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Clinical Investigation

# Associations With Eicosapentaenoic Acid to Arachidonic Acid Ratio and Mortality in Hospitalized Heart Failure Patients

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## ABSTRACT

**Background:** Intake of n-3 polyunsaturated fatty acids (n-3 PUFAs) lowers the risk of atherosclerotic cardiovascular events, particularly ischemic heart disease. In addition, the ratio of eicosapentaenoic acid (EPA; n-3 PUFA) to arachidonic acid (AA; n-6 PUFA) has recently been recognized as a risk marker of cardiovascular disease. In contrast, the prognostic impact of the EPA/AA ratio on patients with heart failure (HF) remains unclear.

**Methods and Results:** A total of 577 consecutive patients admitted for HF were divided into 2 groups based on median of the EPA/AA ratio: low EPA/AA (EPA/AA <0.32 mg/dl, n = 291) and high EPA/AA (EPA/AA ≥0.32, n = 286) groups. We compared laboratory data and echocardiographic findings and followed cardiac mortality. Although body mass index, blood pressure, B-type natriuretic peptide, hemoglobin, estimated glomerular filtration rate, total protein, albumin, sodium, C-reactive protein, and left ventricular ejection fraction did not differ between the 2 groups, cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group (12.7 vs 5.9%, log-rank $P = .004$). Multivariate Cox proportional hazard analysis revealed that the EPA/AA ratio was an independent predictor of cardiac mortality (hazard ratio 0.677, 95% confidence interval 0.453–0.983, $P = .041$) in patients with HF.

**Conclusion:** The EPA/AA ratio was an independent predictor of cardiac mortality in patients with HF; therefore, the prognosis of patients with HF may be improved by taking appropriate management to control the EPA/AA balance. (*J Cardiac Fail 2016;*■■*:*■■–■■)

**Key Words:** Heart failure, n-3 polyunsaturated fatty acids, eicosapentaenoic acid to docosahexaenoic acid ratio, prognosis.

Heart failure (HF) remains one of the major causes of cardiovascular morbidity and mortality, despite therapeutic advances in its treatment. The cardiovascular protective effects of seafood consumption and long-chain n-3 polyunsaturated fatty acid (n-3 PUFA) intake(eg, plaque stabilization, antiarrhythmic and hemodynamic effects) have been reported.[1–6] The balance between dietary n-3 and n-6 fatty acids, especially a low serum ratio of eicosapentaenoic acid (EPA; n-3 PUFA) to arachidonic acid (AA; n-6 PUFA) may be strongly associated with increased risk of cardiovascular disease (CVD).[1,7] Although AA increases inflammation, platelet aggregation, and vasoconstriction through cyclooxygenase and lipoxygenase, EPA impairs inflammatory eicosanoid derived from AA, platelet aggregation, and vasodilatation. EPA competes or cooperates with AA, and thus the balance of EPA and AA may be important.[1] In addition, the EPA/AA ratio has

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a linear relationship with the ratio of prostaglandin $I_3$ and prostaglandin $I_2$ to thromboxane $A_2$.[1] Therefore, the EPA/AA ratio has recently been recognized as a risk marker of CVD including myocardial infarction, sudden cardiac death, stroke, and thromboembolism in various populations.[1,8–11] However, the association between circulating levels of EPA/AA ratio and cardiac mortality in patients with HF still remains unclear. In addition, such an association may vary depending upon several clinical backgrounds, such as age, gender, HF etiology, comorbidities, and treatments.[10,12–16] Furthermore, n-3 PUFA also attracts attention as a therapeutic target[1,10] to reduce the residual risk of CVD after low-density cholesterol-lowering therapy with statins, which is common in the management of CVD and/or HF.[17,18] In the Japan EPA Lipid Intervention Study (JELIS) study, the administration of EPA and statins in dyslipidemia patients resulted in a significant reduction in the risk of CVD events when the EPA/AA ratio was >0.75 (hazard ratio [HR] 0.83, $P = .031$).[19]

Thus, the aim of the present study was to investigate the associations between the EPA/AA ratio and cardiac mortality in patients with HF, with a focus on patients' clinical backgrounds (especially in HF patients with or without statins).

## Methods

### Subjects and Study Protocol

This was a prospective observational study that enrolled consecutive symptomatic HF patients who were hospitalized to treat decompensated HF at Fukushima Medical University between 2009 and 2013. The diagnosis of decompensated HF was defined by several cardiologists based on the Framingham criteria.[20] Patients with acute coronary syndrome, on dialysis, or undergoing n-3 PUFA treatment were excluded. Patients who were selected for this study were divided into 2 groups based on the median value of the EPA/AA ratio: those with high EPA/AA (EPA/AA ≥ 0.32, n = 286) and those with low EPA/AA (EPA/AA < 0.32, n = 291). A fasting blood sample was obtained from each patient within 24 hours of admission, and the serum levels of fatty acids were blindly measured at SRL Co., Ltd. (Tokyo, Japan) using a gas chromatrophy-flame ionization detector system (6890N; Agilent Technologies, Tokyo, Japan).[21] We performed several examinations on admission, such as general laboratory tests and echocardiography, and compared the parameters between the 2 groups. Comorbidities were also defined by several attending physicians. Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure >140 mmHg, and/or diastolic blood pressure >90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value >126 mg/dl, and/or a hemoglobin A1c value >6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value >150 mg/dl, a low-density lipoprotein (LDL) cholesterol value >140 mg/dl, and/or a high-density lipoprotein cholesterol value <40 mg/dl. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 $m^2$.[22] Anemia was defined as a hemoglobin level <12.0 g/dl in females and <13.0 g/dl in males.[23] Reduced left ventricular ejection fraction (LVEF) was defined as less than 50%. The patients were followed up until March 2015 for cardiac mortality, which was the primary outcome of our study. Cardiac death was confirmed by independent experienced cardiologists as death either from worsened HF in accordance with the Framingham criteria,[20] ventricular fibrillation documented by electrocardiograph or implantable devices, or acute coronary syndrome. This follow-up was performed blindly to the analyses of this study. Status and dates of death were obtained from the patients' medical records or their referring cardiologists. Survival time was defined as from the date of hospitalization until the date of death or last follow-up. We could follow-up on all patients. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology along with references to Strengthening the Reporting of Observational Studies in Epidemiology and the broader Enhancing the Quality and Transparency of Health Research guidelines.[24]

### Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using standard techniques. The echocardiographic parameters we investigated included interventricular septum thickness, left ventricular dimension, posterior wall thickness, LVEF, left atrial volume, the ratio of early transmitral flow velocity to mitral annular velocity, inferior vena cava diameter, peak systolic pulmonary artery pressure, and right ventricular fractional area change.[25] LVEF was calculated using a modification of Simpson's method. Early transmitral flow velocity to mitral annular velocity was calculated by transmitral Doppler flow and tissue Doppler imaging. Tissue Doppler imaging was obtained from the average of lateral and septal annulus velocities. Systolic pulmonary artery pressure was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient.[25] The right ventricular fractional area change, defined as (end diastolic area − end systolic area)/end diastolic area × 100, is a measure of right ventricular systolic function.[25] All recordings were performed on ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA).

### Statistical Analysis

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as the median (inter-quartile range). Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. Data of the 2 groups were compared using the independent Student *t* test for normally distributed data and the Mann-Whitney *U* test for nonnormally distributed data. The Kaplan-Meier method was used for presenting cardiac mortality; the log-rank test