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ORIGINAL ARTICLE
Heart Failure

Residual Gensini Score Is Associated With Long-Term Cardiac Mortality in Patients With Heart Failure After Percutaneous Coronary Intervention

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Background: Coronary revascularization is important in heart failure (HF) with ischemic etiology. Coronary scoring systems are useful to evaluate coronary artery disease, but said systems for residual stenosis after revascularization are still poorly understood. Therefore, the aim of the current study was to clarify the prognostic impact of residual stenosis using a coronary scoring system, Gensini score, in HF patients after percutaneous coronary intervention (PCI).

Methods and Results: We analyzed consecutive hospitalized ischemic HF patients (n=199) who underwent PCI. We calculated residual Gensini score after PCI, and divided the patients into 2 groups based on median residual Gensini score. The patients with high scores (≥10, n=101) had a higher prevalence of anemia, lower prevalence of dyslipidemia, and lower left ventricular ejection fraction, compared with those with low scores (<10, n=98). During the median follow-up period of 1,581 days (range, 20–2,896 days), the high-score patients had a higher cardiac mortality than the low-score group (log rank, P=0.001).

Conclusions: In patients with HF after PCI, residual Gensini score was associated with long-term cardiac mortality. Residual Gensini score may be a useful index for risk stratification of HF after PCI.

Key Words: Heart failure; Percutaneous coronary intervention; Prognosis; Residual Gensini score

Many heart failure (HF) patients with ischemic etiology have multivessel coronary artery disease (CAD).[1,2] Coronary revascularization by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) is an important treatment for such patients.[1,3–6] Complete revascularization is expected, but some patients have residual stenosis after PCI. Coronary scoring systems have been developed to evaluate CAD on coronary angiography (CAG) before revascularization, and the scores are related to prognosis after revascularization.[7,8] Coronary scoring systems are also useful for evaluating multivessel CAD. There are many coronary scoring systems based on CAG, such as SYNTAX, Angiographic Indices from the Coronary Artery Surgery Study, Coronary Artery Disease Prognostic Index, Jeopardy, Bypass Angioplasty Revascularization Investigation, Jenkins, Friesinger, Sullivan, Brandt, Leaman, and Gensini.[9–17] Of these, SYNTAX score was recently to evaluate residual stenosis, and the said application was called residual SYNTAX score.[9,18] Residual SYNTAX score was also recently found to be associated with poor prognosis after PCI and transcatheter aortic valve replacement.[9,18,19] Gensini score has been developed to evaluate the severity of CAD, using parameters for each coronary artery lesion: multiplied by the associated location factor.[15,20] Gensini score is simple, and it is one of the most widely used coronary scoring systems, but its prognostic significance for residual stenosis is unknown.[21] In the present study, we defined the Gensini score measured for residual stenosis as the residual Gensini score, and assessed the prognostic impact of residual Gensini score in HF patients after PCI.

Methods

Subjects

In the present study, 203 consecutive hospitalized ischemic HF patients who underwent PCI at Fukushima Medical University Hospital between January 2010 and May 2015 were enrolled. The exclusion criterion was a history of CABG. Patient selection is shown in **Figure 1**. HF was

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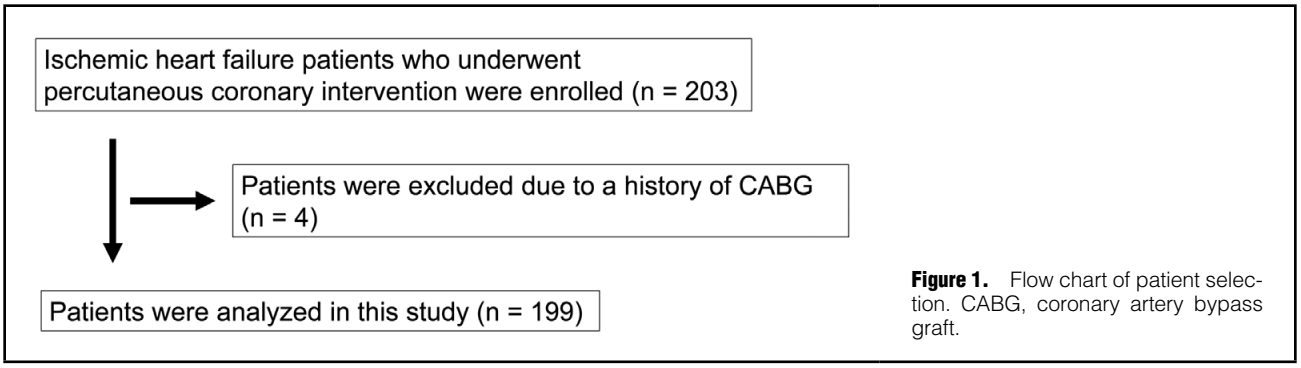

Figure 1. Flow chart of patient selection. CABG, coronary artery bypass graft.

diagnosed by well-trained cardiologists using the American College of Cardiology Foundation and American Heart Association Guidelines.[22] Four patients who had a history of CABG were excluded because an accurate score could not be obtained from such patients. We investigated patient characteristics, such as age, sex, body mass index (BMI), New York Heart Association (NYHA) classification, history of PCI, diseased coronary vessels, comorbidities, smoking history, laboratory data, echocardiography parameters, and medication at discharge. Diagnosis of chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease formula.[23] Anemia was defined as hemoglobin <12.0 g/dL in female patients and <13.0 g/dL in male patients.[22] The patients were followed up for cardiac death as the primary endpoint, the causes of which were classified by independent experienced cardiologists into worsened HF; ventricular fibrillation or ventricular tachycardia documented on electrocardiogram or implantable device; acute coronary syndrome; or sudden cardiac death. In cases of non-cardiac death, causes were also investigated. Survival time was calculated from the initial date of hospitalization until the date of last follow-up or death. We were able to follow up all patients. Written informed consent was obtained from all subjects. The study protocol was approved by the Ethics Committee of Fukushima Medical University (approval no., 823), and was carried out in accordance with the principles outlined in the Declaration of Helsinki.

CAG Scoring System

In all patients, CAG was performed using standard techniques on admission. CAG was analyzed by an experienced cardiologist who was blinded to patient clinical characteristics and prognostic information. Gensini score was calculated as follows:[15,20] a severity score for each coronary stenosis was assigned depending on the degree and location of the stenosis. Luminal stenoses of 25%, 50%, 75%, 90%, 99%, and total occlusion were scored as 1, 2, 4, 8, 16, and 32, respectively. These scores were then multiplied by a factor according to location: 5, left main coronary artery; 2.5, proximal segment of the left anterior descending coronary artery and proximal segment of the circumflex artery; 1.5, mid-segment of the left anterior descending coronary artery; 1.0, right coronary artery, distal segment of the left anterior descending coronary artery, posterior descending artery, and obtuse marginal artery; and 0.5, other segments. Gensini score was calculated as the sum of the scores for all the coronary arteries. SYNTAX score was also calculated as previously described.[24] In the present study, Gensini and SYNTAX scores were calculated using baseline CAG on admission. Residual Gensini and residual SYNTAX scores were calculated using the final CAG after completion of PCI. In the case of patients who underwent staged PCI following the first CAG, the residual Gensini and residual SYNTAX scores were calculated using the CAG performed after the final planned PCI. The endpoint of PCI was determined by attending physicians.

Echocardiography

Echocardiography was performed by experienced echocardiographers using standard techniques.[25] 2-D echocardiography was obtained for the parasternal long and short axes, apical long axis, and apical 4-chamber views. Left ventricular (LV) end-diastolic diameter and LV ejection fraction (LVEF) were measured, and the LVEF was calculated using Simpson's method in 2- and 4-chamber views.

Statistical Analysis

Data were analyzed using SPSS version 26 (SPSS, Chicago, IL, USA). Continuous data are expressed as mean±SD, and skewed data are presented as median (IQR). Categorical variables are expressed as n (%). Statistical significance was analyzed using Student's t-test for parametric continuous variables and the Mann-Whitney U-test for non-parametric continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test. Kaplan-Meier analysis was used for cardiac death, and the log-rank test was used for comparisons. To assess the potential heterogeneity of associations between residual Gensini score and cardiac mortality, we conducted subgroup analyses, but not a multivariate Cox proportional hazard analysis, due to the small number of events (n=32). Interactions between residual Gensini score and clinically important variables for HF patients, such as age (mean, ≥70 years and <70 years), sex (male and female), BMI (mean, ≥24.0 kg/m^2 and <24.0 kg/m^2), NYHA classification III or IV, B-type natriuretic peptide (BNP; median, ≥226 pg/mL and <226 pg/mL), LVEF (mean, ≥47.2% and <47.2%), hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, anemia, and atrial fibrillation (AF), were estimated using a univariate Cox proportional hazard model. Gensini score, SYNTAX score, and residual SYNTAX score were also analyzed using a univariate Cox proportional hazard model. $P<0.05$ was considered statistically significant for all comparisons.

Results

Mean subject age was 70.1 years, and 72.9% were male.

Table 1. Baseline Characteristics vs. Residual Gensini Score

	Residual Gensini score		P-value
	Low (<10, n=98)	High (≥10, n=101)	
Age (years)	69±13	71±11	0.619
Male	76 (75)	69 (70)	0.443
BMI (kg/m²)	25±4	24±4	0.059
NYHA class			
Admission (I/II/III/IV)	7/59/14/18	8/53/15/25	0.361
Discharge (I/II/III/IV)	16/81/1/0	22/77/1/1	0.575
BNP (pg/mL)	220 (64–416)	239 (113–731)	0.066
LVDd (mm)	51±9	53±9	0.450
LVEF (%)	49±15	45±14	0.039
Previous history of MI	29 (30)	34 (34)	0.537
Location of previous MI			
LMCA	0 (0)	1 (1)	1.000
LAD	15 (46)	18 (55)	0.633
LCX	6 (6)	5 (5)	0.718
RCA	14 (14)	12 (12)	0.615
Previous history of PCI	31 (32)	34 (34)	0.760
PCI after admission	80 (82)	86 (85)	0.505
Location of diseased vessel at first angiography			
LMCA	6 (6)	20 (20)	0.004
LAD	64 (65)	85 (84)	0.002
LCX	31 (30)	72 (70)	<0.001
RCA	47 (39)	73 (61)	<0.001
Gensini score at first angiography	32 (11–42)	46 (26–64)	<0.001
Residual Gensini score	5 (3–7)	19 (12–38)	<0.001
SYNTAX score at first angiography	16 (9–25)	30 (21–42)	<0.001
Residual SYNTAX score	5 (2–9)	16 (11–22)	<0.001
Smoking history	63 (64)	72 (71)	0.290
Hypertension	90 (92)	91 (90)	0.669
Dyslipidemia	95 (97)	88 (87)	0.011
Diabetes mellitus	54 (55)	67 (66)	0.105
CKD	55 (56)	64 (63)	0.297
Anemia	55 (56)	71 (70)	0.038
AF	27 (28)	21 (21)	0.265
CRTD	6 (6)	4 (4)	0.533
VAD	0 (0)	0 (0)	–
Medication			
Antiplatelet	97 (99)	98 (97)	0.327
Statin	80 (81)	74 (73)	0.158
RAS inhibitor	83 (85)	91 (90)	0.250
β-blocker	84 (86)	88 (87)	0.771
Oral anticoagulant	36 (37)	32 (32)	0.453
Diuretics	60 (61)	68 (67)	0.369

Data given as n (%), mean±SD, or median (IQR). AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CRTD, cardiac resynchronization therapy with defibrillator; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; RCA, right coronary artery; VAD, ventricular assist device.

Median Gensini score at baseline CAG during this hospitalization was 36 (IQR, 18–56; **Supplementary Figure 1**). Sixty-five subjects (32.7%) had a previous history of PCI. One hundred and sixty-six subjects (83.4%) underwent PCI after admission. Median residual Gensini score was 10 (IQR, 5–19; **Supplementary Figure 2**). We divided all subjects into 2 groups on the basis of median residual Gensini score: the low-score group (residual Gensini score <10, n=98), and the high-score group (residual Gensini score ≥10, n=101). Comparison of baseline clinical characteristics is given in **Table 1**. The high-score group had a higher prevalence of anemia (P=0.038), lower prevalence of dyslipidemia (P=0.011), and lower LVEF (P=0.039), compared with the low-score group. There were no significant differences in

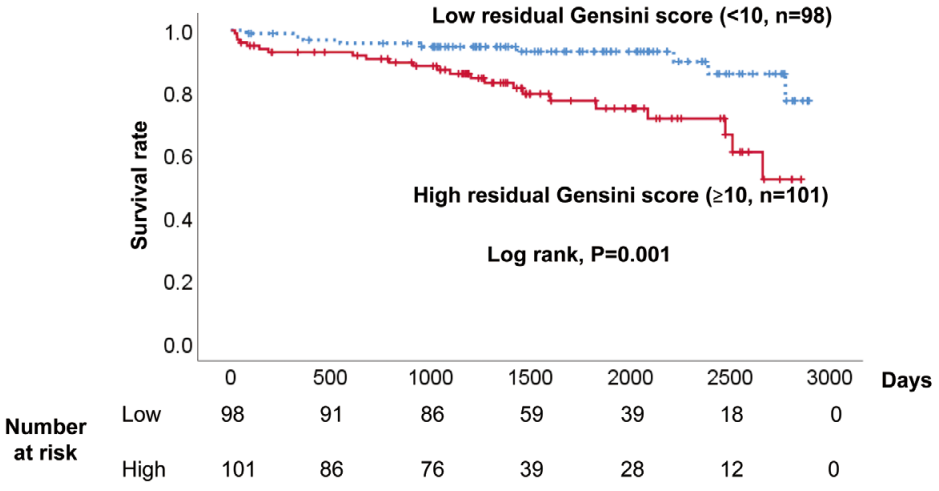

Figure 2. Survival curves for cardiac death according to residual Gensini score.

other clinical characteristics, such as prevalence of diabetes mellitus, chronic kidney disease, or BNP, between the 2 groups.

During the median follow-up period of 1,581 days (range, 20–2,896 days), 32 cardiac deaths and 34 non-cardiac deaths occurred. Of the 32 cardiac deaths, 12 were due to HF, 10 to sudden death, 4 to myocardial infarction and 4 to lethal arrhythmia, and 1 each to multiple organ failure involving the heart and to unknown cause. Of the 34 non-cardiac deaths, 10 were due to infection, 9 to cancer, 4 to respiratory failure, 3 to kidney failure, 2 to ileus and 2 to bleeding, and 1 each to brain infarction, aneurysm, natural death, and unknown cause. The high-score group had a higher cardiac mortality, compared with the low-score group (log rank, P=0.001, **Figure 2**).

On univariate Cox proportional hazard analysis, residual Gensini score was associated with cardiac death (HR, 1.022, 95% CI: 1.011–1.035, P<0.001; **Table 2**). To assess the potential heterogeneity of residual Gensini score impact on cardiac death, we conducted subgroup analyses and examined the interaction terms (**Table 2**). There were no interactions between the prognostic impact of residual Gensini score and age, sex, BMI, NYHA classification, BNP, LVEF, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, anemia, or AF.

On univariate Cox proportional hazard analysis, Gensini score, SYNTAX score, and residual SYNTAX score were also analyzed for cardiac death (**Supplementary Table**). Gensini score (HR, 1.011; 95% CI: 0.999–1.022, P=0.064) was not significantly associated with cardiac death. In contrast, SYNTAX score (HR, 1.020; 95% CI: 1.000–1.039, P=0.049) and residual SYNTAX score (HR, 1.051; 95% CI: 1.023–1.079, P<0.001) were significantly associated with cardiac death.

Discussion

This study is the first to clarify the prognostic impact of residual Gensini score on long-term cardiac mortality in patients with HF after PCI. In addition, high coronary atherosclerotic burden after PCI had a worse long-term prognostic impact in HF.

Coronary revascularization reduced mortality in patients with HF in some studies.[1–3] Some HF patients undergo revascularization with PCI, but complete revascularization with PCI is sometimes difficult. Residual stenosis after PCI has been reported to be associated with worse clinical outcomes in ischemic HF.[26] CAG assesses only the location of narrowing and luminal stenosis, and the data are sometimes difficult to use for risk stratification of multiple CAD, especially in HF patients. For comprehensive evaluation with CAG, coronary scoring systems have been developed, and we used the Gensini score system, which is widely used to assess coronary atherosclerotic burden, to analyze residual stenosis in HF patients with ischemic etiology.[21] A high Gensini score after PCI was associated with higher cardiac mortality in HF patients in the present study, suggesting that residual coronary atherosclerotic burden might lead to a higher risk of cardiac events, including worsening HF, arrhythmia, and coronary artery occlusion. The present results were compatible with those of some previous studies, which reported the importance of complete revascularization to reduce cardiac death.[27,28]

Of the other coronary scoring systems, SYNTAX score has also been used for evaluation of residual stenosis in CAD patients after PCI.[9] There are some differences between SYNTAX score and Gensini score. The SYNTAX score system, which requires multiple factors for calculation, was developed as an angiographic tool to grade the complexity of CAD in order to obtain evidence for coronary revascularization.[24] In contrast, the Gensini score system was developed to evaluate CAD severity, and requires only 2 parameters for each coronary artery lesion: a severity score and a region multiplication factor.[15,20] Therefore, the Gensini score system is simpler than the SYNTAX score system. Some previous studies have reported the inferiority of Gensini score. Watanabe et al reported that the 75-g oral glucose tolerance test is significantly associated with SYNTAX score, but not with Gensini score.[29] In the current study, univariate and subgroup analysis indicated that Gensini score for residual stenosis predicted long-term outcome. These results were similar to those of a previous

Table 2. Subgroup Analysis for Cardiac Death

Factor / Subgroup	n	HR	95% CI	P-value	Interaction P-value
Total	199	1.022	1.011–1.035	<0.001	
Age					0.058
Mean, ≥70 years	118	1.016	1.001–1.031	0.035	
Mean, <70 years	81	1.039	1.015–1.062	0.001	
Sex					0.143
Male	145	1.018	1.003–1.033	0.019	
Female	54	1.031	1.009–1.054	0.007	
BMI					0.831
Mean, ≥24.0 kg/m^2	98	1.018	0.996–1.041	0.116	
Mean, <24.0 kg/m^2	101	1.027	1.012–1.042	<0.001	
NYHA classification					0.536
I, II	127	1.027	1.009–1.044	0.002	
III, IV	72	1.017	0.999–1.035	0.059	
BNP					0.745
Median, ≥226 pg/mL	100	1.020	1.005–1.035	0.010	
Median, <226 pg/mL	99	1.022	1.000–1.044	0.046	
LVEF					0.716
Mean, ≥47.2%	102	1.029	1.011–1.046	0.001	
Mean, <47.2%	97	1.017	0.996–1.038	0.105	
Hypertension					0.280
+	181	1.018	1.004–1.033	0.011	
–	18	1.037	1.006–1.068	0.019	
Dyslipidemia					0.732
+	183	1.020	1.006–1.035	0.006	
–	16	1.011	0.987–1.037	0.368	
Diabetes mellitus					0.073
+	121	1.013	0.996–1.031	0.135	
–	78	1.035	1.016–1.055	<0.001	
CKD					0.973
+	119	1.020	1.007–1.034	0.003	
–	80	1.022	0.989–1.056	0.196	
Anemia					0.052
+	126	1.010	0.992–1.030	0.272	
–	73	1.035	1.018–1.053	<0.001	
AF					0.262
+	151	1.026	1.013–1.039	<0.001	
–	48	0.992	0.936–1.050	0.770	

Abbreviations as in Table 1.

study of residual SYNTAX score.[9]

Coronary revascularization in ischemic HF is carried out using PCI and CABG to improve clinical outcome.[1,2,5,6] There is little consensus, however, on the management of revascularization for ischemic HF.[30] One previous study did not identify the benefits of surgical revascularization, compared with optimal medical therapy, in patients with LV dysfunction and myocardial ischemia.[31] We should be careful when treating patients with HF with ischemic etiology, even after revascularization with PCI. Residual Gensini score was associated with cardiac mortality, and might provide additional information for patient management after revascularization in HF.

Study Limitations

The present study had several limitations. First, only variables during hospitalization for HF were included, and we did not take into consideration changes in variables after discharge. Second, given that this was an observational study, the causal relationships between residual Gensini score and cardiac mortality could not be fully explained, and the importance of complete revascularization could not be fully evaluated. Third, the current study was a single-center study with a small sample size. Fourth, the present results also indicated that Gensini score itself might have a significant impact on cardiac mortality, in addition to residual Gensini score. We were unable to evaluate the difference in prognostic impact on cardiac mortality between Gensini and residual Gensini scores. Thus, the present results should be considered preliminary, and a large multicenter study is necessary to establish the evidence for residual Gensini score in HF patients.

Conclusions

Residual Gensini score was associated with long-term cardiac mortality in HF after PCI.

Disclosures

T. Yokokawa belongs to a department supported by Actelion Pharmaceuticals Japan. A.Y. and T.M. belong to a department supported by Fukuda Denshi. These companies are not associated with the contents of this study. The other authors declare no conflicts of interest.

IRB Information

The reference number of this study was 823 in the Ethics Committee of Fukushima Medical University.

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Supplementary Files

Please find supplementary file(s);
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