Original Article

Prognostic implications of left ventricular geometry in coronary artery bypass grafting patients

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Background: The prognostic implications of left ventricular (LV) mass and geometry have been confirmed in populations with different cardiac diseases. However, the prognostic value of LV geometry in coronary artery bypass grafting (CABG) patients is unclear.

Methods: A total of 2,517 patients undergoing CABG between January 2012 and September 2016 in our cardiac surgery unit were included. Patients were divided into the following 4 groups according to left ventricular mass index (LVMi) and relative wall thickness (RWT): normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy.

Results: The median follow-up period was 47.0 months (interquartile range was 32.5–61.3 months). Compared to the normal geometry group, the concentric remodeling group [hazard ratio (HR): 3.023; 95% confidence interval (CI): 1.134–8.060], the eccentric hypertrophy group (HR: 3.422; 95% CI: 1.395–8.398), and the concentric hypertrophy group (HR: 5.399; 95% CI: 2.289–12.735) have higher main adverse cardiovascular and cerebrovascular event (MACCE) risk. Moreover, increased MACCE risk was associated with higher LVMi (HR: 1.015 per 1 g/m^2 increase in LVMi; 95% CI: 1.005–1.026) and RWT (HR: 1.991 per 0.1-U increase in RWT; 95% CI: 1.343–2.952). We observed similar results concerning mortality. Adding LV geometry to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II significantly improved the area under the curve (AUC) for MACCE (from 0.621 to 0.703; P=0.042). The addition of LV geometry showed significant integrated discrimination improvement (IDI) and net reclassification improvement (NRI) for MACCE (IDI: 0.043, P<0.001; NRI: 0.200, P<0.001) and death (IDI: 0.018, P=0.020; NRI: 0.308, P=0.002), as was the addition of LVMi and RWT.

Conclusions: LV geometry is an independent and incremental prognostic factor for MACCE and death in CABG patients.

Keywords: Left ventricular geometry; coronary artery bypass grafting (CABG); coronary heart disease (CHD); EuroSCORE II; prognosis

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Introduction

As a significant cause of death and disability, coronary heart disease (CHD) can result in myocardial infarction (MI), ischemic cardiomyopathy, and ischemic mitral insufficiency, leading to left ventricular (LV) remodeling (1). Major cardiac remodeling can cause progressive deterioration of cardiac function (2-5). The remodeling process often involves increases in myocardial mass. Irrespective of etiology, LV

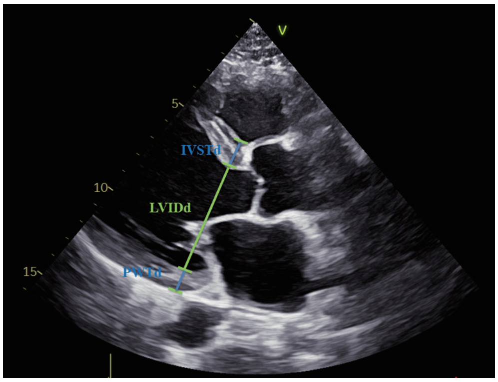

Figure 1 Measurement of echocardiographic variables. IVSTd, interventricular septum thickness at end-diastole; LVIDd, left ventricular end-diastolic internal diameter; PWTd, the posterior wall thickness at end-diastole.

hypertrophy, and increased LV mass are independent risk factors for cardiovascular mortality and morbidity (6-8). In patients with CHD, MI, or hypertension, LV hypertrophy leads to a 2- to 4-fold increase in the incidence of death or nonfatal complications (6).

Coronary artery bypass grafting (CABG) is an effective procedure for treating CHD. Along with the aging of the population and improvements in percutaneous coronary intervention (PCI), the complexity of patients referred to CABG is increasing, and so too are the rate of the patients with LV remodeling and LV hypertrophy. The current systems for evaluating the outcomes of cardiac surgery, including the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the EuroSCORE II, do not consider the impact of LV mass and geometry on surgical outcomes, which hold significant prognostic value (9).

Despite the association between the prognosis of CHD, MI, or hypertension and LV hypertrophy, there is still uncertainty about whether LV geometry, left ventricular mass index (LVMi), and relative wall thickness (RWT) have independent prognostic value on the outcomes of CABG (10). This study aims to explore the prognostic value of LV geometric patterns in CABG patients.

Methods

Study design

The institutional ethics board approved the study of Rui Jin Hospital (No. 2018-15), and informed consent was obtained from all patients. We enrolled patients between January 2012 and September 2016. Patients who underwent CABG and had available preoperative echocardiographic recordings met the criteria for inclusion in this study. Patients undergoing emergency surgery repeated CABG, or undergoing other procedures in addition to CABG were excluded from the study.

Data collection

The baseline characteristics of all participants, including EuroSCORE II values, were obtained from the hospital information system. EuroSCORE II values were calculated at admission. We obtained the preoperative echocardiographic recordings from the local database.

Echocardiographic analysis

Echocardiography was with recommendations from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE), using commercially available systems (11,12). The preoperative echocardiography in this study was transthoracic. Echocardiographic variables include posterior wall thickness at end-diastole (PWTd), left ventricular end-diastolic internal diameter (LVIDd), and interventricular septum thickness at end-diastole (IVSTd). *Figure 1* demonstrates the measurement of these parameters. Following the recommendations of the ASE, the LV mass was calculated using the formula LV mass $=0.60+ [(PWTd + LVIDd + IVSTd)^3 - LVIDd^3] \times 1.04 \times 0.80$. LV mass index (LVMi) was calculated using the formula LVMi =(LV mass)/[body surface area (BSA)], and RWT was calculated using the formula RWT $=2\times$ (PWTd)/(LVIDd) (11,13). We used the Du Bois formula to estimate BSA (14). LV hypertrophy was defined as LVMi >95 g/m^2 for women and >115 g/m^2 for men, and increased RWT was defined as RWT >0.42 (11,13). According to a previous study by Verma *et al.*, we assigned patients into the following 4 groups with LVMi and RWT: normal geometry (normal LVMi and normal RWT), concentric remodeling (normal LVMi and increased RWT), eccentric hypertrophy (LV hypertrophy and normal RWT), and concentric hypertrophy (LV hypertrophy and increased RWT) (15).

Outcome measures

We recorded the incidence of all-cause death, MI, ischemic

Table 1 Baseline characteristics stratified by LV geometric patterns

Baseline characteristics	Normal geometry (n=1,732)	Concentric remodeling (n=176)	Eccentric hypertrophy (n=499)	Concentric hypertrophy (n=110)	P value
Male sex (%)	84.5	80.1	66.7	55.5	<0.001
Mean age (years)	64.9±9.1	66.2±8.8	66.6±8.8	68.8±8.0	<0.001
BMI (kg/m^2)	24.8±3.1	25.0±3.0	24.3±2.7	25.3±3.3	0.001
Hypertension (%)	57.6	68.8	64.9	73.6	<0.001
DM (%)	36.7	39.8	40.7	45.5	0.136
Hyperlipidemia (%)	11.9	15.3	10.0	8.2	0.171
MI (%)	21.4	14.8	28.1	16.4	<0.001
Stroke (%)	9.6	10.8	11.0	10.0	0.793
PCI (%)	9.6	10.8	8.0	7.3	0.542
COPD (%)	2.5	2.8	3.4	3.6	0.707
Smokers (%)	45.0	49.4	41.1	30.9	0.007
Family history (%)	2.0	3.4	2.2	2.7	0.658
PVD (%)	3.0	3.4	4.2	7.3	0.081
EF (%)	62.7±7.9	67.3±4.2	54.9±10.5	65.2±5.3	<0.001
EuroSCORE II (%)	1.9±1.6	1.8±1.6	2.7±2.2	2.9±2.8	<0.001
NYHA class (%)	2.5±0.6	2.4±0.6	2.6±0.6	2.5±0.7	0.008
LM lesion (%)	16.5	19.3	14.2	15.5	0.420
In situ LIMA-LAD (%)	61.5	67.6	50.1	55.5	<0.001
Number of grafts	3.5±0.9	3.5±0.8	3.6±0.9	3.6±1.0	0.306
Systolic blood pressure	130.5±18.8	136.0±18.4	135.1±19.6	145.1±22.8	<0.001
Diastolic blood pressure	74.2±10.8	75.0±10.5	74.9±11.5	75.0±13.0	0.504

LV, left ventricular; BMI, body mass index; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; PVD, Peripheral vascular disease; EF, ejection fraction; NYHA, New York Heart Association; LM, left main coronary artery; LIMA, left internal mammary artery; LAD, left anterior descending artery.

stroke, hospitalized heart failure, and resuscitation after cardiac arrest. The primary outcome measures were all-cause death and main adverse cardiovascular and cerebrovascular events (MACCE), and a composite outcome of MI, ischemic stroke, death, hospitalized heart failure and resuscitation after cardiac arrest.

Follow-up

The database was reviewed yearly to identify regular follow-up information. Furthermore, we contacted all participants in this study again by phone using standard forms and procedures.

Statistical analysis

The propensity scores of all patients were established by using a multivariate logistic regression model. The variables in *Table 1*, except systolic blood pressure and diastolic blood pressure, are the prespecified covariates. Concentric hypertrophy patients were matched with the normal geometry, concentric remodeling, and eccentric hypertrophy patients by using nearest-neighbor propensity score matching. Categorical variables are summarized as percentages, and continuous variables as median (the 25th percentile, the 75th percentile) or mean (± standard deviation). ANOVA or a Kruskal-Wallis test was used

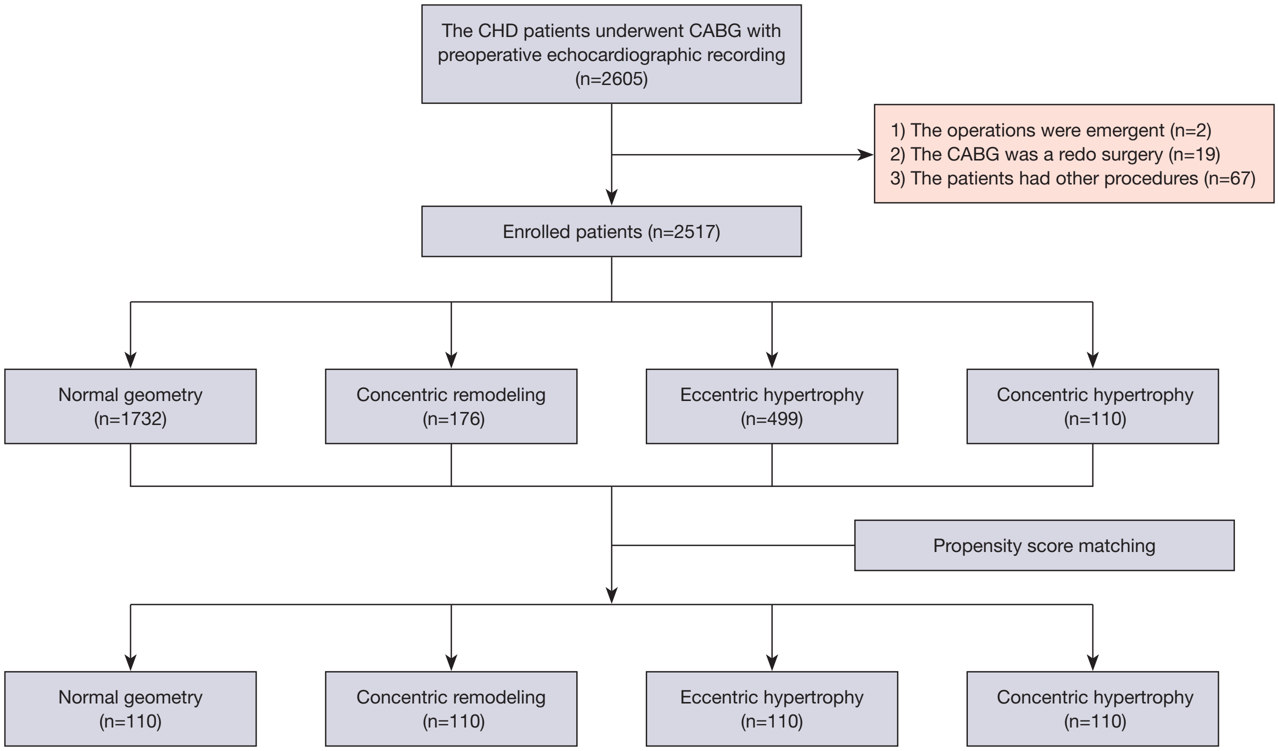

Figure 2 Flow diagram of the study design. CHD, coronary heart disease; CABG, coronary artery bypass grafting.

to compare continuous variables of more than 2 groups. A Mann-Whitney U test or Student's t-test was used to compare continuous variables between 2 groups. Fisher's exact test or χ^2 test was used to compare categorical variables. The Kaplan-Meier method and the log-rank test were used to calculate and compare the cumulative survival rate and freedom from MACCE. The independent predictors of MACCE or death were determined by using a Cox proportional hazard model. Variables associated with MACCE or death in the univariate analysis (P<0.1) are included in the multivariate analysis as confounding variables. The area under the curve (AUC), category-free net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were used to evaluate the predictive value of LV geometry for MACCE and death. AUC was calculated by using receiver operating characteristic (ROC) analysis, and NRI and IDI were obtained by using the R package PredictABEL (Suman Kundu, Yurii S. Aulchenko, and A. Cecile J.W. Janssens, 2014). We performed all analyses using R version 3.4.3 and SPSS version 22.0 (IBM, Chicago, Illinois). P values <0.05 were considered significant. A Bonferroni's test was used for post-hoc comparisons.

Results

Patient characteristics

A total of 1,732, 176, 499, 110 patients were assigned into the normal geometry group, the concentric remodeling group, the eccentric hypertrophy group, and the concentric hypertrophy group, respectively. After the propensity score matching (PSM), each group had 110 patients. *Figure 2* shows a detailed flow diagram of this study. Patient characteristics before and after PSM are listed in *Tables 1* and *2*. Before PSM, gender, age, body mass index (BMI), hypertension history, MI history, smoking history, preoperative ejection fraction (EF), EuroSCORE II, New York Heart Association (NYHA) class, *in situ* left internal mammary artery (LIMA)-left anterior descending coronary artery (LAD), graft completion, and systolic blood pressure was significantly different between the 4 groups (P<0.05) (*Table 1*). After the PSM, all baseline characteristics, except systolic blood pressure (P=0.003), were similar among the 4 groups (P>0.05) (*Table 2*).

Table 2 Baseline characteristics stratified by LV geometric patterns after PSM

Baseline characteristics	Normal geometry (n=110)	Concentric remodeling (n=110)	Eccentric hypertrophy (n=110)	Concentric hypertrophy (n=110)	P value
Male sex (%)	50.9	68.2	56.4	55.5	0.062
Mean age (years)	68.8±9.2	67.7±8.5	68.8±8.2	68.8±8.0	0.682
BMI (kg/m^2)	25.5±3.7	25.1±3.1	25.3±2.8	25.3±3.3	0.874
Hypertension (%)	75.5	72.7	73.6	73.6	0.974
DM (%)	50.0	41.8	44.5	45.5	0.673
Hyperlipidemia (%)	13.6	9.1	6.4	8.2	0.270
MI (%)	13.6	16.4	19.1	16.4	0.754
Stroke (%)	9.1	10.0	11.9	10.0	0.925
PCI (%)	9.1	7.3	7.3	7.3	0.944
COPD (%)	2.7	3.6	3.6	3.6	0.976
Smokers (%)	24.5	40.9	31.8	30.9	0.076
Family history (%)	1.8	0.9	1.8	2.7	0.797
PVD (%)	5.5	3.6	5.5	7.3	0.703
EF (%)	65.5±6.7	66.3±4.4	64.8±6.2	65.2±5.3	0.233
EuroSCORE II (%)	2.7±3.0	2.1±1.8	2.8±2.7	2.9±2.8	0.095
NYHA class (%)	2.5±0.6	2.5±0.6	2.5±0.7	2.5±0.7	0.857
LM lesion (%)	22.7	18.2	12.7	15.5	0.241
In situ LIMA-LAD (%)	50.9	61.8	47.3	55.5	0.156
Number of grafts	3.5±0.9	3.5±0.8	3.6±0.9	3.6±1.0	0.306
Systolic blood pressure	137.0±20.9	135.7±17.4	136.7±16.9	145.1±22.8	0.003
Diastolic blood pressure	73.8±11.4	74.1±9.9	73.0±10.6	75.0±13.0	0.659

LV, left ventricular; BMI, body mass index; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; PVD, Peripheral vascular disease; EF, ejection fraction; NYHA, New York Heart Association; LM, left main coronary artery; LIMA, left internal mammary artery; LAD, left anterior descending artery.

The relationship between LV geometry and outcomes after CABG

The median follow-up period was 47.0 months (interquartile range, 32.5 to 61.3 months), and the follow-up rate was 93.6%. A total of 74 patients (18.0%) had MACCE events, and 45 (10.9%) died. The patients with concentric hypertrophy had the highest MACCE rate (P<0.001) and mortality (P=0.018) compared to the other 3 groups (*Table 3*). It was determined that the cumulative freedom from MACCE in concentric hypertrophy (P<0.001) or eccentric hypertrophy (P=0.013) patients was significantly lower than the normal geometry patients (*Figure 3*). Similarly, the cumulative survival rate in concentric hypertrophy patients was lower compared to the other 3 groups (P=0.006) (*Figure 4*). The cumulative freedom from MACCE and the cumulative survival rate of the concentric remodeling patients were lower than the normal geometry patients. However, there was no statistical difference (P>0.05) (*Figures 3* and *4*).

Table 4 shows the results from the Cox proportional hazard models. In univariate analysis, concentric hypertrophy (MACCE: P<0.001; death: P=0.005) and eccentric hypertrophy (MACCE: P=0.017; death: P=0.049)

Table 3 Impact of LV geometry on mid-term adverse events in CABG patients

Mid-term adverse events	Normal geometry (n=103)	Concentric remodeling (n=103)	Eccentric hypertrophy (n=101)	Concentric hypertrophy (n=105)	P value
MACCE (%)	6.8	14.6	19.8	30.5	<0.001
Death (%)	4.9	7.8	13.9	17.1	0.018
MI (%)	0.0	2.9	2.0	6.7	0.035
Ischemic stroke (%)	2.9	5.8	5.9	9.5	0.260
Hospitalized heart failure	0.0	1.0	5.0	12.4	<0.001
Resuscitation after cardiac arrest	0.0	0.0	1.0	4.8	0.011

LV, left ventricular; CABG, coronary artery bypass grafting; MACCE, main adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.

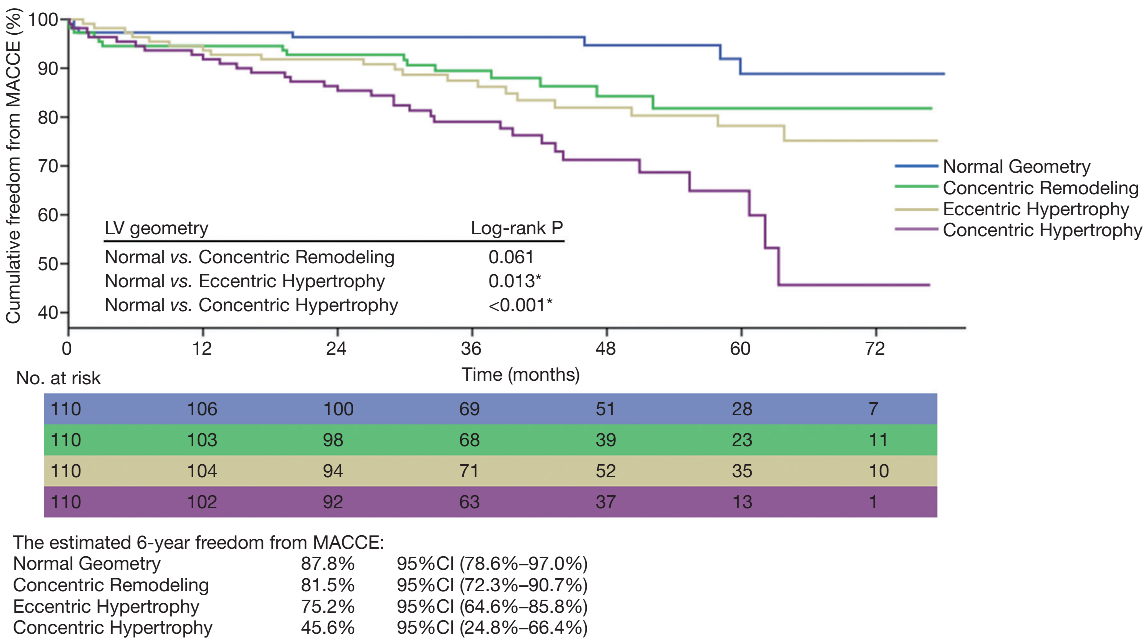

Figure 3 Kaplan-Meier curves of freedom from MACCE. The Kaplan–Meier method and the log-rank test were used to calculate and compare freedom from MACCE. The cumulative freedom from MACCE in concentric hypertrophy patients was significantly lower than the normal geometry patients (P<0.001). The cumulative freedom from MACCE in eccentric hypertrophy or concentric hypertrophy patients was lower than the normal geometry patients. However, there was no statistical difference (P>0.05). K-M, Kaplan-Meier; MACCE, main adverse cardiovascular and cerebrovascular events; LV, left ventricular.

were significant determinants for MACCE or death, however concentric remodeling (MACCE: P=0.069; death: P=0.370) was not statistically different. In multivariate analysis, concentric hypertrophy had a significant association with increased risk of MACCE (P<0.001), as did eccentric hypertrophy (P=0.007) and concentric remodeling (P=0.027). The significant determinants for death were eccentric hypertrophy (P=0.024) and concentric hypertrophy (P=0.033). LVMi (MACCE: P=0.004; death: P=0.014) and RWT (MACCE: P=0.001; death: P=0.007) as continuous variables are significantly associated with an increased risk of MACCE or death in multivariate analysis. Systolic blood pressure and diastolic blood pressure are not significant determinants for MACCE or death (P>0.05).

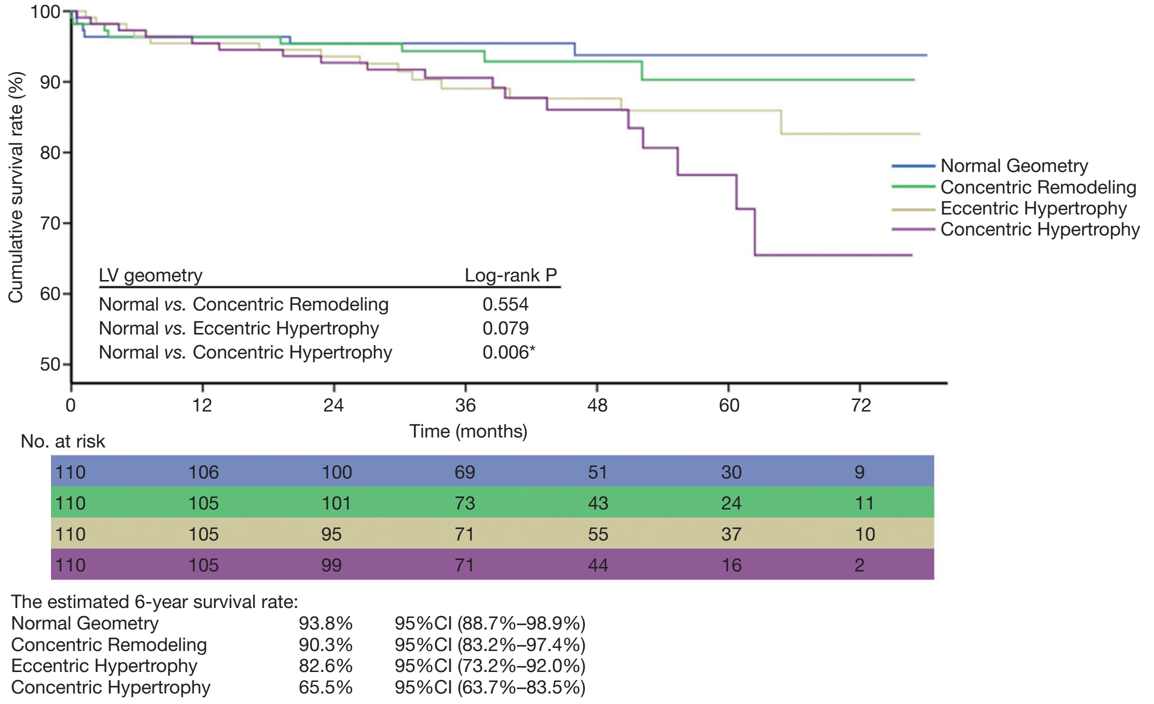

Figure 4 Kaplan-Meier survival curves. The Kaplan–Meier method and the log-rank test were used to calculate and compare cumulative survival rates. The cumulative survival rate of concentric hypertrophy patients was significantly lower than the normal geometry patients (P=0.006). The cumulative survival rate of the eccentric hypertrophy or concentric hypertrophy patients was lower than the normal geometry patients; however, there was no statistical difference (P>0.05).

Incremental prognostic value of LV geometry over EuroSCORE II

Adding LV geometry to EuroSCORE II did not significantly increase the AUC to predict MACCE (from 0.621 to 0.696; P=0.054) or death (from 0.648 to 0.691; P=0.218) (*Table 5*). After adding LVMi and RWT to EuroSCORE II as continuous variables, the AUC for MACCE increased significantly (from 0.621 to 0.703; P=0.042), but not for death (from 0.648 to 0.713; P=0.134) (*Table 5*). Reclassification measures (NRI and IDI) for MACCE or death improved significantly after incorporating either LVMi and RWT or LV geometry (*Table 5*). Compared with EuroSCORE II, the addition of LV geometry resulted in an IDI of 0.043 for MACCE (P<0.001) and 0.018 for death (P=0.020), which indicated an absolute increase of 4.3% in mean MACCE risk and 1.8% in mean death risk for patients with events compared to patients without events over EuroSCORE II. The addition of LVMi and RWT resulted in an IDI of 0.068 for MACCE (P<0.001) and 0.060 for death (P=0.001). The new model, including LV geometry, had an NRI of 0.200 for MACCE (P<0.001) and 0.308 for death (P=0.002). Moreover, the model, including LVMi and RWT, had an NRI of 0.212 for MACCE (P<0.001) and 0.256 for death (P=0.043).

Discussion

The results of this study confirmed that LV geometry was an independent prognostic factor for MACCE or death in patients undergoing CABG. Furthermore, the predictive ability of MACCE or death in CABG patients was improved significantly by incorporating LVMi and RWT or LV geometry with EuroSCORE II.

Increased LV mass and abnormal LV geometric patterns, including concentric ventricular remodeling, eccentric hypertrophy, and concentric hypertrophy, result from volume and pressure overload (6,15). They are considered to reflect the chronicity and severity of cardiovascular risk factors and may have better prognostic ability than current predictors (16,17). The prognostic implications of LV mass and geometry have been confirmed in populations with different cardiac diseases, including CHD, left ventricular

Table 4 Unadjusted and adjusted Cox regression analysis for MACCE and death

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
MACCE						
Categorical variables						
Normal geometry (reference)	1.000					
Concentric remodeling	2.304	0.938–5.659	0.069	3.023	1.134–8.060	0.027
Eccentric hypertrophy	2.843	1.202–6.725	0.017	3.422	1.395–8.398	0.007
Concentric hypertrophy	5.916	2.588–13.526	<0.001	5.399	2.289–12.735	<0.001
Continuous variables						
LVMi	1.022	1.012–1.031	<0.001	1.015	1.005–1.026	0.004
RWT×10	1.932	1.353–2.760	<0.001	1.991	1.343–2.952	0.001
Death						
Categorical variables						
Normal geometry (reference)	1.000					
Concentric remodeling	1.668	0.545–5.103	0.370	2.492	0.703–8.833	0.157
Eccentric hypertrophy	2.789	1.004–7.742	0.049	3.419	1.176–9.938	0.024
Concentric hypertrophy	4.155	1.532–11.268	0.005	3.077	1.092–8.670	0.033
Continuous variables						
LVMi	1.025	1.013–1.037	<0.001	1.017	1.003–1.031	0.014
RWT×10	2.170	1.365–3.450	0.001	2.106	1.232–3.602	0.007

MACCE, main adverse cardiovascular and cerebrovascular events; CI, confidence interval; LVMi, left ventricular mass index; RWT, regional wall thickness. HRs have been adjusted by age, history of peripheral vascular disease, NYHA class, ejection fraction, EuroSCORE II, and systolic blood pressure when admitted.

Table 5 Impact of adding LV geometry to EuroSCORE II on predicting outcomes

	AUC		Category-free NRI		IDI	
	Value	P value	Value	P value	Value	P value
MACCE						
EuroSCORE II (reference)	0.621					
EuroSCORE II + LV geometry	0.696	0.054	0.200	<0.001	0.043	<0.001
EuroSCORE II + LVMi + RWT	0.703	0.042	0.212	<0.001	0.068	<0.001
Death						
EuroSCORE II (reference)	0.648					
EuroSCORE II + LV geometry	0.691	0.218	0.308	0.002	0.018	0.020
EuroSCORE II + LVMi + RWT	0.713	0.134	0.256	0.043	0.060	0.001

AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; MACCE, main adverse cardiovascular and cerebrovascular events; LV, left ventricular; LVMi, left ventricular mass index; RWT, regional wall thickness.

systolic dysfunction and aortic stenosis (18-20). However, clinical data on the prognostic value of LV geometry in CABG patients is lacking. CABG is an essential treatment for CHD. CABG patients usually have severe CHD, and an increasing proportion of patients referred for CABG have severe complications and LV geometric adaptations. Since LV geometry has predictive value for CHD prognosis, there may be predictive potential for CABG patients.

This study demonstrated a significant association between abnormal LV geometry and cardiovascular risk. According to the multivariate Cox regression analyses, all LV geometric adaptations are independent risk factors for MACCE, and concentric LV hypertrophy has the highest risk of adverse events, therefore confirming the prognostic value of LV geometry in CABG patients. The renin-angiotensin-aldosterone system and hypertension play essential roles in the progression of LV hypertrophy and CHD. Increased LV mass that exceeds the scope of compensation for the increased cardiac load is a pathological process found in concentric LV hypertrophy (21,22). Moreover, there is abnormal collagen deposition around the intramyocardial coronary arteries and the extracellular matrix in patients with pathological increases in LV mass, inducing medial thickening, and stenosis of coronary arteries (23,24). For CABG patients, the extracellular collagen deposition is also associated with the calcification and failure of vein graft (25). LV hypertrophy induces disorganization of the sarcomere, loss of myocytes with fibrotic replacement, changes in glycolytic metabolism, alterations in calcium handling, adaptations in contractility, diastolic and systolic dysfunction, and electrical remodeling (26). These changes in structure, metabolism, and function may facilitate the association between LV hypertrophy and graft lesions, heart failure, or adverse cardiovascular events.

The rapidly growing use of PCI for myocardial revascularization and the aging of the population has led to many patients with severe complications, and abnormal LV geometry refers to CABG, which increases the risk of adverse events. Hence, better risk stratification and tailored treatment strategies are needed. There have been some evaluation systems used to predict the risk of perioperative and long-term adverse events in patients undergoing cardiac surgery, including EuroSCORE and EuroSCORE II (27-31). None of these evaluation systems incorporate information about LV geometry, despite being significantly associated with adverse events after CABG, as observed in this study. We demonstrated that LV mass or geometry provided an incremental prognostic value EuroSCORE II to predict mid-term MACCE or death in patients after CABG. Given that echocardiography is one of the routine tests before CABG, echocardiographic based LV geometry assessment can, therefore, be a practical and useful clinical tool for improving risk prediction and risk management in CABG patients.

This initial analysis of LV mass and geometry focused on individuals undergoing CABG. There is an additional need for accurate cardiovascular risk prediction for other cardiac interventions. Furthermore, this study is non-randomized, and another potential limitation of this study is that there might still be residual confounders. Moreover, patients without echocardiographic measurements at admission were not included in this study, which might have introduced selection bias.

Conclusions

LV geometry was an independent and incremental prognostic factor for MACCE and death in CABG patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-19-926). The authors have no conflicts of interest to declare.

Ethical Statement: The institutional ethics board approved the study of Rui Jin Hospital (NO. 2018-15), and informed consent was taken from all the patients.

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