

# Prognostic Significance of Serum Cholinesterase Level in Patients With Acute Decompensated Heart Failure With Preserved Ejection Fraction: Insights From the PURSUIT-HFpEF Registry

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**Background**—Malnutrition is one of the most important comorbidities in patients with heart failure with preserved ejection fraction. We recently reported the prognostic significance of serum cholinesterase level and superior predictive power of cholinesterase level to other objective nutritional indices such as the controlling nutritional status score, prognostic nutritional index, and geriatric nutritional risk index in patients with acute decompensated heart failure. The aim of this study was to clarify the prognostic role of cholinesterase in patients with heart failure with preserved ejection fraction/acute decompensated heart failure and investigate incremental cholinesterase value.

**Methods and Results**—We prospectively studied 274 consecutive patients from the PURSUIT-HFpEF (Prospective Multicenter Observational Study of Patients with Heart Failure With Preserved Ejection Fraction) study. During a follow-up period of  $1.2 \pm 0.6$  years, 56 patients reached the composite end points (cardiovascular death and readmission for worsening heart failure). In the multivariable Cox analysis, cholinesterase level was significantly associated with the composite end points after adjustment for major confounders. A Kaplan–Meier analysis revealed that patients with low cholinesterase levels (stratified by tertile) had significantly greater risk of reaching the composite end points than those with middle or high cholinesterase levels ( $P=0.0025$ ). Cholinesterase level showed the best C-statistics (0.703) for prediction of the composite end points among the objective nutritional indices. C-statistics of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score for prediction of the composite end points were improved when cholinesterase level was added (C-statistics, from 0.601 to 0.705;  $P=0.0408$ ).

**Conclusions**—Cholinesterase was a useful prognostic marker for prediction of adverse outcome in patients with heart failure with preserved ejection fraction/acute decompensated heart failure. (*J Am Heart Assoc.* 2020;9:e014100. DOI: 10.1161/JAHA.119.014100.)

**Key Words:** cholinesterase • heart failure • malnutrition • nutritional indices • risk stratification

Although treatment of heart failure (HF) has remarkably progressed over the past several decades, HF is still a serious disease characterized by high risks of mortality and repetitive hospitalization.<sup>1</sup> Given that the number of patients with HF is increasing, HF is becoming a major health problem.<sup>2</sup> Recently, approximately half of patients with HF

have been shown to have HF with preserved left ventricular ejection fraction (HFpEF), and patients with HFpEF had a higher comorbidity burden than those with HF with reduced ejection fraction.<sup>3</sup> Malnutrition, which is one of the most important comorbidities of HF, has been reported as a powerful prognostic factor in patients with HFpEF.<sup>4–8</sup> Some

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## Clinical Perspective

### What Is New?

- In acute heart failure patients with preserved left ventricular ejection fraction, serum cholinesterase level is a simple and strong prognostic factor for prediction of poor outcome and tends to provide more-powerful prognostic information than other objective nutritional indices (eg, the Controlling Nutritional Status score, Prognostic Nutritional Index, and Geriatric Nutritional Risk Index).
- Serum cholinesterase level provides incremental value over the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score in acute heart failure patients with preserved left ventricular ejection fraction.

### What Are the Clinical Implications?

- Cholinesterase provides a more-accurate nutritional risk evaluation of patients than other objective nutritional indices.
- This may allow early implementation of appropriate nutritional intervention in daily practice and lead to better outcomes in acute heart failure patients with preserved left ventricular ejection fraction.

recent studies have shown the potential of dietary intervention to improve HF symptoms or cardiorespiratory fitness.<sup>9–11</sup> Therefore, accurate nutritional evaluation is indispensable to improve the prognosis of patients with HF.<sup>12</sup>

Serum cholinesterase level has been used for the evaluation of nutritional status in daily practice,<sup>13</sup> and its prognostic value was reported in patients with chronic HF (CHF).<sup>14</sup> In addition, we have recently reported the prognostic significance of cholinesterase level and shown that cholinesterase level has superior predictive power to other objective nutritional indices, such as the Controlling Nutritional Status (CONUT) score, Prognostic Nutritional Index (PNI), and Geriatric Nutritional Risk Index (GNRI), in patients with acute decompensated HF (ADHF).<sup>15</sup> However, the prognostic value of cholinesterase remains to be fully evaluated in ADHF patients with preserved ejection fraction.

Risk stratification of patients with HFpEF is clinically relevant because of the lack of therapies with proven efficacies. As one of the several HF risk models, the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score was originally developed from a large international database of patients with CHF, and its prognostic usefulness was externally validated in CHF patients with preserved ejection fraction<sup>16</sup> and patients with ADHF.<sup>17</sup> Therefore, the present study was conducted to achieve the following objectives using the multicenter HFpEF registry: (1) investigation of the prognostic role of cholinesterase level and

comparison with other nutritional indexes in HFpEF-ADHF and (2) investigation of the prognostic usefulness of the MAGGIC risk score in patients with ADHF with preserved ejection fraction and the incremental prognostic value of cholinesterase level over the MAGGIC risk score.

## Methods

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions. However, the study materials that support the findings of this study and the methods used in the analyses will be provided by the corresponding author upon reasonable request.

## Subjects

Patient data were obtained from the PURSUIT-HFpEF (Prospective Multicenter Observational Study of Patients with Heart Failure With Preserved Ejection Fraction) study. The PURSUIT-HFpEF study is a prospective, multicenter, observational study in which collaborating hospitals in Osaka record clinical, echocardiographic, and outcome data of patients with ADHF and preserved left ventricular ejection fraction (LVEF;  $\geq 50\%$ ; UMIN-CTR ID: UMIN000021831). Consecutive patients with ADHF and preserved ejection fraction were prospectively registered and agreed to be followed up for collection of outcome data. ADHF was diagnosed on the basis of the following criteria: (1) clinical symptoms and signs according to the Framingham Heart Study criteria and (2) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) level of  $\geq 400$  pg/mL or brain natriuretic peptide level of  $\geq 100$  pg/mL. Between June 2016 and December 2017, 345 patients were enrolled. We excluded patients with in-hospital death ( $n=8$ ), missing cholinesterase data ( $n=45$ ), or missing follow-up data ( $n=18$ ). Ultimately, 274 patients with ADHF were analyzed in this study. All patients provided written informed consent for participation in this study, which was approved by the ethics committee of each participating hospital. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki.

## Data Collection

All patients underwent echocardiography and venous blood sampling at discharge. On echocardiography, left ventricular end-diastolic dimension and end-systolic dimensions and left atrial dimension were measured using the standard technique. LVEF was measured using the modified Simpson method. Diastolic left ventricular function was measured using the ratio of early transmitral filling velocity, which was measured

with pulse-wave Doppler ultrasonography, to early diastolic mitral annular velocity, which was determined using spectral tissue Doppler imaging ( $E/e'$ ). Systolic right ventricular function was measured using tricuspid annular plane systolic excursion. Tricuspid regurgitation pressure gradient was measured using continuous-wave Doppler imaging. Blood samples were obtained at discharge for assessment of complete blood count and serum levels of sodium, chloride, potassium, creatinine, blood urea nitrogen, albumin, uric acid, aspartate aminotransaminase, alanine aminotransferase, total bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase, C-reactive protein, cholinesterase, and NT-proBNP levels.

The CONUT score was calculated from 3 variables, namely serum albumin level, total cholesterol level, and lymphocyte count (range, 0–12, with higher values indicating worse nutritional status), as previously reported.<sup>18</sup> We also calculated PNI ( $10 \times \text{serum albumin level [g/dL]} + 0.005 \times \text{total lymphocyte count [}/\text{mm}^3]$ ) and GNRI ( $14.89 \times \text{serum albumin level} + 41.7 \times \text{body mass index [BMI]}/22$ ).<sup>19,20</sup>

The MAGGIC risk score was calculated from 13 variables as follows: age, sex, BMI, systolic blood pressure, LVEF, creatinine level, current smoking, diabetes mellitus, chronic obstructive pulmonary disease, New York Heart Association class, HF duration of >18 months,  $\beta$ -blocker use, and angiotensin-converting enzyme inhibitor use, as previously reported.<sup>21</sup>

## Clinical Outcomes

After discharge, all patients were followed up in each hospital. Survival data were obtained by dedicated coordinators and investigators by direct contact with patients and their physicians at the hospital or in an outpatient setting or by a telephone interview with their families or by mail. The primary end points of this study were the composites of cardiovascular death and hospitalization for worsening HF (composite end points). The secondary end points were all-cause mortality and cardiovascular death.

## Statistical Analyses

All continuous variables are expressed as mean (SD) or median (25th–75th percentile), as appropriate, and categorical variables are expressed as percentage. Patients were stratified according to the tertile of serum cholinesterase value. The Student *t* test or 1-factor ANOVA was used to compare differences in normally distributed continuous variables. The Kruskal–Wallis rank-sum test was used to compare differences in nonnormally distributed data. Fisher's exact test and chi-square test were used to compare between-group differences in categorical variables.

Correlations of serum cholinesterase level to serum levels of albumin, aspartate aminotransaminase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and C-reactive protein and BMI, CONUT score, GNRI, and PNI were assessed using Spearman correlation coefficients. The Kaplan–Meier method and log-rank test were used to estimate cardiac event-free rates. Cox regression analyses were conducted to investigate the impact of low and middle level of cholinesterase on study outcomes, while taking hazard ratio (HR) of high cholinesterase group as a reference. Cox proportional hazards regression models were used to identify patients at risk of the primary and secondary end points to calculate multivariable-adjusted HRs and 95% CIs. Two multivariable models (clinical and biomarker models) were constructed. Covariates considered to be clinically relevant were selected a priori and forced into the models. The clinical model included age, sex, BMI, and history of diabetes mellitus, which were selected because they were basic clinical parameters and known as factors that could influence cholinesterase value.<sup>13</sup> The biomarker model included hemoglobin level, estimated glomerular filtration rate, albumin level, and log-transformed NT-proBNP level. These variables were selected because comorbidities, such as anemia, renal failure, malnutrition, and NT-proBNP level, were well-established risk predictors in patients with HFpEF.<sup>16,22,23</sup> To avoid overfitting, especially in the prediction of cardiovascular death, the covariates of the clinical model were restricted to age and sex and those of the biomarker model to hemoglobin and estimated glomerular filtration rate. To evaluate for potential collinearity among the covariates, we calculated the variance inflation factor for each adjusted model after the models were constructed. Multicollinearity was defined such that the maximum variance inflation factor value exceeded a recommended threshold of 10.<sup>24</sup> The areas under the curve of cholinesterase level and other objective nutritional indices were compared using a receiver-operating characteristic curve analysis for prediction of the composite end point within 1 year. The significance criterion was adjusted to  $P < 0.017$  by using Bonferroni's correction to control the multitesting issue. Furthermore, to clarify improvement of risk prediction by cholinesterase level over the MAGGIC risk score, a receiver-operating characteristic curve analysis was performed for the logistic regression models of MAGGIC only and MAGGIC plus cholinesterase, for prediction of the composite end point within 1 year. Areas under the curve were compared according to the method of DeLong et al.<sup>25</sup> Net reclassification improvement and integrated discrimination improvement attained by the addition of cholinesterase to the MAGGIC risk score were also calculated. MedCalc (version 17.11.564 bit; MedCalc Software bvba, Ostend, Belgium) and EZR software (version 1.03; Saitama Medical Center, Jichi Medical University, Saitama, Japan) were used to

perform all statistical analyses.  $P < 0.05$  was considered statistically significant.

## Results

### Baseline Patient Characteristics

Distribution of cholinesterase levels is shown in Figure 1. Median value (interquartile range) was 208 U/L (166–255 U/L). The study population ( $n=274$ ) was categorized by cholinesterase level tertiles as follows: low cholinesterase level  $\leq 180$  U/L ( $n=93$ );  $180$  U/L  $<$  cholinesterase level  $\leq 236$  U/L ( $n=90$ ); and cholinesterase level  $> 236$  U/L ( $n=91$ ).

In all study patients, mean age was 80 years, the proportion of male patients was 46%, and the LVEF was  $61\% \pm 7\%$ . Patients' baseline characteristics stratified according to cholinesterase level tertiles are shown in Table 1. Compared with patients with high cholinesterase levels, those with low cholinesterase levels had significantly higher age, higher proportion of males, lower BMI, lower incidence rate of dyslipidemia, smaller left ventricular end-diastolic dimension and tricuspid annular plane systolic excursion, lower hemoglobin level, platelet count, and sodium and albumin levels, and higher NT-proBNP and gamma-glutamyl transpeptidase levels. As for the nutritional indices, patients with lower cholinesterase had a significantly higher CONUT score and lower PNI and GNRI.

Serum cholinesterase level had moderate correlations with albumin level ( $r=0.448$ ;  $P < 0.0001$ ), BMI ( $r=0.327$ ;  $P < 0.0001$ ), CONUT score ( $r=-0.528$ ;  $P < 0.0001$ ), PNI ( $r=0.533$ ;  $P < 0.0001$ ), and GNRI ( $r=0.499$ ;  $P < 0.0001$ ). Cholinesterase level had weak correlations with C-reactive protein level ( $r=-0.152$ ;  $P=0.0122$ ). Cholinesterase level had no significant correlation with aspartate aminotransaminase

( $r=-0.084$ ;  $P=0.1675$ ), alkaline phosphatase ( $r=-0.106$ ;  $P=0.0800$ ), total bilirubin ( $r=-0.047$ ;  $P=0.4434$ ), or alanine aminotransferase level ( $r=0.047$ ;  $P=0.4396$ ).

### Clinical Outcomes and Prognostic Analysis

During a mean follow-up period of  $1.3 \pm 0.5$  years, 56 patients reached the composite end points, 38 patients died, and 15 patients had a cardiovascular death.

The Kaplan–Meier analysis revealed that patients with low cholinesterase levels ( $\leq 80$  U/L defined by tertile) had a significantly greater risk of reaching the composite end points than those with middle or high cholinesterase levels (31% versus 16% versus 14%;  $P=0.0025$ ; adjusted HR, 2.56 [95% CI, 1.33–4.93]; adjusted HR, 1.27 [95% CI, 0.59–2.76]; Figure 2). Patients with low cholinesterase levels had greater risks of all-cause mortality and cardiovascular death than those with middle or high cholinesterase levels (Figure 2).

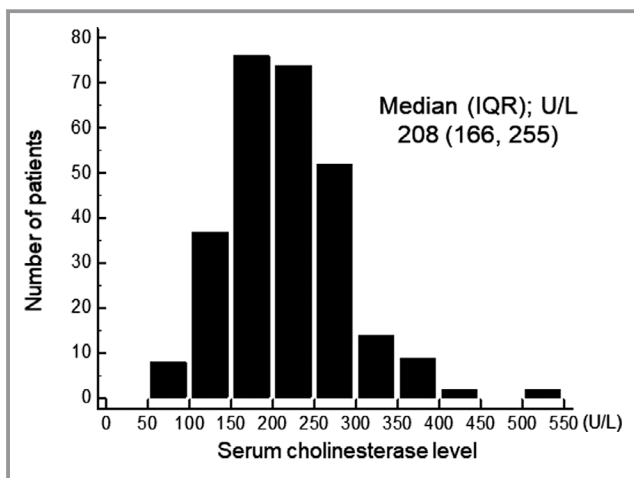
Results of the multivariable Cox proportional hazards analysis for prediction of the composite end points, all-cause mortality, and cardiovascular death are shown in Table 2. Cholinesterase level was significantly associated with the composite end points, all-cause mortality, and cardiovascular mortality in both the clinical and biomarker models. No collinearity was identified among the covariates used in the analyses because all the variance inflation factor values were  $< 10$ .

### Comparison With Other Nutritional Indices

The receiver-operating characteristic analysis for identification of the composite end point within 1 year is shown in Figure 3. Cholinesterase level had the greatest areas under the curve among all the objective nutritional indices for identification of the composite end points (cholinesterase level, 0.703 [95% CI, 0.642–0.758]; CONUT score, 0.672 [95% CI, 0.610–0.729]; PNI, 0.676 [95% CI, 0.615–0.733]; GNRI, 0.619 [95% CI, 0.556–0.679]; Figure 3). Differences between cholinesterase level and the other nutritional indices were not statistically significant (cholinesterase level versus CONUT score,  $P=0.5631$ ; cholinesterase level versus PNI,  $P=0.6418$ ; cholinesterase level versus GNRI,  $P=0.1724$ ).

### Prognostic Value of HF Risk Scores and the Incremental Prognostic Value of Cholinesterase Level Over the HF Risk Scores

The MAGGIC risk score tended to be greater in patients with than in those without the composite end points ( $25 \pm 6$  versus  $24 \pm 5$ ;  $P=0.0877$ ). The MAGGIC risk score was significantly



**Figure 1.** Distribution of serum cholinesterase level. IQR indicates interquartile range.

**Table 1.** Baseline Characteristics of the Patients With Acute Decompensated Heart Failure Stratified by Serum Cholinesterase Level Tertile

	Overall (n=274)	Lowest Tertile Cholinesterase Level ≤180 (n=93)	Middle Tertile 180 <Cholinesterase Level ≤236 (n=90)	Highest Tertile 236 <Cholinesterase Level (n=91)	P Value
<b>Clinical data</b>					
Age, y	80±10	82±7	81±9	76±11	<0.001
Sex (male, %)	46	52	51	34	0.0255
BMI	21.8±4.8	20.1±3.6	21.6±4.3	23.5±4.6	<0.001
NYHA class I/II/III, %	42/52/4	35/55/10	40/55/5	51/46/3	0.096
SBP, mm Hg	119±17	118±18	119±19	121±16	0.528
Heart rate, bpm	71±12	71±12	71±12	70±12	0.588
Atrial fibrillation, %	36	31	44	32	0.111
Hypertension, %	87	89	82	88	0.339
Diabetes mellitus, %	35	30	30	44	0.086
Dyslipidemia, %	47	40	44	61	0.019
Previous HF hospitalization, %	29	34	30	22	0.172
<b>Medications</b>					
ACEI or ARB, %	52	42	54	59	0.051
β-blocker, %	57	52	57	63	0.319
Loop diuretics, %	97	97	97	99	0.748
Aldosterone blocker, %	37	37	33	40	0.685
Tolvaptan, %	17	21	13	15	0.446
Statin, %	33	25	37	37	0.122
<b>Echocardiography</b>					
LVEF, %	61±7	62±8	62±7	61±7	0.559
LVDd, mm	46±7	44±8	45±6	47±6	0.013
LAD, mm	44±8	43±9	44±9	45±7	0.475
E <sub>a</sub>	13 (10–17)	13 (10–18)	13 (10–17)	13 (10–18)	0.912
TAPSE, mm	18±5	16±4	18±5	18±5	0.011
TRPG, mm Hg	26 (21–31)	28 (22–34)	25 (22–30)	26 (21–31)	0.137
IVC diameter, mm	14 (10–16)	14 (9–18)	14 (11–16)	13 (10–16)	0.827
<b>Laboratory data</b>					
Hemoglobin, g/dL	11.1 (9.8–12.6)	10.4 (8.9–11.6)	11.5 (10.2–13.1)	11.7 (10.7–13.1)	<0.001
Platelet count, 10 <sup>4</sup> /mL	21 (17–27)	19 (15–24)	22 (18–25)	22 (18–29)	0.049
Lymphocyte count, count/mL	1391 (1015–1815)	1173 (918–1474)	1363 (1034–1779)	1645 (1260–1952)	<0.001
Sodium, mEq/L	138±4	137±4	139±3	139±4	<0.001
Chloride, mEq/L	102±4	102±4	103±4	103±4	0.738
Potassium, mEq/L	4.2±0.6	4.1±0.6	4.3±0.6	4.3±0.5	0.018
Creatinine, mg/dL	1.10 (0.90–1.50)	1.10 (0.90–1.60)	1.20 (0.90–1.60)	1.00 (0.80–1.50)	0.110
BUN, mg/dL	24 (18–35)	24 (17–35)	26 (20–38)	23 (18–34)	0.218
eGFR	41 (30–55)	40 (26–54)	41 (28–55)	44 (33–57)	0.357
Uric acid, mg/dL	6.7±2.0	6.3±2.0	7.1±2.0	6.8±2.1	0.034
Albumin, g/dL	3.4±0.5	3.1±0.5	3.5±0.4	3.7±0.4	<0.001
Total cholesterol, mg/dL	161±35	147±34	164±31	171±37	<0.001

Continued

Table 1. Continued

	Overall (n=274)	Lowest Tertile Cholinesterase Level ≤180 (n=93)	Middle Tertile 180 <Cholinesterase Level ≤236 (n=90)	Highest Tertile 236 <Cholinesterase Level (n=91)	P Value
C-reactive protein, mg/dL	0.25 (0.11–0.81)	0.32 (0.12–1.23)	0.24 (0.11–0.89)	0.20 (0.10–0.44)	0.053
Log NT-proBNP	7.0±1.3	7.6±1.3	7.0±1.1	6.5±1.1	<0.001
AST, U/L	23 (17–30)	23 (18–31)	23 (17–32)	21 (17–27)	0.256
ALT, U/L	15 (10–24)	15 (10–23)	17 (11–26)	14 (10–24)	0.666
GGT, U/L	34 (20–62)	43 (22–78)	32 (20–69)	27 (19–46)	0.024
ALP, U/L	257 (202–322)	261 (209–363)	245 (196–294)	257 (195–3203)	0.087
Total bilirubin, mg/dL	0.60 (0.40–0.80)	0.60 (0.43–0.80)	0.60 (0.40–0.73)	0.60 (0.50–0.80)	0.760
Cholinesterase, U/L	208 (166–255)	151 (126–167)	209 (198–219)	274 (255–311)	<0.001
Nutritional indices					
CONUT score	3 (2–5)	5 (3–6)	3 (2–5)	2 (1–3)	<0.001
PNI	42±6	38±6	42±5	45±6	<0.001
GNRI	92±12	85±11	92±11	99±11	<0.001
Heart failure model					
MAGGIC risk score	24±5	26±4	25±5	21±5	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, the Controlling Nutritional Status score; GGT, gamma-glutamyl transpeptidase; GNRI, Geriatric Nutritional Risk Index; HF, heart failure; IVC, inferior vena cava; LAD, left atrial dimension; LVDD, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MAGGIC risk score, the Meta-Analysis Global Group in Chronic Heart Failure risk score; NYHA, New York Heart Association; PNI, Prognostic Nutritional Index; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitant pressure gradient.

associated with the composite end point (HR, 1.05 [95% CI, 1.00–1.11];  $P=0.0455$ ), all-cause mortality (HR, 1.15 [95% CI, 1.08–1.23];  $P<0.0001$ ), and cardiovascular death (HR, 1.13 [95% CI, 1.02–1.26];  $P=0.0260$ ).

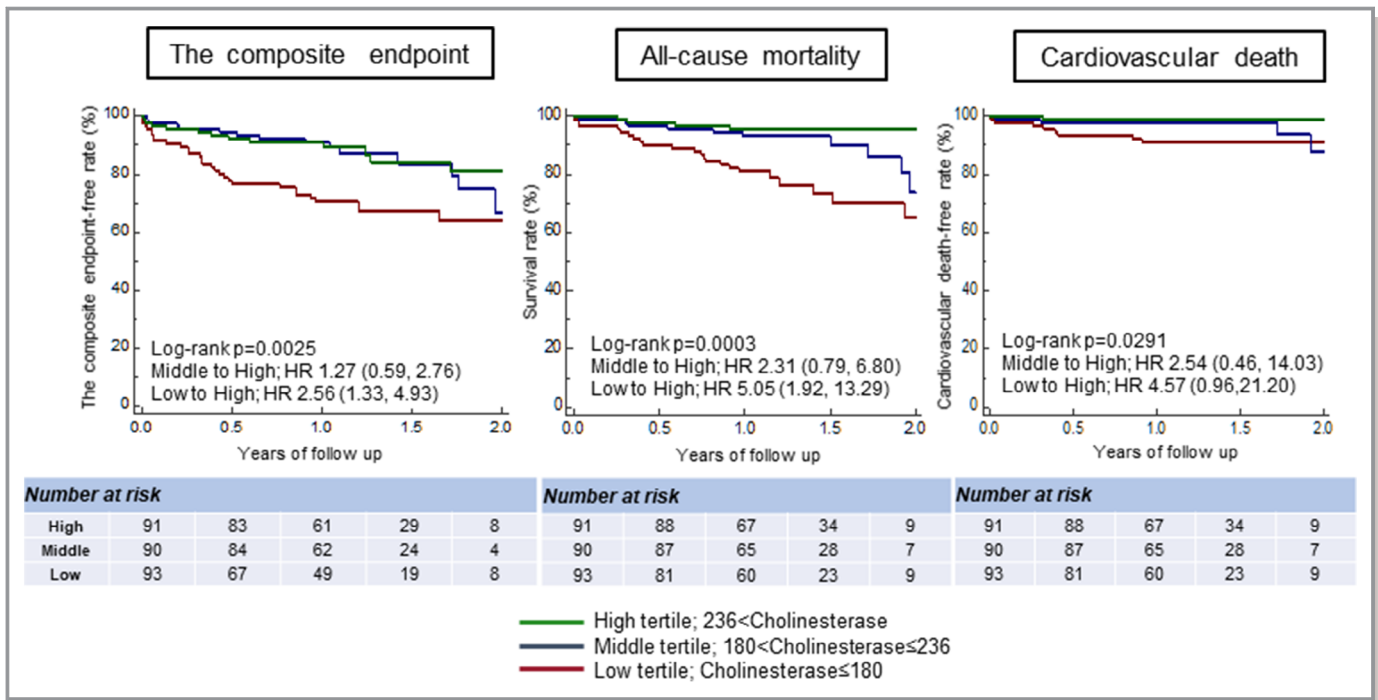
C-statistics of the MAGGIC risk score for prediction of the composite end points within 1 year was significantly improved when cholinesterase level was added to the MAGGIC risk score (from 0.601 to 0.705,  $P=0.0408$ ; Figure 4). Net reclassification improvement and integrated discrimination improvement attained by the addition of cholinesterase level to the MAGGIC risk score were also statistically significant for prediction of the composite end points within 1 year (net reclassification improvement: 0.6313 [95% CI, 0.3149–0.9477],  $P<0.0001$ ; integrated discrimination improvement: 0.0687 [95% CI, 0.0033–0.1043],  $P=0.0002$ ).

## Discussion

The present study examined patients admitted for ADHF with preserved LVEF and demonstrated that low cholinesterase level was independently associated with poor outcome. In addition, predictive power of cholinesterase level tended to be greater than those of other objective indices. Furthermore, cholinesterase level provided an incremental value over the MAGGIC risk score in ADHF with preserved LVEF.

## Previous Studies

Evaluating comorbidities is clinically important, especially in patients with HFpEF because the prognosis of HFpEF is strongly influenced by comorbidities.<sup>26</sup> As for malnutrition, Kinugasa et al used GNRI and showed that malnutrition risk was associated with functional decline and poor prognosis in patients with HFpEF.<sup>5</sup> They found that GNRI had better predictive power than BMI or serum albumin level alone by their complementary effects. Cheng et al showed the long-term prognostic role of PNI in patients with HFpEF.<sup>6</sup> As for the evidence to support the usefulness of cholinesterase level, Sato et al showed the prognostic role of cholinesterase level in patients with CHF.<sup>14</sup> In addition, we previously showed the prognostic value of cholinesterase level in patients with ADHF. In our previous study, we demonstrated its prognostic role regardless of LVEF by conducting a subgroup analysis using heart failure with reduced ejection fraction (LVEF<40%), HF with mid-range ejection fraction (40%; ≤LVEF<50%), and HFpEF (LVEF≥50%).<sup>15</sup> However, because the data were obtained from a single-center registry study, the number of study subjects with HFpEF was relatively limited. To overcome the limitation of our previous study, this study was conducted by using data from a multicenter HFpEF registry (PURSUIT-HFpEF registry). The present study demonstrated that low cholinesterase levels



**Figure 2.** Kaplan–Meier estimates of the composite end-point–free survival rate and cardiovascular-death–free curves for patients stratified by serum cholinesterase level tertile. HR indicates hazard ratio.

provided prognostic information in ADHF patients with preserved LVEF.

**Possible Mechanism**

Decreased serum cholinesterase level is observed in many clinical conditions such as malnutrition, inflammation, and liver damage. In the present study, patients with low cholinesterase levels showed significantly lower BMI, lower albumin level, higher CONUT score, and lower PNI and GNRI. Furthermore, cholinesterase level also had a moderate correlation with albumin level, BMI, and the other nutritional indices and a weak or no correlation with liver function test results and C-reactive protein level. These results support our

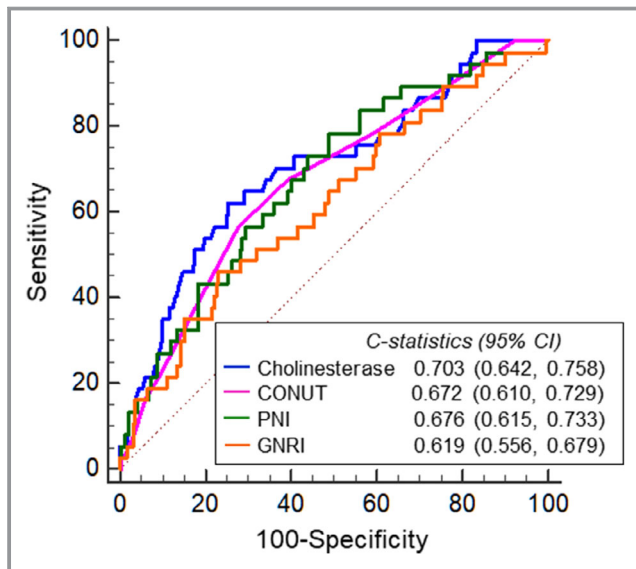
view that cholinesterase level was mainly driven by malnutrition, rather than inflammation or hepatic function, in our study patients.

Considering the phenotypes of malnutrition, such as cachexia, sarcopenia, and sarcopenic obesity, is clinically important because they affect patients’ cardiorespiratory fitness and quality of life, and they have different prognoses.<sup>27,28</sup> Cholinesterase level has been reported to be a good biomarker for identifying elderly subjects at risk of sarcopenia.<sup>29</sup> Furthermore, cholinesterase plays an important role in lipid metabolism, whether directly or through a synergistic action with cholesterol esterase.<sup>13</sup> Thus, theoretically, cholinesterase level can be a comprehensive malnutritional biomarker of both sarcopenia and cachexia.

**Table 2.** Cox Multivariable Proportional Hazard Models of Cholinesterase for the Prediction of Composite End Points, All-Cause Mortality, and Cardiovascular Death

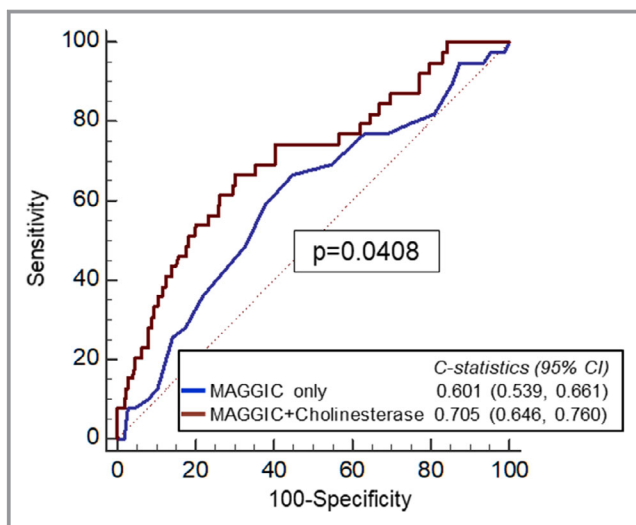
	Clinical Model		Biomarker Model	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Composite end point	0.90 (0.86–0.95)*	0.0001	0.93 (0.88–0.99) <sup>†</sup>	0.0166
All-cause mortality	0.85 (0.80–0.92)*	<0.0001	0.88 (0.82–0.95) <sup>†</sup>	0.0007
Cardiovascular death	0.86 (0.77–0.96) <sup>‡</sup>	0.0059	0.88 (0.79–0.98) <sup>§</sup>	0.0164

BMI indicates body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; log NT-pro BNP, log-transformed n-terminal pro-brain natriuretic peptide.  
 \*Clinical model: Cholinesterase level (10 U/L) was adjusted for age, sex, BMI, and DM.  
<sup>†</sup>Biomarker model: Cholinesterase level (10 U/L) was adjusted for eGFR, hemoglobin level, log NT-proBNP level, and albumin level.  
<sup>‡</sup>Clinical model: Cholinesterase level (10 U/L) was adjusted for age and sex.  
<sup>§</sup>Biomarker model: Cholinesterase level (10 U/L) was adjusted for eGFR and hemoglobin level.



**Figure 3.** Receiver-operating characteristic curve analysis of cholinesterase level, Controlling Nutritional Status score, Prognostic Nutritional Index, and Geriatric Nutritional Risk Index for the prediction of the composite endpoint within 1 year. CHE indicates Cholinesterase; CONUT, the Controlling Nutritional Status score; PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index.

The mechanism of malnutrition in patients with HF has been explained in a complicated pathway. Advanced HF causes peripheral hypoperfusion, which leads to enhanced neurohormonal activation, oxidative stress, and systemic inflammatory activity.<sup>30,31</sup> These conditions would lead to insulin resistance,



**Figure 4.** Receiver-operating characteristic curve analysis of the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score and MAGGIC plus cholinesterase level for the prediction of the composite end point within 1 year. CHE indicates Cholinesterase.

impaired protein and lipid metabolisms, anabolic deficiency, and anabolic-catabolic imbalance. Thus, pleiotropic nutritional indices, such as the CONUT score, PNI, and GNRI, would be more-appropriate screening tools for malnutrition in HF than albumin level or BMI alone. In that context, serum cholinesterase level is a better pleiotropic biomarker because it reflects various factors such as malnutrition, systemic inflammation, and hepatocellular impairment.<sup>13</sup>

Cholinesterase is a family of enzymes that hydrolyze acetylcholine and other choline esters.<sup>13</sup> It is of 2 main types: acetylcholinesterase and butyrylcholinesterase. We usually measure only butyrylcholinesterase in daily blood chemistry and call it cholinesterase. Although butyrylcholinesterase has been known for decades as a marker of nutrition and hepatic protein synthesis, its specific physiological role had not been clarified until recently. Chen et al reported that butyrylcholinesterase has a specific physiological role in hydrolyzing the appetite-promoting hormone, ghrelin.<sup>32,33</sup> Their group also reported that butyrylcholinesterase was not just a hydrolase of ghrelin, but also an important regulator of the butyrylcholinesterase-ghrelin axis.<sup>34</sup>

On the other hand, one of the mechanisms of malnutrition in patients with HF has been considered to be catabolic-anabolic imbalance and appetite loss, which is partly caused by ghrelin resistance.<sup>35</sup> Elevated ghrelin concentration has also been reported to be a compensatory mechanism in patients with malnutrition and a powerful prognostic factor in HF patients.<sup>36–38</sup> Taking into account these findings altogether, butyrylcholinesterase level might be decreased to elevate ghrelin level to maintain homeostasis as a compensatory mechanism in patients with ghrelin resistance and serves as a severity marker of catabolic-anabolic imbalance. Thus, the predictive power of cholinesterase level could be explained not only by its pleiotropic characteristics, but also by identifying patients at high risk of malnutrition by the butyrylcholinesterase-ghrelin axis, which is one of the leading mechanisms of malnutrition in HF.

### Butyrylcholinesterase as a Therapeutic Target

In addition, butyrylcholinesterase inhibition has the potential to treat malnutrition in HF by elevating the activated ghrelin concentration. In fact, the appetite-improving effect of rivastigmine, which is an acetylcholinesterase and butyrylcholinesterase inhibitor used for patients with dementia in daily practice, has already been observed in patients with dementia treated with rivastigmine by increased active-to-inactive ghrelin ratio.<sup>39</sup> However, considering that butyrylcholinesterase level is already decreased as a compensatory mechanism in malnourished patients with HF, whether further butyrylcholinesterase inhibition is effective remains to be clarified.



## Incremental Value of Cholinesterase Level Over the HF Risk Model

Although several HF risk models have been developed, the number of validated risk models for patients with HFpEF is relatively limited. The MAGGIC risk score is a well-established comprehensive risk model and was externally validated for CHF patients with preserved LVEF<sup>16</sup> and patients with ADHF.<sup>17</sup> In the present study, we first demonstrated its prognostic value in ADHF patients with preserved LVEF. Furthermore, we showed the incremental prognostic role of cholinesterase level over the MAGGIC risk score, which is mainly composed of daily applicable measurements. The MAGGIC risk score also includes BMI, which is a component of GNRI. However, cholinesterase level was associated with poor outcome even after adjustment for BMI in the present study, which supports the concept that cholinesterase level has an incremental prognostic value over the MAGGIC risk score.

## Clinical Implications

As a clinical prognostic factor, simplicity is indispensable for daily use. Cholinesterase level is a more easily available biomarker than other nutritional indices in daily practice, although the statistical superiority of cholinesterase level to the other nutritional indices was not shown in this study. This biomarker possibly provides a more-accurate nutritional risk evaluation of patients with HFpEF than other objective nutritional indices, possibly allowing early implementation of appropriate nutritional intervention in daily practice, which leads to better outcomes in patients with HF.

## Study Limitations

Several limitations of this study should be acknowledged. First, the relatively small and empirically chosen population sample size was a major limitation, and the follow-up period was relatively short. Second, the patients in our study population were significantly older and had lower BMIs than those in a previous large-scale HFpEF study.<sup>40</sup> Furthermore, ethnic differences should be taken into account when generalizing our results to non-Japanese populations. Third, although, ideally, individual body composition must be considered in defining sarcopenia, cachexia, or sarcopenic obesity when discussing malnutrition in patients with HF,<sup>27</sup> body composition data obtained using dual-energy x-ray absorptiometry or bioelectric impedance analysis or body-weight data were not available. Fourth, serum cholinesterase level would be strongly influenced by the patient's dietary intake, but precise dietary information or nutritional history taken before HF admission and after discharge was not

available in the present study. Finally, we could not obtain data on serum prealbumin level, which has also been established as a marker of cardiac cachexia.<sup>41</sup> However, in our previous study,<sup>15</sup> cholinesterase level remained a significant predictor of all-cause mortality that was independent of prealbumin level.

## Conclusions

Serum cholinesterase level was a simple prognostic indicator for prediction of adverse outcome and tended to provide more-powerful prognostic information than other objective nutritional indices in ADHF patients with preserved LVEF. Furthermore, cholinesterase level provided an incremental value over the MAGGIC risk score in ADHF with preserved LVEF. These findings suggest that serum cholinesterase level is a clinically significant risk-stratification biomarker in patients with HFpEF.

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