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ORIGINAL RESEARCH ARTICLE

# Predictors of cardiac function in acute heart failure patients with mid-range ejection fraction: AURORA study

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## Abstract

**Aim** The factors correlated with prognosis in heart failure with mid-range ejection fraction (HFmrEF) is unclear, especially for acute heart failure (AHF) with HFmrEF. Thus, we investigated the factors correlated with the improvement in the ejection fraction (EF) over 1 year in AHF patients with HFmrEF.

**Methods and results** In Acute Heart Failure Registry in the Osaka Rosai Hospital, we examined 159 consecutive HFmrEF patients out of 1051 HF patients who were admitted to our hospital for AHF from January 2015 to December 2017. We divided them into improved EF (IM) group whose EF improved (≧10%) and non-IM group who had no improvement. We compared the baseline characteristics, echocardiographic data, medications, examinations for ischaemia, invasive treatments, and clinical outcomes between IM group and non-IM group. IM group consisted of 21 patients (20%). IM group had a significantly more *de novo* heart failure, higher serum albumin (Alb), lower EF, smaller left ventricular dimension during diastole, more frequent coronary angiogram during hospitalization, and coronary intervention. Multivariate analysis revealed that Alb, left ventricular dimension during diastole, and coronary angiogram performed during hospitalization were independently associated with the improvement in the EF. In addition, IM group had less rehospitalizations over 1 year and a greater reduction in the B-type natriuretic peptide level during the follow-up than non-IM group.

**Conclusions** In AHF patients with HFmrEF, we should evaluate for any ischaemic heart disease during hospitalization, especially in patients with non-enlarged left ventricular and non-reduced serum Alb. AHF patients with HFmrEF who showed improvement in the EF tended to have better prognosis than those without improvement.

**Keywords** Acute heart failure; Heart failure with mid-ranged ejection fraction; Outcomes; Prognosis

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## Introduction

European Society of Cardiology guidelines on heart failure (HF) in 2016 introduced a new phenotype based on the ejection fraction (EF), called HF with mid-range EF (HFmrEF).[1] In the previous guidelines, the HF phenotypes were classified into a left ventricular EF (LVEF) of ≥50%, which defined HF with a preserved EF (HFpEF), and an LVEF of ≤40% or 35%, which defined HF with a reduced EF (HFrEF); therefore, most of the previous studies focused on HFpEF and HFrEF. HFmrEF had been excluded from the clinical trials, and regarding not only its EF but also its pathology, optimal medical treatment, and prognosis were considered a 'grey zone'. However, recently, several studies have shown data on chronic HF (CHF) with HFmrEF. Tsuji *et al.*[2] reported that a change in the EF was very

important for the prognosis, and ischaemic heart disease and a large left ventricular dimension were negative predictors of an improvement in the EF in CHF patients with HFmrEF.

On the other hand, AHF is the leading cause of hospitalizations,[3] but little is known about HFmrEF in AHF as compared with CHF. Thus, in this study, we investigated the factors correlated with an improvement in the EF over 1 year in AHF patients with HFmrEF and compared the prognosis between HFmrEF patients with an improvement in the EF and those with no improvement (*Figure 1*).

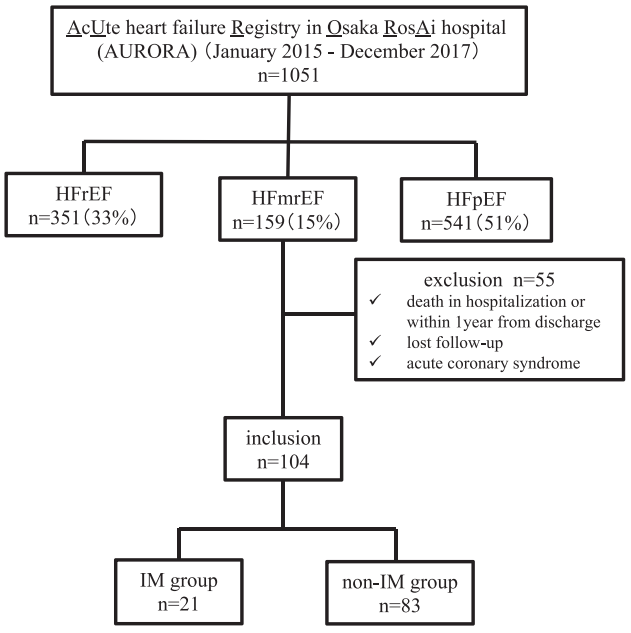
# Methods

## Study patients

Acute Heart Failure Registry in the Osaka Rosai Hospital (AURORA) is a single centre registry that collected consecutive HF patients who needed hospitalization for treatment at Osaka Rosai Hospital. From AURORA, we examined 159 consecutive HFmrEF patients (15%) out of 1051 HF patients who were admitted to our hospital for AHF from January 2015 to December 2017. The diagnosis of AHF was defined using Framingham criteria.[4] A total of 55 patients were excluded because of death on admission, lost to follow-up, or acute coronary syndrome. Finally, complete follow-up data were available for 104 patients. We divided our patients into an improved mid-range EF (IM) group in whom their EF improved (≧10%) over 1 year and a non-IM group who showed no improvement.

We compared the age, gender, body mass index, aetiology including ischaemic and valvular, *de novo* HF or a readmission, atrial fibrillation, past history including hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, smoker, old myocardial infarction, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft, previous other cardiac surgery, and previous cardiac resynchronized therapy, laboratory data including the B-type natriuretic peptide (BNP), sodium, and albumin (Alb), echocardiographic parameters including the LVEF, left ventricular dimension during diastole (LVDd)/left ventricular dimension during systole, left atrial dimension, wall thickness, mitral valvular regurgitation, tricuspid regurgitation pressure gradient, and inferior venous cava diameter, vital signs including the systolic blood pressure/diastolic blood pressure and heart rate, medications including beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and mineral corticoid receptor antagonists, examinations for ischaemia including a coronary angiogram (CAG), and myocardial scintigraphy, invasive treatment including a PCI, defibrillation cardioversion, and catheter ablation, and the clinical outcome including rehospitalizations during the 1 year and follow-up BNP level, between the IM group and the non-IM group.

**Figure 1** Patient inclusion flow chart. HFmrEF, heart failure with a mid-range ejection fraction; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with a reduced-ejection fraction; IM group, improved mid-range ejection fraction group.




## Echocardiography

Echocardiography was performed by one or two experienced echocardiographers in our hospital using the standard techniques.[5] The LVEF was calculated using the modified biplane Simpson's method. Aplio Artida (Toshiba Medical Systems, Tokyo, Japan) or IE33 (Koninklijke Philips N.V., Amsterdam, Dutch) equipped with phased-array 3.5-MHz transducer were used. Echocardiographic examinations were performed in hospitalization and at 1-year follow-up after the discharge.

## Definition of the improvement in the ejection fraction

Improvement of EF in HFmrEF is not clearly defined as compared with HFrEF. If follow-up EF ≧ 50% is defined as the improvement of EF in HFmrEF, patients with a few increasing of EF, for example, from 49–50%, are included in the improvement. However, this change may be within the margin of error, inter-observer/intra-observer variability. Thus, we assumed that increasing on LVEF of 10% showed all of patients with LVEF of 40–49% changed to HFpEF and enough

for exclusion of measurement error. Therefore, we defined an increased LVEF of more than 10% as an improvement.

### Statistical analysis

Continuous variables were presented as the median with the interquartile range as appropriate and were compared by a Wilcoxon rank sum test. Categorical variables were presented as counts and percentages and were compared by the Fisher's exact test. A multivariate analysis was performed using the factors with a $P$ value $<0.05$ in the univariate analysis. The statistical analyses were performed using JMP version 13.0 software (SAS Institute Inc., Cary, North Carolina, USA).

## Results

### Patient characteristics

The baseline characteristics were shown in *Table 1*. The IM group consisted of 21 patients (20%). There were no significant differences in terms of the baseline characteristics except for *de novo* or readmission between the two groups. It was confirmed that three patients who had performed cardiac resynchronized therapy were eligible at the time of device implantation. The findings from the admission data are summarized in *Table 2*. The IM group had a significantly higher Alb, lower LVEF, and smaller LVDd on admission. The medications, examinations for ischaemia, and invasive treatments are summarized in *Table 3*. Approximately 70% of the patients with HFmrEF in this study were revealed to be taking beta-blockers and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, and there were no significant differences in the oral medications between the two groups. In terms of the examinations for ischaemia and invasive treatments, more CAG during hospitalization and more PCIs within 6 months from the hospitalization were performed in the IM group.

### Predictors of the improvement in the ejection fraction over 1 year in heart failure with mid-range ejection fraction patients

We performed a multivariate logistic regression analysis using the factors with a $P$ value $<0.05$ in the univariate analysis. As a result, the LVDd, Alb, and CAG performed during hospitalization were significantly and independently associated with an improvement in the EF (*Table 4*).

### Prognosis

We examined the difference in the prognosis between the IM group and the non-IM group. The IM group had less rehospitalizations over the 1-year [0 (0.0) vs. 28 (27.2), $P = 0.004$] (*Figure 2*) and a greater reduction in the BNP level during the follow-up [−74.2 (−96.9 to −35.4) vs. −50.4 (−86.8 to −0.3), $P = 0.027$] (*Figure 3*) as compared with the non-IM group.

## Discussion

The present study demonstrated that in the AHF patients with HFmrEF (i) the LVDd, Alb, and in-hospital CAG were

**Table 1** Baseline characteristics

| | IM group ($n = 21$) | Non-IM group ($n = 83$) | $P$ value |
|---|---|---|---|
| Age, years | 78 (69–80) | 79 (71–84) | 0.077 |
| Male | 13 (61.9) | 48 (57.8) | 0.808 |
| BMI, kg/m$^2$ | 21.2 (19.7–25.9) | 22.3 (19.6–25.3) | 0.977 |
| Aetiology | | | |
| Ischaemic | 7 (33.3) | 27 (36.0) | 1.000 |
| Valvular | 8 (38.1) | 28 (34.2) | 0.800 |
| *De novo* | 17 (81.0) | 46 (54.2) | 0.028 |
| AF | 11 (52.4) | 37 (44.6) | 0.626 |
| Hypertension | 15 (71.4) | 59 (72.0) | 1.000 |
| Dyslipidaemia | 9 (42.9) | 31 (37.4) | 0.802 |
| Diabetes mellitus | 8 (38.1) | 36 (43.4) | 0.806 |
| CKD | 9 (42.9) | 46 (55.4) | 0.336 |
| Smoker | 9 (47.4) | 36 (43.4) | 0.802 |
| OMI | 2 (10.0) | 19 (22.9) | 0.352 |
| Previous PCI | 3 (14.3) | 14 (16.9) | 1.000 |
| Previous CABG | 1 (4.8) | 5 (6.0) | 1.000 |
| Previous other cardiac surgery | 0 (0.0) | 7 (8.4) | 0.340 |
| Previous CRT | 0 (0.0) | 3 (3.6) | 1.000 |

Values are $n$ (%) or median (interquartile range). AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CRT, cardiac resynchronized therapy; OMI, old myocardial infarction; PCI, percutaneous coronary intervention.

**Table 2** Findings in hospitalization

| | IM group ($n$ = 21) | Non-IM group ($n$ = 83) | $P$ value |
|---|---|---|---|
| Laboratory data | | | |
| BNP, pg/mL | 800.5 (300.1–1416.4) | 977.2 (659.5–1573.9) | 0.287 |
| Na, mEq/L | 139 (138–141) | 140 (137–142) | 0.542 |
| Alb, g/dL | 3.7 (3.4–3.9) | 3.4 (3.0–3.7) | 0.015 |
| Echocardiographic data | | | |
| LVEF, % | 43 (41–45) | 45 (42–47) | 0.031 |
| LVDd, mm | 52 (49–56) | 57 (53–60) | 0.001 |
| LVDs, mm | 42 (39–44) | 44 (39–47) | 0.082 |
| LAD, mm | 49 (47–52) | 48 (45–53) | 0.505 |
| Wall thickness, mm | 9.5 (9–10) | 9 (8–10) | 0.250 |
| MR (moderate to severe) | 5 (23.8) | 25 (30.1) | 0.788 |
| TRPG, mmHg | 40 (31–48) | 41 (32–48) | 0.975 |
| IVCD, mm | 19 (14–21) | 15 (12–19) | 0.097 |
| Vital signs | | | |
| SBP, mmHg | 166 (132–184) | 151 (123–173) | 0.111 |
| DBP, mmHg | 104 (76–118) | 85 (70–100) | 0.063 |
| HR, b.p.m. | 90 (83–124) | 87 (73–106) | 0.310 |

Values are $n$ (%) or median (interquartile range). Alb, albumin; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; HR, heart rate; IVCD, inferior venous cava diameter; LAD, left atrial dimension; LVDd, left ventricular dimension at diastole; LVDs, left ventricular dimension at systole; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; Na, sodium; SBP, systolic blood pressure; TRPG, tricuspid valve regurgitation pressure gradient.

**Table 3** Medication, examination for ischaemi, and invasive treatment

| | IM group ($n$ = 21) | Non-IM group ($n$ = 83) |
|---|---|---|
| Medication | | |
| Beta-blocker | 15 (71.4) | 59 (71.1) |
| ACE-I/ARB | 16 (76.2) | 59 (71.1) |
| MRA | 8 (38.1) | 40 (48.2) |
| Examination for ischaemia | | |
| CAG | | |
| Pre-hospital | 6 (30.0) | 38 (45.8) |
| In-hospital | 15 (71.4) | 23 (27.7) |
| Myocardial scintigraphy | | |
| Pre-hospital | 2 (9.5) | 14 (16.9) |
| In-hospital | 0 (0.0) | 4 (4.82) |
| Invasive treatment | | |
| PCI[a] | 5 (23.8) | 6 (7.2) |
| ABL or DC[a] | 2 (9.5) | 4 (4.8) |

Values are $n$ (%). ABL, catheter ablation; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CAG, coronary angiogram; DC, defibrillation; MRA, mineral corticoid receptor antagonist; PCI, percutaneous coronary intervention.
[a]Performed within 6 months from hospitalization.

**Table 4** Predictors of improvement of EF in AHF with HFmrEF

| | Univariate | Multivariate | |
|---|---|---|---|
| | $P$ value | OR (95% CI) | $P$ value |
| Alb | 0.015 | 9.04 (1.80–45.4) | 0.008 |
| *De novo* | 0.028 | 1.72 (0.39–7.69) | 0.475 |
| LVDd | 0.001 | 0.82 (0.73–0.93) | 0.001 |
| In-hospital CAG | <0.001 | 5.65 (1.24–25.7) | 0.025 |
| PCI[a] | 0.043 | 1.98 (0.39–10.0) | 0.408 |

AHF, acute heart failure; Alb, albumin; CAG, coronary angiogram; CI, confidence interval; EF, ejection fraction, HFmrEF, heart failure with mid-range ejection fraction; LVDd, left ventricular dimension at diastole; OR, odds ratio; PCI, percutaneous coronary intervention.
[a]Performed within 6 months from hospitalization.

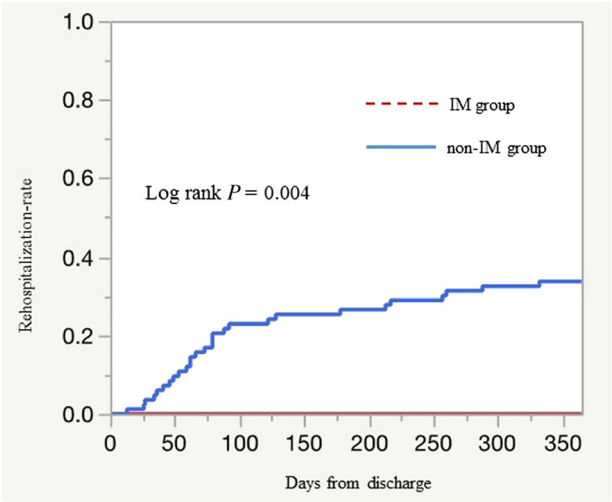
factors correlated with an improvement in the EF at 1 year and (ii) the patients who had an improved EF had a significantly greater reduction in the BNP level and fewer rehospitalizations during the 1 year.

Several previous studies have examined the differences in the epidemiology, pathology, optimal medications, and prognoses among HF subgroups in CHF patients.[2,6–10] However, there have been little data on AHF patients with HFmrEF. Thus, we focused on the predictors correlated with an improvement in the EF and prognosis in HFmrEF patients using the AURORA that collected AHF patients. To the best of our knowledge, this is the first study to investigate the improvement in the EF in AHF patients with HFmrEF.

## Predictors of the improvement in the ejection fraction

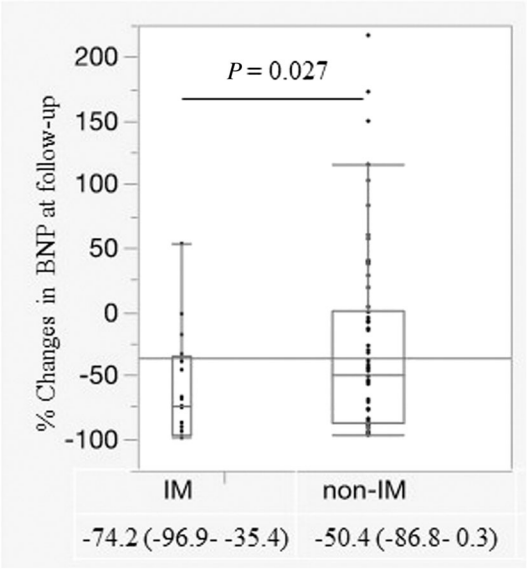
A multivariate analysis revealed that the LVDd, serum Alb, and in-hospital CAG were significant and independent factors correlated with an improvement in the EF at 1 year in AHF patients with HFmrEF. It has been reported that a large LVDd is a negative predictor of an improvement in the EF in HFmrEF patients with CHF,[2] which may support our data regarding AHF. There was no data about the correlation between serum Alb and the improvement of EF in AHF patients with HFmrEF, but Nishi *et al.*[11] have shown that nutritional status is associated with prognosis in HF patients. Accordingly, we believe

**Figure 2** Rehospitalization-rate between the IM group and the non-IM group. IM group, the improved mid-range ejection fraction group.




| No. of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| IM group | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 21 |
| non-IM group | 83 | 76 | 65 | 63 | 62 | 60 | 57 | 56 | 55 |

**Figure 3** Percentage changes in BNP at follow-up between IM group and non-IM group. Value, median/(pg/nL) (interquartile range). BNP, B-type natriuretic peptide; IM group, improved mid-range ejection fraction group.




that the nutrition including Alb may be one of the key factors correlating with the improvement of EF in AHF patients with HFmrEF. Medications were not associated with the improvement of EF in the present study. Some reported association medications with prognosis of HFmrEF in CHF[12,13]; however, it is unclear in AHF. We examined only data in discharge. Therefore, if we check follow-up data in detail, maximum dose, or interruption, we may get some association with the improvement of EF or prognosis. Regarding the in-hospital CAG, Flaherty *et al.*[14] have reported that the use of in-hospital CAG in AHF patients is associated with a significantly lower mortality and rehospitalization risk because receiving revascularization, aspirin, statins, beta-blockers, and angiotensin converting enzyme inhibitors is increased. Focusing on AHF in the HFmrEF patients in our study, we could obtain similar results.

Heart failure with mid-range ejection fraction is known to have 'intermediate' characteristics between HFrEF and HFpEF,[2,7,10] and limited evidence is now available in terms of its pathology. Appropriate treatments for HFmrEF including revascularization, beta-blocker therapy, rate control, and decongestion may be dependent on the aetiology of the HF. In addition, it has been reported that patients who have evolved from HFmrEF to HFpEF show a better prognosis,[7] and the prevalence of ischaemic heart disease is larger in HFmrEF than HFpEF[10]. The percentage of patients with ischaemic aetiology were similar in the present study. Accordingly, ischaemia itself might not be a predictor of EF improvement and the appropriate revascularization or optimal medications for non-ischaemic aetiology may be more important. Moreover, it is obvious that AHF is more unstable and needs a more rapid treatment than CHF. Therefore, it is more important to clarify whether the cause of the HF is ischaemic or not, in AHF patients with HFmrEF more than with HFrEF and HFpEF, as early as possible.

## Prognosis

Improvement in the EF is an important predictor of the prognosis in HFrEF[15]; however, it is unclear in HFmrEF. A previous study on CHF showed that HFmrEF transitions into HFpEF in 44% at 1 year, and patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or transition into HFpEF.[2] On the other hand, another study in CHF showed that a change from HFmrEF to HFpEF has a better prognosis than in the other groups.[7] The present study, focusing on AHF, showed that patients who improved from HFmrEF to HFpEF had fewer rehospitalizations over 1 year. In addition, our study showed that an improvement in the EF over 1 year was associated with a greater reduction in the BNP level during the follow-up. Savarese *et al.*[16] revealed that the change in the BNP level during the follow-up was associated with the prognosis. Thus, we think that AHF patients with HFmrEF who evolve from HFmrEF to HFpEF have a better prognosis.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### Limitation

The present study was not powerful enough to assess the relationship between the improvement of EF and clinical events. These results should be verified over the long term and with a larger sample size.

## Conclusions

In AHF patients with HFmrEF, we should examine whether the cause of the HF is ischaemia or not as early as possible from hospitalization in order to obtain an optimal treatment, especially for patients with a non-enlarged left ventricle and non-reduced serum Alb. AHF patients with HFmrEF who show an improvement in the EF are likely to have a better prognosis than those without an improvement.

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## Conflict of interest

None declared.

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