Title: Staging Cardiac Damage in Patients with Hypertension

Manuscript number: HYPE201913797R2

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Running title: Staging Cardiac Damage

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Abstract

Ventricular and extraventricular response to pressure overload may be a common process in aortic stenosis and hypertension. We aimed to evaluate the association of a newly defined staging classification characterizing the extent of cardiac damage, originally developed for aortic stenosis, with long-term outcomes in patients with hypertension. We retrospectively analyzed 1639 patients with hypertension who had undergone both scheduled transthoracic echocardiography and electrocardiography in 2013 in a Japanese hospital, after excluding severe and moderate aortic stenosis, aortic regurgitation, mitral stenosis, previous myocardial infarction, or cardiomyopathy. We classified patients according to the presence or absence of cardiac damage as detected on echocardiography as follows: stage 0, no cardiac damage (n = 858; 52.3%); stage 1, left ventricular damage (n = 358; 21.8%); stage 2, left atrial or mitral valve damage (n = 360; 22.0%); or stage 3-4, pulmonary vasculature, tricuspid valve, or right ventricular damage (n = 63; 3.8%). The primary outcome was a composite of all-cause death and major adverse cardiac events. Cumulative 3-year incidence of the primary outcome was 15.5% in stage 0, 20.7% in stage 1, 31.8% in stage 2, and 60.6% in stage 3. After adjusting for confounders, the stage was incrementally associated with higher risk of the primary outcome (per 1-stage increase: HR, 1.46 [95% CI, 1.31-1.61]; P < .001)**.** The staging classification characterizing the extent of cardiac damage, originally developed for aortic stenosis, was associated with long-term outcomes in patients with hypertension in a stepwise manner.

Keywords: staging; hypertension; clinical; retrospective, risk

Introduction

Hypertension is a major public health issue related to both cardiovascular and kidney disease [1-3] and remains a serious problem associated with considerable morbidity and mortality. Hypertension can cause structural and functional damage of the heart, involving ventricular and atrial myocardium as well as epicardial and intramural coronary arteries [1, 4-7]. Previous studies reported definition and classification of "hypertensive heart disease" based on the main changes to the heart induced by chronic blood pressure elevation: left ventricular hypertrophy, atrial fibrillation, and combined ischemic heart disease [8-13]. However, no established staging definition is available and clinically meaningful classification of hypertensive cardiac damage is currently unknown. Thus, there is urgent need to develop individual risk stratification and subsequent treatment strategy for the given patient with hypertension.

Recently, a new staging classification which characterizes the extent of cardiac damage associated with aortic stenosis has important prognostic implications for clinical outcomes from the view point of pressure overload due to stenotic valve [14-15]. This new multiparametric staging system characterizes the extent of anatomical and functional cardiac damage in patients with aortic stenosis. Ventricular and extraventricular response to pressure overload may be common process in aortic stenosis and hypertension. Considering that aortic stenosis and hypertension are characterized by the pressure overload and its response [16-19],

we hypothesized that this new staging classification for aortic stenosis may also be applicable to hypertension.

In the present study, we categorized the different types of cardiac damage (left ventricular dysfunction vs left atrial enlargement and mitral regurgitation vs pulmonary hypertension and right ventricular damage) in patients with hypertension using the staging classification for aortic stenosis used in previous studies [14, 15].We also assessed the impact of these stages on long-term clinical outcomes in a Japanese hospital-based patients with hypertension.

Methods

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study population

We retrospectively analyzed 4444 patients who had undergone simultaneous scheduled transthoracic echocardiography and electrocardiography at Kitano Hospital in 2013 [20-23] ordered at the physician's discretion. A flowchart of the study population is shown in Figure 1. We excluded patients with severe or moderate aortic stenosis (n=133), aortic regurgitation (n=133), mitral stenosis (n=9), previous myocardial infarction (n=420),

cardiomyopathy (n=271), or severe form of congenital heart disease or pericardial disease (n=0) due to the effects of these conditions on cardiac dimensions. We also excluded patients with incomplete or unavailable baseline echocardiogram study for review to allow for adequate staging classification.

The study population comprised 1639 patients, who were categorized into 4 groups depending on the presence or absence of hypertensive cardiac damage or dysfunction detected on transthoracic echocardiography as follows: stage 0, no cardiac damage; stage 1, left ventricular damage defined as presence of left ventricular hypertrophy (left ventricular mass index > 95 g/m^2 for women or > 115 g/m^2 for men) [24], severe left ventricular diastolic dysfunction (E/e' > 14), or left ventricular systolic dysfunction (left ventricular ejection fraction < 50%) [24]; stage 2, left atrium or mitral valve damage or dysfunction defined as presence of enlarged left atrium (> 34 mL/m^2), atrial fibrillation (from the electrocardiogram database, we extracted data on cardiac rhythm and recorded them as they were documented), or moderate or severe mitral regurgitation; or stage 3-4, pulmonary artery vasculature or tricuspid valve damage or dysfunction defined as presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure > 60 mmHg) or moderate or severe tricuspid regurgitation. We did not have data on right ventricular function, although patients with right ventricular dysfunction showed the features of stage 3; therefore, patients with right ventricular dysfunction were included in stage 3-4. Patients were classified in a

given stage (worst stage) if at least 1 of the criteria was met within that stage [14, 15]. These criteria were adopted based on their broad acceptance, as markers of abnormal cardiac function, their simplicity of examination and used previous studies in patients with aortic stenosis [14]. In addition, we also analyzed the data using the modified staging classification in which stage 1 was defined as left ventricular hypertrophy and left ventricular ejection fraction <60% instead of <50% (Table S1) [25].

The research protocol was approved by the Institutional Review Board of Kitano Hospital (approval number: P16-02-005). Informed consent was waived due to the retrospective design of the study. We disclosed the details of the present study to the public as an opt-out method and the notice clearly informed patients of their right to refuse enrollment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's Human Research Committee. Patients' records and information were anonymized and de-identified before analysis.

Data collection

Using the transthoracic echocardiography database, we extracted data regarding wall thickness, left ventricular diastolic dimensions, left ventricular systolic dimensions, left atrial dimension, left atrial volume index, left ventricular ejection fraction, and body mass index. From the electrocardiogram database, we extracted data on cardiac rhythm and recorded them as they were documented; therefore, we could not determine whether atrial fibrillation was

paroxysmal or persistent. Based on the transthoracic echocardiography data along with the catheter suite's database, we identified patients who had previous myocardial infarction or structural heart disease. Left ventricular mass index and relative wall thickness were calculated using the formula recommended by the American Society of Echocardiography [24]. Pulmonary systolic pressure was calculated as follows: right ventricular systolic pressure was determined from the tricuspid regurgitation jet velocity using the simplified Bernulli equation, and combining this value with an estimate of the right atrial pressure by the diameter and collapsibility of the inferior vena cava that was added to the calculated gradient to yield pulmonary systolic pressure [26, 27]. Tricuspid regurgitation was evaluated in the apical four-chamber view, the parasternal short-axis view at the level of the aortic valve, and the right ventricular inflow view. The e' was measured on the apical 4-chamber view, while the E/e' ratio was calculated at the interventricular septum. Data from 2-dimensional transthoracic echocardiography were analyzed at baseline. Left ventricular ejection fraction was measured using the Teichholz method or modified Simpson rule. All transthoracic echocardiography measurements were determined using the average of at least 3 cardiac cycles. We also extracted patient information from their electronic medical records at our institution, including age, sex, and type of disease (i.e., ischemic heart disease, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition [ICD-10] codes I20, I21, I22, I23, I24, and I25; hypertension, ICD-10 codes I10, I11, I12, I13, I14, and

I15; dyslipidemia, ICD-10 code E78; diabetes mellitus, ICD-10 codes E10, E11, E12, E13, and E14; and chronic kidney disease, ICD-10 code N18) [20-23]. Follow-up data from serial clinic visits during June 2017 were also collected retrospectively from electronic medical records [20-23].

Outcome measures

The primary outcome was a composite of all-cause death and major adverse cardiac events defined as acute heart failure, acute myocardial infarction, unstable angina pectoris, cerebral infarction, cerebral hemorrhage, and emerging aorta and peripheral vascular disease, including treatment for aortic aneurysm, all of which required unplanned hospitalization. Secondary outcomes were all-cause death and major adverse cardiac events, separately.

Statistical analyses

Categorical variables are presented as number and percentage and were compared using the chi-square or Fisher exact test. Trends across the 3 groups were assessed using the Cochran-Armitage trend test. Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR); based on their distribution, continuous variables were compared using 1-way analysis of variance or the Kruskal-Wallis test.

We compared 3-year clinical outcomes according to stage of cardiac damage. Cumulative incidence of clinical events was estimated using the Kaplan-Meier method and

intergroup differences were assessed using the log-rank test. Multivariable Cox proportional hazards models were used to estimate risk of the primary and secondary outcomes according to stage or in other clinically relevant risk-adjusted variables (age >80 years, male, diabetes mellitus, dyslipidemia, ischemic heart disease, and chronic kidney disease). Results were expressed as the hazard ratio (HR) and 95% confidence interval (CI). We selected the clinically relevant risk-adjusted variables (Table 1) for use in the main analysis. Next, we used a multivariable logistic regression model including stage as a continuous variable. Finally, we compared the net re-classification improvement level and integrated discrimination improvement degree among the original staging classification and the modified one regarding the improvement of prognosis prediction accuracy.

All statistical analyses were performed by physicians (Y.S., Y.M. and T.K.) using JMP version 14 (SAS Institute Inc, Chicago, IL, USA), R 3.4.1 (R Foundation for Statistical Computing, Austria), and the R package of survIDINRI (version 1.1.1). All reported P values were 2-tailed and those < .05 were considered statistically significant.

Results

Baseline clinical and echocardiographic characteristics

Of 1639 patients with hypertension, 858 (52.3%) were classified in stage 0, 358 (21.8%) in stage 1, 360 (22.0%) in stage 2, and 63 (3.8%) in stage 3-4 (Figure 1). Baseline characteristics of the study population are presented in Table 1. There were significant differences in age, sex, history of atrial fibrillation, diabetes, ischemic heart disease, chronic kidney disease, and echocardiographic parameters among the groups (Table 1).

Clinical outcomes

Median follow-up duration after the index echocardiography was 1280 days (IQR, 755-1498 days), with a follow-up rate of 88.3%, 82.0%, and 75.0% at 1, 2, and 3 years, respectively. Cumulative 3-year incidence of the primary and secondary outcomes increased with each stage of cardiac damage (Figure 2A-C). After adjusting for confounders, excess risk of the primary outcome in stage 2 (HR, 2.01 [95% CI, 1.57-2.57]; P < .001) and stage 3-4 (HR, 3.28 [95% CI, 2.20-4.75]; P < .001) relative to stage 0 remained significant (Table 2). Excess risk of all-cause death in stage 3-4 relative to stage 0 also remained significant (HR, 3.33 [95% CI, 2.08-5.17]; P < .001). Excess risk of major adverse cardiac events in stage 2 (HR, 3.10 [95% CI, 2.25-4.29]; P < .001) and stage 3-4 (HR, 4.68 [95% CI, 2.81-7.54]; P < .001) relative to stage 0 also remained significant (Table 2). Excess risk of the

primary outcome in other clinically relevant risk-adjusted variables are presented in Table S2.

When stage of cardiac damage was entered as a continuous variable in the multivariable model, the stage was incrementally associated with higher risk of the primary outcome (per 1-stage increase: HR, 1.46 [95% CI, 1.31-1.61]; P < .001) (Figure 2A), all-cause death (per 1-stage increase: HR, 1.31 [95% CI, 1.14-1.50]; *P* < .001) (Figure 2B), and major adverse cardiac events (per 1-stage increase: HR, 1.74 [95% CI, 1.52-1.99]; P < .001) (Figure 2C).

Subgroup analysis

We performed post hoc subgroup analysis stratified by the following factors: age > 70 years, sex, and comorbid disease (diabetes, dyslipidemia, ischemic heart disease, and chronic kidney disease) (Table 3). There were no interactions between presence or absence of age > 70 years, sex, diabetes, ischemic heart disease, or chronic kidney disease and stage for risk of the primary outcome. However, there was a significant interaction between presence of dyslipidemia, mild aortic stenosis and stage for incremental risk of the primary outcome.

Additional analysis using modified criteria

When we used the modified staging classification in which stage 1 was defined as left ventricular hypertrophy and left ventricular ejection fraction <60% instead of <50%

(Table S1), the results were fully consistent with the main analysis (Figure S1A-C and Tables S3 and S4). According to integrated discrimination improvement and net reclassification improvement analysis (Table S5), the improvement of prognosis prediction accuracy did not differ significantly between the modified staging and original one.

Discussion

The main finding of this study was that the new staging classification based on the extent of cardiac damage, originally proposed for aortic stenosis, was associated with long-term clinical outcomes in patients with hypertension.

There is hypertension causes structural and functional cardiac changes, such as left ventricular and left atrial dilation as well as systolic and diastolic dysfunction [4-7]. Hypertensive cardiac damage encompasses a broad spectrum, including asymptomatic left ventricular hypertrophy and clinical heart failure. Several reports have discussed classification of hypertensive cardiac damage [8-13]. For example, in patients with hypertension, high left atrial volume index or high left ventricular mass index is associated with adverse cardiovascular risk profile and is a predictor of cardiovascular events [28-33]. However, a stepwise classification according to the extent of cardiac damage had not been proposed. To the best of our knowledge, this is the first report using a large clinical database to show an incremental association between extent of cardiac damage and long-term outcomes in patients with hypertension.

Both aortic stenosis and hypertension are associated with pressure overload [16-20]. With aortic stenosis progression, pressure overload leads to compensatory left ventricular hypertrophy, diastolic dysfunction, increased left atrial size, development of mitral regurgitation, and finally, development of pulmonary heypertension and right ventricular dysfunction [34, 35]. Previous studies have reported successful staging classification of aortic

stenosis according to the extent of cardiac damage not only in patients who underwent aortic valve replacement but in symptomatic and asymptomatic patients [14, 15, 25, 36]. However, as mentoiond in these studies [14, 15, 25, 36], the stage classification of cardiac damage is not limited to aortic stenosis. In the present study, this severity classification showed an incremental association with adverse events in patients with hypertension who underwent scheduled transthoracic echocardiography. Staging classification of cardiac damage, originally proposed for aortic stenosis, fit well in patients with hypertension. Subgroup analysis implied that the association of severity classification with clinical outcomes was observed regardless of the presence or absence of comorbid disease. In the presence of dyslipidemia, the association was directionally and strongly observed. This may be attributed that hyperlipidemia may be linked to the atherosclerotic burden that led to the cardiovascular events [37, 38]. The staging classification was associated with long-term outcomes in hypertensive patients without mild aortic stenosis. However, there was an interaction between presence of mild aortic stenosis and stage for incremental risk of the primary outcome in our study First, the small number of patients with mild aortic stenosis may hamper the association between staging and outcomes in the present study. Second, mild aortic stenosis after excluding patients with severe or moderate aortic stenosis may not match the staging, because aortic stenosis is progressive [39]. Further research is needed in patients who had both hypertension and aortic stenosis to draw solid conclusions. Although hypertension and aortic

stenosis may share some pathophysiologic mechanisms, we need to clarify the distinction of timeframe of natural course between aortic stenosis and hypertension. Aortic stenosis is progressive disease with limited ways to delay progression [14, 16] while hypertension can be treated and controlled with optimal therapy. Although we did not have the data on treatment of hypertension such as drug class or on the duration of hypertension, optimal management may have the impact of the subsequent staging classification and outcomes.

There is a considerable risk in patients with hypertension in our study; thus, there is a need to enhance risk stratification in this subset. Staging classification may reflect the adaptation and maladaptation to overload ranging from left ventricular hypertrophy stage, which may be asymptomatic phase but predispose to acute heart failure due to afterload mismatch, to pulmonary congestion due to left heart failure, which may be symptomatic. In the present study, the population analyzed was hospital-based patients with hypertension and who had undergone scheduled transthoracic echocardiography and electrocardiogram. Thus, caution must be exercised when extrapolating the present study results to general population. However, our study may indicate the importance of assessing left ventricular hypertrophy, left atrial size, diastolic function, and systolic function, all of which are measured in the context of routine clinical practice in out-patient clinic. For a given patient with hypertension, we might assess the risk stratification of patients with hypertension, along with the treatment of hypertension and intervention to life style.

This study had several limitations. First, electrocardiogram and transthoracic echocardiography were ordered at the discretion of the treating physician, with no standardized indications. Second, patient data were extracted from electronic medical records; thus, we did not have data regarding treatment of hypertension and duration of hypertension. Third, data on right ventricular function were lacking. Tricuspid annulus systolic velocity and/or tricuspid annular plane systolic excursion were not obtained. Forth, as this was a single-center study performed in Japan, possible selection bias could not be excluded despite the large sample size. Further research is warranted to apply this result in non-Japanese patients. Fifth, although the echocardiographic parameters were usually obtained in the context of routine examination, measurement errors and variability might exist. Since the definition of each stage is a multiparameter approach, the staging did not rely on a single parameter.

Perspectives

This is the first report using a large clinical database to show an incremental association between extent of cardiac damage and long-term outcomes in patients with hypertension. Both hypertension and aortic stenosis are very common disorders in today's society. This study contributes the novel finding that a stage classification on cardiac damage originally proposed for aortic stenosis can also be applied to patients with hypertension. The

clinical implication of the present study is that assessment of staging cardiac damage based on pressure overload is important for risk stratification in patients with hypertension as well as for treatment of hypertension.

Author contribution

Y. S. and T. K.: conceived the design, and wrote manuscript. Y.S, Y.M., and T.K.: performed statistical analysis, M. S., Y.M., Y. Y., Y. H., E. N., T. H. and M.I.: collected the data and made critical revision.

Source of Funding: None

Declarations of interest: None

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Novelty and Significance:

1) What Is New?

This is the first report using a large clinical database to show an incremental association between extent of cardiac damage and long-term outcomes in patients with hypertension.

2) What Is Relevant?

This study has the novel finding that a stage classification on cardiac damage originally proposed for aortic stenosis can also be applied to patients with hypertension.

Summary

The clinical implication of the present study is that assessment of staging cardiac damage based on pressure overload is important for risk stratification in patients with hypertension as well as for treatment of hypertension.

Figure Legends

Fig 1. Flowchart of the study population

AR, aortic regurgitation; AS, aortic stenosis; E, transmitral early filling velocity; e', early diastolic mitral annular velocity; ECG, electrocardiography; LAVI, left atrial volume index; LV, left ventricle; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; OMI, old myocardial infarction; RV; right ventricle; TTE, transthoracic echocardiography.

Fig 2. Cumulative incidence of the primary outcome (a composite of all-cause death and MACE) and secondary outcomes (all-cause death or MACE)

(A)Composite of all-cause death and MACE. (B) All-cause death. (C) MACE. MACE was defined as acute heart failure, acute myocardial infarction, unstable angina pectoris, cerebral infarction, cerebral hemorrhage, aortic dissection, or treatment for aortic aneurysm. MACE, major adverse cardiac events.