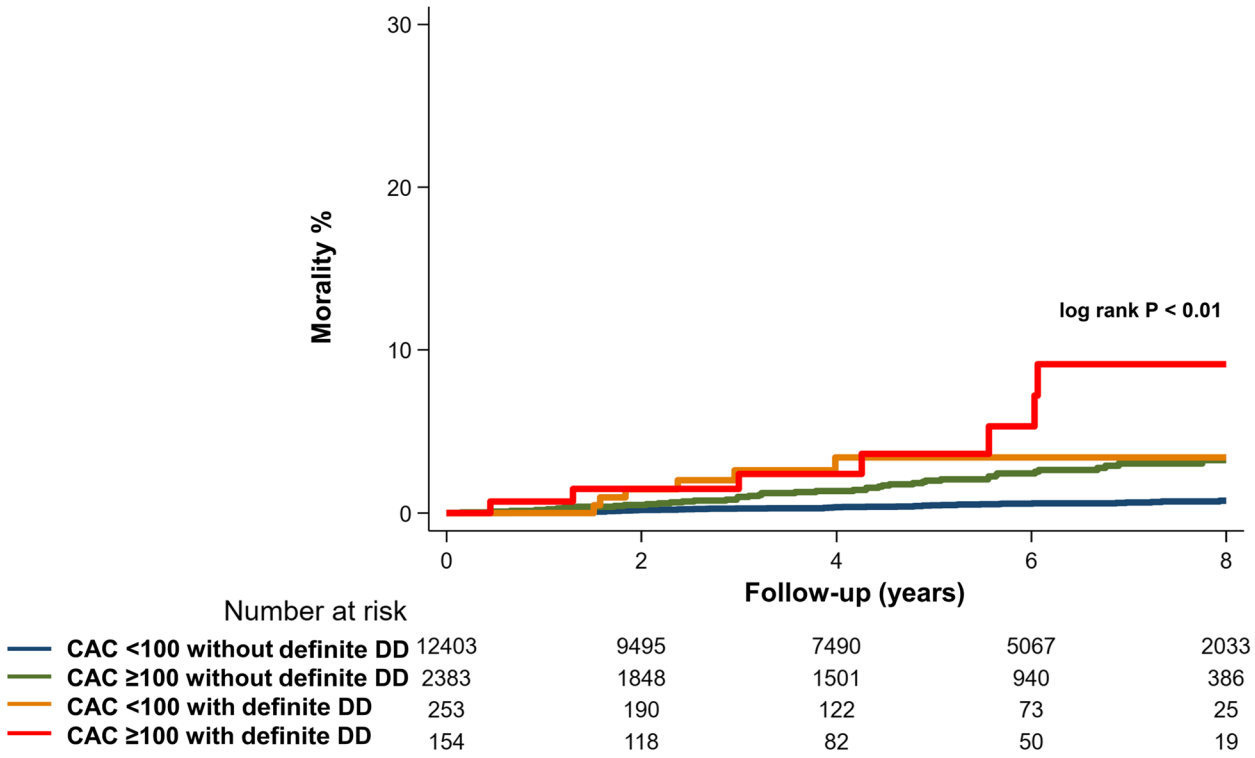

Fig. 2 Kaplan–Meier curve for all-cause mortality by DD and CAC score. Abbreviations: CAC, coronary artery calcium; DD, diastolic dysfunction

Table 3 Hazard ratio for mortality by CAC score and diastolic dysfunction

	8-year cumulative mortality, % (95% CI)	Adjusted hazard ratio (95% CI)[a]	*p* value
CAC < 100 without definite DD	0.96 (0.68, 1.35)	Reference	
CAC ≥ 100 without definite DD	3.62 (2.56, 5.10)	2.56 (1.67, 3.94)	< 0.01
CAC < 100 with definite DD	3.27 (1.47, 7.20)	3.08 (1.28, 7.39)	0.012
CAC ≥ 100 with definite DD	9.94 (4.51, 21.14)	3.91 (1.68, 9.10)	< 0.01

Abbreviations: BMI Body mass index, *CAC* Coronary artery calcium, *CI* Confidence interval, *DD* Diastolic dysfunction

[a] Adjusted for age, sex, BMI category, smoking status (never, ever, or missing), drinking status, diabetes, hypertension, hyperlipidemia, atrial fibrillation, history of cancer, aspirin use, and statin use at baseline

program. The principal findings of this study were as follows. First, the prevalence ratio of definite or probable DD was significantly higher in participants with CAC ≥ 100 compared to those without CAC, even after adjustment for confounding factors including age. In particular, CAC as a continuous variable was significantly correlated with baseline E/e′. Second, after stratification according to CAC score and definite DD, individuals with CAC ≥ 100 and definite DD showed the highest risk of mortality. Third, in longitudinal analysis, significant CAC (≥ 100) was associated with accelerated progression in DD over time, with more rapid elevation of LV filling pressure as measured by E/e′.

Associations between CAC and DD and their effects on mortality

Both CAC and DD were associated with advanced age, hypertension, diabetes mellitus, and obesity [1–3, 22, 23]. These comorbidities are believed to trigger a systemic proinflammatory state, leading to coronary microvascular dysfunction, followed by structural and functional alterations such as myocardial inflammation and interstitial fibrosis [24], and these changes may affect both LV diastolic stiffness and formation of calcified coronary plaques. In this regard, several previous studies have been conducted to evaluate the association between CAC and DD [25–27]. However, none of these studies had a large sample size. Therefore, the

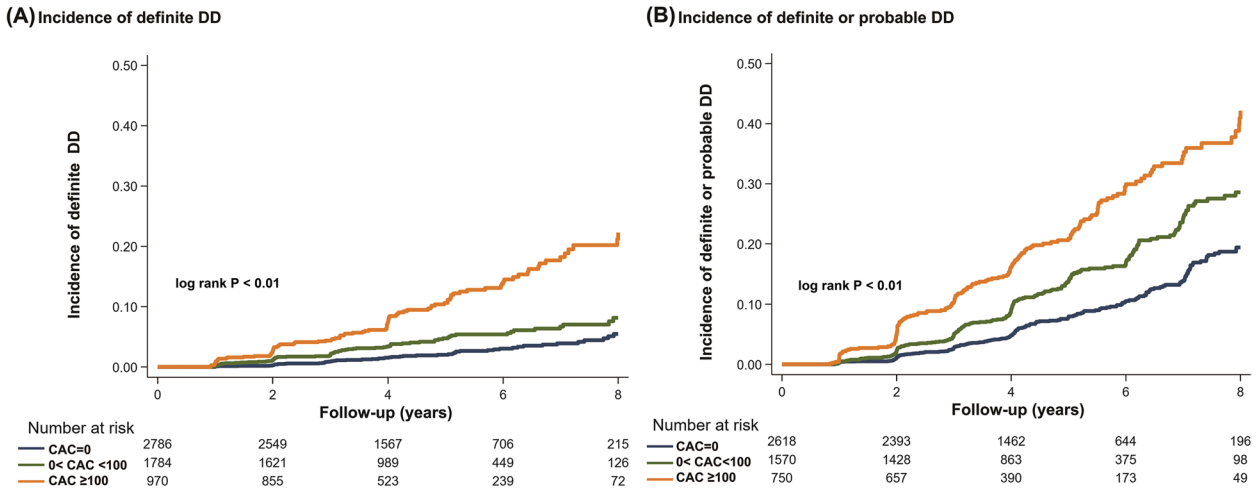

Fig. 3 Kaplan–Meier curve for incidence of definite (**A**) and definite or probable (**B**) DD by CAC score. Abbreviations: CAC, coronary artery calcium; DD, diastolic dysfunction

Table 4 Hazard ratios for incidence of diastolic dysfunction by CAC score among participants without dysfunction at baseline

	Number of events (incidents % per year)	Adjusted hazard ratio (95% CI)[a]	*p* value
Definite DD (*N* = 5540)	240 (0.95)		
CAC = 0	62 (0.48)	Reference	
0 < CAC < 100	77 (0.95)	1.32 (0.90, 1.95)	0.125
CAC ≥ 100	101 (2.34)	1.95 (1.16, 3.26)	< 0.01
Definite or probable DD (*N* = 4703)	606 (2.72)		
CAC = 0	217 (1.82)	Reference	
0 < CAC < 100	218 (3.08)	1.17 (0.96, 1.44)	0.103
CAC ≥ 100	171 (5.23)	1.46 (1.13, 1.88)	< 0.01

The hazard ratio was estimated using inverse probability weighting (see text for details) for generalizability

Abbreviations: BMI Body mass index, *CAC* Coronary artery calcium, *CI* Confidence interval, *DD* Diastolic dysfunction

[a] Adjusted for age, sex, BMI, smoking status (never, ever, or missing), drinking status, diabetes, hypertension, hyperlipidemia, atrial fibrillation, history of cancer, aspirin use, and statin use at baseline

association between CAC and DD is currently inconclusive, with conflicting results after adjusting for common shared comorbidities. The current study found that the overall prevalence of definite DD for 2.6% and an independent association between CAC score and DD, even after adjustment for various comorbidities in a large cohort of a general population without a previous history of cardiovascular disease. Interestingly, CAC score was continuously correlated with baseline E/e′. In addition, a higher CAC score was associated with the prevalence of DD irrespective of age category. These results imply that CAC score offers incremental information beyond traditional risk factors for predicting DD or high filling pressure.

The presence of both CAC and DD is an independent predictor of cardiovascular outcomes in numerous cohorts [8–11, 28]. However, there is a scarcity of data regarding the effects on mortality when patients have both subclinical CAC and DD. In the current study, participants with either DD or a significant CAC score (≥ 100) had an increased risk of all-cause mortality during follow-up compared to those without DD and significant CAC, and those with both conditions exhibited the highest risk. There was no significant difference in the risk of mortality between CAC ≥ 100 without definite DD and CAC < 100 with definite DD. This integration of subclinical parameters suggests compounded cardiovascular risk, likely mediated by shared pathophysiological pathways such as microvascular dysfunction, inflammation, and myocardial fibrosis. Importantly, the increased trend of NT-proBNP with increasing CAC scores highlights the potential overlap with decompensated HFpEF phenotypes, although the mean NT-proBNP level was lower than the cutoff value of HFpEF even in the CAC ≥ 100 group. These results underscore the need for early detection and monitoring of patients with subclinical CAC and DD, as they may represent a population at heightened risk for progression to overt heart failure and cardiovascular mortality.

Progression of DD according to presence of CAC

Although CAC and DD share some pathophysiology and risk factors, their independent effects on each other are

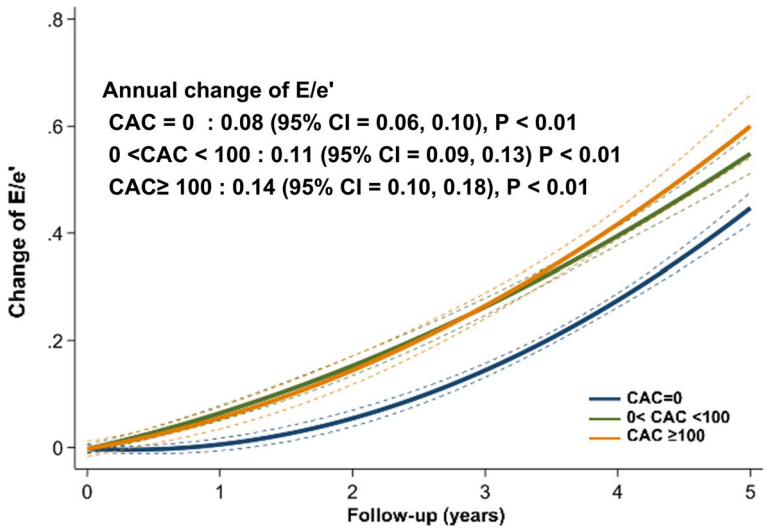

Fig. 4 Average trajectories of E/e′ by CAC group. Trajectories were obtained from mixed linear models for longitudinal data with random intercepts and random slopes. Models were adjusted for age, sex, BMI category, smoking status (never, ever, or missing), drinking status, diabetes, hypertension, hyperlipidemia, atrial fibrillation, history of cancer, aspirin use, and statin use at baseline. Abbreviations: BMI, body mass index; CAC, coronary artery calcium

not well characterized. Therefore, we hypothesized that participants with a significant CAC score at baseline have more highly accelerated progression of DD over time than those without CAC, independent of other clinical characteristics. If substantiated, this would establish CAC as a crucial biomarker for preclinical HFpEF, enhancing its utility in guiding more effective preventive interventions. In our longitudinal dataset of participants with a significant CAC score and no DD at baseline, 1.9% developed definite and 5.2% developed definite or probable DD each year. The HR for definite DD and definite or probable DD was 1.95 and 1.46, respectively, in participants with CAC ≥ 100, compared to participants with CAC = 0, after adjusting for age, sex, BMI, or other potential confounders including comorbidities. Considering that patients with a CAC ≥ 400 showed the highest prevalence ratio of DD, CAC score and development of DD might have a dose–response relationship. The current study also showed a significant CAC score was associated with a more rapid increase of E/e′ during follow-up than in patients without CAC. Furthermore, patients with increased CAC ≥ 100 during follow-up were associated with a higher prevalence of DD. To our knowledge, this is the first study to confirm that significant CAC or rapid increase of CAC affects the progression of DD, even after adjustment for other clinical variables. These findings suggest that individuals with higher CAC scores or rapid increment of CAC during follow-up are at an increased risk of developing subclinical or overt HFpEF, emphasizing the need for early recognition by active surveillance and timely intervention.

Limitations

Several limitations should be considered in the interpretation of our findings. First, this study was derived from retrospective observational data; therefore, unmeasured confounding factors could have influenced the study results. Second, the severity of symptoms related to DD or CAC was not quantified in this study. Third, additional echocardiographic parameters from the 2016 ASE/EACVI recommendations, such as pulmonary venous flow or deceleration time or LV strain, were not included in the current study and could provide helpful guidance in the accurate assessment of diastolic function. Fourth, in the longitudinal dataset, there was a loss of sample size in the analysis of DD progression according to CAC by requiring participants to have undergone at least two echocardiograms. However, there were near 5000 participants in whom progression of DD was confirmed; therefore, the number of samples was sizable. Fifth, the follow-up duration was not standardized, potentially leading to variations in the timing of subsequent evaluations. Consequently, patients with more severe conditions might have undergone more frequent assessments, influencing the diagnosis of DD during follow-up. Sixth, specific causes of death information and other cardiovascular adverse events were not available in the current cohort. Seventh, our study was conducted in Korean men and women attending regular health screening examinations, and our findings may not be generalizable to other populations, particularly other ages, or race/ethnicity.

Conclusions

In a general population that underwent a comprehensive health screening exam with simultaneous echocardiography and CAC scan, there was strong association between CAC and DD. If patients had both subclinical parameters, their risk of mortality further increased compared to those who had only one. Moreover, the presence of a significant CAC score (≥100) might affect the progression of DD independent of other clinical factors. These findings highlight the potential of CAC as a biomarker for preclinical HFpEF and the importance of considering subclinical parameters for risk assessment in the general population.

Abbreviations

ASE	American Society of Echocardiography
BMI	Body mass index
CAC	Coronary artery calcium
CI	Confidence interval
CT	Computed tomography
DD	Diastolic dysfunction
EACVI	European Association of Cardiovascular Imaging
EF	Ejection fraction
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
IPW	Inverse probability weights
LAVI	Left atrial volume index
LV	Left ventricle
TR	Tricuspid regurgitation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03956-9.

Additional file 1. Tables S1–S3 and Figure S1. Table S1 Diastolic parameters measured by echocardiography in the study participants according to the presence of CAC (N = 15,193). Table S2 Hazard ratio for mortality by CAC score and diastolic dysfunction. Table S3 Hazard ratios for incidence of definite diastolic dysfunction by change of CAC score among participants without dysfunction at baseline and second visits who had at least 3 visits (N = 2059). Fig. S1 Prevalence of definite DD (A) and definite or probable DD (B) according to age by CAC group. Abbreviation: CAC, coronary artery calcium; DD, diastolic dysfunction.

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Authors' contributions

Drs. KHC, DK, SJC, and JHY had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Samsung Medical Center approved this study (SMC-2020–07-030) and waived the requirement for informed consent as we used only de-identified data routinely collected during health screening visits.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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