Differential Impact of the Renal Resistive Index on Future Cardiovascular Events in Hospitalized Atherosclerotic Cardiovascular Patients According to Left Ventricular Ejection Fraction
— The Jichi Vascular Hemodynamics in Hospitalized Cardiovascular Patients (J-VAS) Study —

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Background: Determinants of poor outcome in atherosclerotic cardiovascular disease (ASCVD) according to left ventricular ejection fraction (LVEF) are unclear. The renal resistive index (RRI) correlates well with atherosclerotic vascular damage, which, in turn, is correlated with cardiovascular outcomes. This study investigated whether high RRI is associated with poor cardiovascular outcomes in ASCVD patients classified by LVEF.

Methods and Results: Records of 1,598 acute coronary syndromes (ACS) and acute decompensated heart failure (ADHF) patients, categorized into preserved (p), mid-range (mr), and reduced (r) ejection fraction (EF) groups (EF ≥50% [n=1,130], 40–50% [n=223], and <40% [n=245], respectively), were analyzed retrospectively. The primary endpoint was any cardiovascular-related event: fatal and non-fatal ACS, ADHF, stroke, and sudden cardiac death. Over 1.9-years follow-up (3,030 person-years), 233 events occurred: 122, 37, and 74 in the pEF, mrEF, and rEF groups, respectively. Adjusted Cox regression analysis revealed RRI ≥0.8 was associated with the primary endpoint in the pEF group (hazard ratio [HR] 1.67; 95% confidence interval [CI] 1.09–2.56), but not in the mrEF or rEF groups. The primary endpoint risk of pEF patients with an RRI ≥0.8 was comparable to that of mrEF patients using the pEF+RRI <0.8 group as the reference (HR 1.89 [95% CI 1.26–2.83] and 1.77 [95% CI 1.19–2.63], respectively).

Conclusions: RRI was associated with the risk of cardiovascular events in ASCVD patients with pEF.

Key Words: Atherosclerotic disease; Left ventricular ejection fraction; Preserved ejection fraction; Renal resistive index (RRI)
Taking these prior findings into account, we postulated that a high RRI may contribute to poor cardiovascular outcomes in ASCVD patients classified according to LVEF. To test our hypothesis, we used data of patients in the Jichi Vascular Hemodynamics in Hospitalized Cardiovascular Patients (J-VAS) study,\textsuperscript{17} which enrolled ASCVD patients with different LVEF values.

**Methods**

**Setting and Study Design**

We retrospectively analyzed the data of patients from the J-VAS study, which has been described in detail elsewhere.\textsuperscript{17} Briefly, the J-VAS study is a single-center, retrospective cohort study of Japanese adults with cardiovascular diseases who were admitted to the cardiovascular unit of Jichi Medical University Hospital, a tertiary care center in Tochigi, Japan. All patients underwent non-invasive vascular hemodynamic measurements, including clinical blood pressure (BP), cardiac echocardiography, renal and carotid artery Doppler ultrasonography, ankle-brachial index, and arterial pulse wave velocity. The Institutional Review Board of Jichi Medical University approved the present retrospective study with the need for patient consent waived.

**Study Subjects**

In the present study we first examined the records of 2,390 patients who were diagnosed with acute coronary syndrome (ACS), acute decompensated HF (ADHF), acute aortic disease, or peripheral arterial disease. Of these patients, 1,444 ACS and 634 ADHF patients were initially enrolled in the study. Of the ADHF patients, 474 who had HF from atherosclerotic causes (i.e., ischemic heart disease [IHD], hypertensive heart disease, and aortic stenosis [AS]) were included in study, whereas 160 patients who had ADHF due to dilated cardiomyopathy, arrhythmias, and valvular insufficiency excluding AS were excluded; a further 314 patients whose follow-up data were incomplete were also excluded. This left a final total of 1,598 patients for the present analyses (Supplementary Figure). The patients’ baseline clinical characteristics, including BP data and laboratory results, are provided in Table 1.

**Echocardiography**

Patients underwent echocardiography in the echocardiogram unit on the day of admission after treatment of the acute phase or just before discharge. Assessments were performed by a specially trained echocardiographer who was blinded to patients’ clinical data using a Vivid S5 ultrasound machine (GE Healthcare, Chicago, IL, USA) with a 2.5-MHz pulsed Doppler frequency and a 3.5-MHz convex array transducer. The patients were in the left lateral decubitus position during the examinations. Left ventricular (LV) contractility and wall motion were initially examined in 2-dimensional views. LVEF was calculated by manual planimetry according to Simpson’s formula.\textsuperscript{18} The resulting LVEF was the average of 2 measurements. The last LVEF values obtained during the admission period were used in the final analyses, with the 3 LVEF categories defined in accordance with the most recent recommendations\textsuperscript{8} as follows: pEF=LVEF ≥50%; mrEF=LVEF 40–49%; and rEF=LVEF <40%.

**Renal Doppler Ultrasonography**

An experienced ultrasonographer who was blinded to patients’ clinical data performed Doppler ultrasound examinations on the day of admission after the treatment of the acute phase or just before discharge. Examinations were performed using a Vivid S5 ultrasound machine (GE Healthcare) with a 2.5-MHz pulsed Doppler frequency and 3.5-MHz convex array transducer in patients in a supine position. The transducer was placed on the lumber region. Intrarenal Doppler signals were obtained bilaterally from the 3 most manifest proximal segmental arteries. The RRI was calculated using the following equation:

\[
RRI = (\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}
\]

The mean RRI of the left and right kidneys was used in statistical analyses.

**Dependent Variables and Outcome**

The patients were followed-up for a mean (±SD) of 1.9±0.9 years (3,030 person-years). All patients were followed-up with a standard-of-care hospital visit. To assess associations between potential risk factors and prognoses, the primary endpoint chosen was the incidence of the first subsequent cardiovascular disease event from the time of discharge, where “cardiovascular disease event” was defined as a composite of fatal and non-fatal cardiovascular diseases including sudden cardiac death, ADHF, ACS, and stroke. The attending physicians determined the cardiovascular disease events. Cardiovascular disease events during the follow-up period were ascertained by cardiologists and by annual or more frequent reviews of patient medical records. The criteria for making diagnoses of sudden cardiac death, ADHF, ACS, and stroke are given in the Supplementary Material. When patients failed to come to the hospital, they and/or their families were interviewed by telephone.

**Statistical Analyses**

Patients’ baseline characteristics and clinical measurements are presented as the mean±SD or as percentages for continuous and categorical variables, respectively. Comparisons of baseline characteristics among the pEF, mrEF, and rEF groups were made using Pearson’s Chi-squared test for proportions and analysis of variance (ANOVA) for continuous variables.

Unadjusted Cox proportional hazard analysis was used to examine the relationship between the primary endpoint and potential risk factors, which were chosen on the basis of expert clinical judgment and included age, sex, body mass index (BMI), acute kidney injury (AKI; for a definition of AKI, see the Supplementary Material), systolic BP (SBP), RRI, and other conventional cardiovascular risk factors and are presented as unadjusted hazard ratios (HRs).

Considering clinical importance and using P<0.05 as a criterion, age, sex, BMI, dyslipidemia, diabetes, smoking, AKI, SBP, and estimated glomerular filtration rate (eGFR) were included in adjusted Cox proportional hazard regression models together with the RRI to examine adjusted HRs and 95% confidence intervals (95% CIs). The proportionality assumption for the Cox analyses was confirmed graphically and via the inclusion of a time×BP interaction. Based on acceptable accuracy and several previous reports that investigated the effects of RRI ≥0.8 on decreased event-free survival in patients with HFpEF\textsuperscript{9} and in the elderly,\textsuperscript{20} we used 0.8 as the cut-off point for RRI in the

\[
\text{mrEF}=LVEF\ 40–49\%;\ \text{rEF}=LVEF<40\%
\]

\[
\text{peak systolic velocity} - \text{end diastolic velocity} / \text{peak systolic velocity}
\]

\[
RRI = (\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}
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\]
Results

Patients’ Clinical Characteristics

Table 1 provides the demographic data and clinical characteristics of the study population. The mean age of the total population was 67.3±11.6 years and was similar among the 3 EF groups. Most patients were men (75.6%), with the lowest prevalence in the pEF group (73.3%), compared with 81% in the mrEF group and 82% in the rEF group. There were 1,161 ACS patients (72.7%), and 437 atherosclerotic ADHF patients (27.3%) included in the present study. Regarding comorbidities, the prevalence of hypertension was lowest in the rEF group (69.4%), compared with the mrEF and pEF groups (75.3% and 74.4%, respectively). The prevalence of diabetes was highest in the mrEF group (48.4%) and was lowest in the pEF group (36.5%). The present study. Patients with pEF were further divided into 2 groups based on RRI values (RRI ≥0.8 and <0.8). In addition, the RRI cut-off point was determined as the most appropriate outcome-driven RRI cut-off point from Youden’s J statistic. Survival analysis was conducted using Kaplan-Meier statistics for pEF patients with an RRI ≥0.8, pEF patients with an RRI <0.8, the mrEF group, and the rEF group.

Adjusted Cox proportional hazard regression analysis was used to explore relationships between the primary endpoint and pEF patients with an RRI ≥0.8, pEF patients with an RRI <0.8, mrEF patients and rEF patients, as well as pre-selected covariates (age, sex, BMI, dyslipidemia, diabetes, smoking, AKI, SBP, and eGFR) as described above.

Table 1. Baseline Characteristics of the Total Population and Among Patients With Preserved, Mid-Range and Reduced Ejection Fraction Separately

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population (n=1,598)</th>
<th>pEF (n=1,130)</th>
<th>mrEF (n=223)</th>
<th>rEF (n=245)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.3±11.6</td>
<td>67.5±11.4</td>
<td>67.4±11.9</td>
<td>65.9±13.9</td>
<td>0.135</td>
</tr>
<tr>
<td>Male sex</td>
<td>1,208 (75.6)</td>
<td>828 (73.3)</td>
<td>180 (80.7)</td>
<td>200 (81.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7±4.0</td>
<td>24.9±3.8</td>
<td>24.6±4.0</td>
<td>24.2±4.9</td>
<td>0.059</td>
</tr>
<tr>
<td>Smoking</td>
<td>446 (27.9)</td>
<td>291 (25.8)</td>
<td>78 (35.0)</td>
<td>77 (31.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,179 (73.8)</td>
<td>841 (74.4)</td>
<td>168 (75.3)</td>
<td>170 (69.4)</td>
<td>0.221</td>
</tr>
<tr>
<td>Diabetes</td>
<td>618 (38.7)</td>
<td>413 (36.5)</td>
<td>108 (48.4)</td>
<td>97 (39.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>CKD</td>
<td>600 (37.5)</td>
<td>377 (33.4)</td>
<td>89 (39.9)</td>
<td>134 (54.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI</td>
<td>295 (18.5)</td>
<td>181 (16.0)</td>
<td>48 (21.5)</td>
<td>66 (26.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>288 (18.0)</td>
<td>148 (13.1)</td>
<td>63 (28.3)</td>
<td>108 (44.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2±1.2</td>
<td>6.2±1.1</td>
<td>6.6±1.6</td>
<td>6.4±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.65±0.92</td>
<td>2.65±0.90</td>
<td>2.69±1.06</td>
<td>2.59±0.87</td>
<td>0.494</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>65.9±27.7</td>
<td>67.8±26.4</td>
<td>65.9±32.0</td>
<td>56.8±27.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data are given as n (%) or mean±SD. The primary endpoint included cardiovascular death and sudden death or the first subsequent non-fatal acute coronary syndrome (ACS), acute decompensated heart failure (ADHF), and stroke episode during the follow-up period. ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; EDV, end-diastolic velocity; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mrEF, mid-range ejection fraction; pEF, preserved ejection fraction; PSV, peak systolic velocity; PWV, pulse wave velocity; rEF, reduced ejection fraction; RRI, renal resistive index; SBP, systolic blood pressure.
prevalence of CKD, AKI, and atrial fibrillation (AF) during admission was highest in the rEF group (54.7%, 26.9%, and 44.1%, respectively).

**Primary Endpoint and Determinants**

In all, 233 events (76.9/1,000 patient-years) that met the primary endpoint criteria were detected throughout the study period. Detailed patient outcomes are presented in Supplementary Table 1. The incidence of the primary endpoint increased incrementally from pEF to rEF. The adjusted Cox regression model showed that after adjusting for age, sex, BMI, dyslipidemia, diabetes, smoking, AKI, AF, SBP, and eGFR, patients with rEF or mrEF had a significant risk of cardiovascular events compared with those who had pEF (HR per 1SD 1.12; 95% CI 0.94–1.35) for the total population. A lower eGFR was significantly associated with the risk of the primary endpoint regardless of LVEF group.

Table 2 shows the results of unadjusted Cox proportional analysis of the relationship between the primary endpoint and potential cardiovascular risk factors according to the 3 LVEF groups. Age was a significant risk for the primary endpoint regardless of LVEF group. However, diabetes presented a risk of the primary endpoint only in the pEF group (HR 1.54; 95% CI 1.08–2.20), as did AF (HR 1.97; 95% CI 1.30–2.99). Higher SBP was a risk for the primary endpoint in the pEF group (HR per 1SD 1.12; 95% CI 0.94–1.35), whereas lower diastolic BP (DBP) was a risk in all EF groups. A lower eGFR was significantly associated with the risk of the primary endpoint regardless of LVEF group.

In the unadjusted model, an RRI ≥0.8 was associated with the primary endpoint in the total population, but this association was not found in the adjusted model. An RRI ≥0.8 had a significant effect on the primary endpoint in the pEF (HR 2.89; 95% CI 1.98–4.21) and mrEF (HR 2.14; 95% CI 1.06–4.33) groups, but not in the rEF group (HR 1.06; 95% CI 0.60–1.89). In the patients with pEF, adjusted Cox regression analysis showed that an RRI ≥0.8 was associated with a significant risk of the primary endpoint after adjusting for age, sex, BMI, smoking, dyslipidemia, diabetes, AKI, AF, SBP, and eGFR (HR 1.67; 95% CI 1.09–2.56), but not in the other LVEF groups (Table 2). An RRI cut-off point of 0.72 was shown to be the most appropriate outcome-driven RRI cut-off point from the Youden’s J statistic. Using this cut-off point, a higher RRI was associated with a risk of the primary endpoint in the unadjusted model (HR 1.70; 95% CI 1.33–2.18; P<0.001), but the association disappeared in the adjusted model in the total population.

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**Table 2. Unadjusted and Adjusted HRs for the Primary Endpoint**

<table>
<thead>
<tr>
<th>Events/no. patients</th>
<th>Total population</th>
<th>pEF</th>
<th>mrEF</th>
<th>rEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 1SD</td>
<td>1.42 (1.24–1.64)</td>
<td>1.47 (1.19–1.80)</td>
<td>1.94 (1.31–2.88)</td>
<td>1.29 (1.04–1.58)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.92 (0.69–1.23)</td>
<td>0.81 (0.55–1.19)</td>
<td>0.73 (0.34–1.54)</td>
<td>0.96 (0.54–1.72)</td>
</tr>
<tr>
<td>BMI, per 1SD</td>
<td>0.87 (0.76–1.00)</td>
<td>0.958 (0.79–1.16)</td>
<td>0.87 (0.62–1.22)</td>
<td>0.88 (0.71–1.09)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.74 (0.55–1.01)</td>
<td>0.68 (0.43–1.06)</td>
<td>0.82 (0.41–1.63)</td>
<td>0.64 (0.38–1.10)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.76 (0.59–0.98)</td>
<td>0.68 (0.48–0.98)</td>
<td>0.90 (0.47–1.70)</td>
<td>1.16 (0.74–1.84)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.47 (1.14–1.90)</td>
<td>1.54 (1.08–2.20)</td>
<td>1.67 (0.87–3.22)</td>
<td>1.21 (0.76–1.92)</td>
</tr>
<tr>
<td>AKI</td>
<td>1.79 (1.35–2.38)</td>
<td>1.90 (1.27–2.84)</td>
<td>1.36 (0.67–2.75)</td>
<td>1.28 (0.79–2.09)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.25 (1.73–2.94)</td>
<td>1.97 (1.30–2.99)</td>
<td>1.32 (0.68–2.54)</td>
<td>1.43 (0.92–2.24)</td>
</tr>
<tr>
<td>SBP per 1SD</td>
<td>0.93 (0.82–1.06)</td>
<td>1.12 (0.94–1.35)</td>
<td>1.00 (0.76–1.32)</td>
<td>0.85 (0.68–1.07)</td>
</tr>
<tr>
<td>DBP per 1SD</td>
<td>0.86 (0.75–0.99)</td>
<td>0.87 (0.71–1.06)</td>
<td>0.82 (0.60–1.12)</td>
<td>0.79 (0.67–1.05)</td>
</tr>
<tr>
<td>eGFR per 1SD</td>
<td>0.65 (0.57–0.74)</td>
<td>0.71 (0.59–0.86)</td>
<td>0.71 (0.53–0.94)</td>
<td>0.68 (0.53–0.86)</td>
</tr>
<tr>
<td>RRI ≥0.8</td>
<td>2.14 (1.61–2.85)</td>
<td>2.89 (1.98–4.21)</td>
<td>2.14 (1.06–4.33)</td>
<td>1.06 (0.60–1.89)</td>
</tr>
</tbody>
</table>

**Adjusted model**

| eGFR per 1SD        | 0.75 (0.65–0.86)| 0.90 (0.74–1.09)| 0.74 (0.54–1.00)| 0.69 (0.53–0.89) |
| RRI ≥0.8            | 1.19 (0.87–1.63)| 1.67 (1.09–2.56)| 1.03 (0.47–2.26)| 0.71 (0.39–1.28) |

*The primary endpoint included cardiovascular death and sudden death or the first subsequent non-fatal ACS, ADHF, and stroke episode during the follow-up period. One-SD increments for each measure were as follows: age, per 11.8 years; BMI, per 4.0 kg/m2; SBP, per 17 mmHg; DBP, per 12 mmHg; eGFR, per 28 mL/min/1.73 m2. The adjusted model included age, sex, BMI, dyslipidemia, diabetes, smoking, SBP, AKI, atrial fibrillation, and eGFR. HR, hazard ratio. Other abbreviations as in Table 1.
survival (Figure).

Adjusted Cox regression analysis of the 4 groups (using the pEF with RRI <0.8 group as the reference group) revealed that after adjusting for age, sex, BMI, eGFR, SBP, diabetes, dyslipidemia, and smoking, rEF had the greatest effect on the primary endpoint (HR 3.90; 95% CI 2.80–5.46).

A similar effect was observed for both pEF with RRI ≥0.8 (HR 1.89; 95% CI 1.26–2.83) and mrEF (HR 1.77; 95% CI 1.19–2.63). Using the RRI cut-off point (0.72) from the outcome-driven analysis, a higher RRI was associated with a risk of the primary endpoint in the unadjusted model (HR 1.86; 95% CI 1.32–2.63; P<0.001), but the association disappeared in the adjusted model in the pEF group.

Discussion

In this study we explored the effect of a renal Doppler parameter (i.e., the RRI) on future cardiovascular events in hospitalized ACS and atherosclerotic ADHF patients categorized according to LVEF values. The risk of future cardiovascular events increased incrementally from pEF to rEF, which is consistent with an earlier study of a general population. The most interesting finding of the present...
study was that the RRI was associated with a significant risk for future cardiovascular events independent of other conventional cardiovascular risk factors (including eGFR, CKD, and AKI status) in the patients with pEF, but not in those with mrEF or rEF. Moreover, pEF with an RRI ≥0.8 presented a risk of future cardiovascular events that was similar to that of mrEF.

LVEF is one of the main predictors of future cardiovascular events in certain groups of cardiovascular patients, including those with IHD, ADHF, peripheral artery disease, or those taking antiarrhythmic drugs. A lower LVEF in these patients often leads to a poorer outcome. The present study demonstrated that patients with mrEF or rEF were at higher risk for the primary composite endpoint than patients with pEF. However, the burden of cardiovascular risk in some patients with a borderline or normal LVEF is still high; this indicates hidden risks beyond LVEF.

Renal impairment has been described as an important risk factor for a poor outcome in cardiovascular patients. Various renal parameters obtained by invasive and non-invasive methods can indicate renal impairment. The RRI, a non-invasive parameter, has been established as a marker of renal function, and its prognostic power for a poor cardiovascular outcome was greater than that of the eGFR in selected cardiovascular patients. The present analyses revealed that an RRI ≥0.8 was associated with a risk of future cardiovascular events in patients with pEF or mrEF. Even after adjustment for conventional cardiovascular risk factors, including the eGFR, a significant effect of RRI remained in the group of patients with pEF. This concurs well with the findings reported by Ennezat et al, who showed that the severity of RRI was associated with a poor outcome in HFpEF patients; however, patients with ACS were excluded from that study. The subjects in the present study were ACS patients and atherosclerotic ADHF patients. To the best of our knowledge, we are the first to study the impact of RRI on cardiovascular outcomes in this particular group of patients. The most important result of the present study was that patients with pEF who had an RRI ≥0.8 had a risk of future cardiovascular events that was comparable to the risk among patients with mrEF.

This finding provides compelling evidence that a high RRI indicates the burden of risk of cardiovascular events beyond LVEF in patients with ASCVDs.

The potential mechanisms underlying the impact of RRI on cardiovascular events that was observed specifically in pEF patients remain to be elucidated, but there are several hypotheses. First, a high RRI may provoke abnormal volume distribution and an HF event because it has been shown that a high RRI is associated with an increase in plasma renin activity, albeit in a selected group of cirrhotic patients. This correlates well with a distinct pathophysiological cause of HFpEF, namely abnormal volume distribution rather than volume overload. There is evidence that treatment of HFpEF patients with renin-angiotensin-aldosterone system inhibitors is associated with lower HF-related hospitalization. Second, the RRI reflects renal structural abnormality, concerning not only the atherosclerotic process, but also renal interstitial damage. The RRI is one of the observable indicators of renal impairment, which itself is an important cardiovascular risk factor. Even though one-quarter of the present study population consisted of HF patients, the results of our analyses are in line with those of previous studies showing a larger effect.

### Table 1

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Follow up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>pEF with RRI &lt;0.8</td>
<td>956</td>
</tr>
<tr>
<td>pEF with RRI ≥0.8</td>
<td>174</td>
</tr>
<tr>
<td>mrEF</td>
<td>223</td>
</tr>
<tr>
<td>rEF</td>
<td>245</td>
</tr>
</tbody>
</table>

**Figure.** Kaplan-Meier curves demonstrating the highest event-free survival in patients with preserved ejection fraction (pEF) with a renal resistive index (RRI) <0.8 and the lowest in patients with reduced ejection fraction (rEF). pEF patients with an RRI ≥0.8 and patients with a mid-range ejection fraction (mrEF) had similar intermediate survival.
size of renal impairment in HFpEF than HFrEF patients. Third, the RRI was shown to correlate well with both large and small vascular resistance in several studies, as well as in the present study. The Pearson correlation coefficients showed a strong correlation between pulse wave velocity and RRI. Vascular resistance has the potential to affect HFpEF patients more than the other LVEF groups because accumulating evidence points to HFpEF as a disease involving the abnormal regulation of vascular tone that leads to worsening cardiac hypertrophy and remodeling.

In contrast with the pEF patients in the present study, there was no significant effect of the RRI on the primary composite endpoint in the patients with mrEF or rEF, which may be explained by the extremely low mean LVEF in the mrEF and rEF groups (44% and 28%, respectively) compared with the pEF group (64%). Therefore, the effect of LVEF on the primary composite endpoint may outweigh the effect of the RRI, especially in our patients with rEF, whose mean LVEF was much lower than the universal upper cut-off point.

The strengths of the present study include its enrollment of a large number of patients who were admitted with common cardiovascular diseases, including ACS and ADHF from atherosclerotic causes, which makes the generalization of our findings feasible. An earlier study found that HFpEF patients were affected by a high RRI, and the present analyses also demonstrated that, in addition to HFpEF patients, ACS patients with pEF have an associated incremental cardiovascular risk if their RRI is ≥0.8. We also obtained novel findings on the differential impact of the RRI on cardiovascular patients based on their LVEF. The findings of this study may lead to new research directions regarding modifications of risk factors (e.g., the RRI) to improve outcomes for pEF patients.

The present study also has a number of limitations that could have affected the results. First, because renal Doppler ultrasonography was performed during the admission period, some treatments, such as fluid management, may have confounded the ultrasonographic results in some patients. Second, results were obtained from analyses of a retrospective dataset in evaluations of associations, but not causation, regarding the relationship between the RRI and the primary composite endpoint. We acknowledge that there were several patients whose follow-up data were lost or incomplete, although the number of patients with incomplete data did not differ much among the pEF, mrEF, and rEF groups (16%, 17.5%, and 19%, respectively); thus, care should be taken when interpreting the results. Furthermore, we did not collect data on the detailed indices of echocardiography, such as LV cavity size, LV wall thickening, and diastolic function, among others. From the least biased study type (i.e., epidemiological studies), concentric LV hypertrophy remodeling was not uncommon in HFpEF patients, whereas eccentric LV hypertrophy was also be found but on rare occasions. The LV geometry data, especially LV hypertrophy, is known to affect death and hospitalization from HF in patients with HFpEF independent of clinical factors. One of the important limitations of the present study is that EF measurements were not obtained during the follow-up visit, therefore we cannot classify the HF outcomes as HFpEF, HFmrEF, or HFrEF.

Although we found that high RRI was associated with a poorer cardiovascular outcome in pEF patients and that RRI is a promising parameter for predicting cardiovascular risk in this selected group of patients, future studies may be required to examine the non-inferiority or superiority of RRI compared with the other vascular stiffness parameters, such as the ankle-brachial index and pulse wave velocity; in addition, urinary albumin:creatinine ratio data should be added to the adjusted model because eGFR alone may not be strong enough to stress out the role of RRI above and beyond conventional renal function tests. The RRI cut-off point used in this study was minimally higher than the threshold of RRI given by the outcome-driven analysis (0.8 vs. 0.72, respectively). Although, the RRI cut-off point of 0.8 has been recognized as a threshold of potential risk in many studies, further investigations are needed to identify the appropriate cut-off point for an abnormal RRI. Finally, the patients in this study were all Japanese, and their biological, genetic, and cultural backgrounds may differ from those of other populations; thus, care should be taken when extrapolating the results of this study to other populations.

Conclusions

The findings of this study demonstrate that the RRI, which has been associated with renal vascular hemodynamic changes and systemic atherosclerosis, was associated with a risk of cardiovascular events in hospitalized ASCVD patients with pEF. In pEF patients with an RRI ≥0.8, the risk of cardiovascular events was comparable to that of patients with mrEF. Measurement of the RRI is a safe and non-invasive, and may be useful in determining the burden of cardiovascular risk in ASCVD patients with pEF.

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Disclosures

The authors declare no conflicts of interest related to this study.

References


**Supplementary Files**

Please find supplementary file(s):

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