Hemodynamic correlates of nutritional indexes in heart failure

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ABSTRACT

Background: Malnutrition in heart failure (HF) is related to altered intestinal function, which could be due to hemodynamic changes. We investigated the usefulness of novel nutritional indexes in relation to hemodynamic parameters.

Methods: We retrospectively analyzed 139 HF patients with reduced ejection fraction who underwent right heart catheterization. We investigated correlations between right side pressures and nutritional indexes, which include controlling nutritional (CONUT) score and geriatric nutritional risk index (GNRI). Receiver operating characteristic (ROC) curves were generated to investigate the prognostic accuracy of CONUT score and GNRI for a composite of death or HF hospitalization in 12 months. Logistic regression analysis was performed to investigate whether hemodynamic correlates were associated with malnutrition, which was defined based on CONUT score or GNRI.

Results: Higher right side pressures were positively correlated with worse nutritional status according to CONUT score, but were negatively correlated with worse nutritional status according to GNRI. Area under ROC curve for the composite endpoint was 0.746 in CONUT score and 0.576 in GNRI. The composite endpoint occurred in 40% of CONUT score ≥ 3 and in 11% of CONUT score < 3 (< 0.001). These relationships were also investigated with GNRI (40% of GNRI < 95 vs. 17% of GNRI ≥ 95, p = 0.002). In multivariate analysis, higher right atrial pressure was significantly associated with higher CONUT score, while no hemodynamic parameter was related to GNRI.

Conclusions: CONUT score was associated with right side congestion, while no association between GNRI and right side congestion was noted. CONUT score had better predictive value than GNRI.

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Introduction

Malnutrition is common in heart failure (HF). Cardiac cachexia, an involuntary non-edematous weight loss within 6–12 months [1–4], is observed in 5–15% of patients with HF and is associated with poor prognosis [5,6]. The malnutrition in HF is related to altered intestinal function, which could be due to hemodynamic changes. Intestinal hypoperfusion and congestion lead to bowel edema and increased adherent bacteria, resulting in chronic inflammation and malnutrition [7–12]. These findings were mainly investigated in HF patients with reduced ejection fraction (EF), which is associated with more severe hemodynamic deteriorations than HF with preserved EF.

Several nutritional indexes have been utilized in HF. Controlling nutritional (CONUT) score is calculated using serum albumin, total cholesterol, and the number of lymphocytes [13]. Serum albumin reflects protein reserve, total cholesterol reflects caloric depletion, and the number of lymphocytes reflects immune defense. These three variables have a prognostic effect in HF [14–17]. Higher CONUT score indicates worse nutritional status [13]. A post hoc analysis of 3421 patients in a prospective registry of chronic HF showed that 3-year survival in patients with CONUT score 0–1, 2, and ≥3 was 95.5%, 92.3%, and 73.2%, respectively (< 0.001) [18].
Geriatric nutritional risk index (GNRI) is another nutritional index, which is calculated using serum albumin and body weight [19]. Contrary to CONUT score, lower GNRI indicates worse nutritional status [19]. Although patients with obesity were associated with higher risks of developing HF, previous studies reported a survival advantage for obese and overweight patients compared with patients with normal or low weight [20,21]. Cardiovascular death or HF hospitalization at 28 months occurred in 15%, 23%, 38%, and 54% within 28 months in a cohort of 388 HF patients with GNRI > 98, 98–92, 82–91, and <82, respectively [22]. Another study reported that HF patients with GNRI < 92 had higher mortality at 2 years than those with GNRI ≥ 92 [hazard ratio 2.667, 95% confidence interval (CI) 1.527–4.651, p < 0.001] [23].

CONUT score and GNRI, which are novel nutritional indexes, are objective and useful in predicting prognosis [18,22,24]. However, whether they are associated with hemodynamic parameters and further reflect the pathophysiology of malnutrition in patients with HF remains uncertain. Therefore, we investigated the usefulness of these nutritional indexes in relation to hemodynamic parameters in the prognosis of HF patients with reduced EF.

Methods

Study population

Consecutive HF patients who underwent right heart catheterization (RHC) have been prospectively registered in our institutional database since January 2012. Of these patients, those with reduced EF (EF ≤ 40%) were analyzed from January 2012 to December 2015. We excluded patients with brain natriuretic peptide (BNP) level < 100 pg/ml, with acute coronary syndrome (ACS), or undergoing hemodialysis. We also excluded patients without echocardiography data of EF.

Patient characteristics and medical history were recorded upon admission. Ischemic etiology was defined as the presence of at least one of the following: previous myocardial infarction, previous percutaneous coronary intervention, or previous coronary bypass grafting. Left ventricular EF was calculated using the modified Simpson method. Ultrasonographers performed echocardiography, and specialists of the Japanese Society of Echocardiography approved the findings. Vital signs, laboratory data, and medication at the time of RHC were also recorded.

All patients provided written informed consent. All data were anonymized throughout the analysis. The study was conducted in accordance with the Declaration of Helsinki.

Right heart catheterization

RHC was performed after optimal treatment with diuretics, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), β-blocker, and other pharmacologic therapies, which are based on the physician’s discretion. RHC was performed in the supine position and was conducted using a 6-F balloon-tipped catheter (Swan-Ganz Thermodilution Catheter, Edwards Lifesciences, Irvine, CA, USA). Transducers were zeroed at the mid-axilla and measured by calipers. Under fluoroscopic guidance, the catheter was inserted through a femoral vein to a pulmonary artery. Wedge position of the catheter was confirmed by fluoroscopy and pressure wave forms. Hemodynamic data were measured at the end of expiration and represent the mean of ≥3 beats. Cardiac output was measured using the thermodilution method and indexed to body surface area (cardiac index). Right ventricle stroke work index (RVSWI) was calculated as follows: (cardiac index/heart rate) × [mean pulmonary artery pressure – mean right atrium pressure (RAP)] × 13.6.

Nutritional indexes

Nutritional indexes were calculated based on the data at the time of RHC. CONUT score consists of three variables: serum albumin, total cholesterol, and total lymphocyte count (Table 1) [13]. GNRI is calculated as follows: GNRI = 14.98 × serum albumin (g/dl) + 41.7 × present body weight (BW) (kg)/ideal BW. Ideal BW is calculated as follows: body height (BH; cm) – 100 – [(BH – 150)/4] for males and BH (cm) – 100 – [(BH – 150)/2.5] for females [19].

Clinical endpoints

The endpoints were death, cardiovascular (CV) death, HF hospitalization, and composite of death or HF hospitalization within 12 months. CV death was defined as fatal myocardial infarction, pump failure, sudden death, stroke, pulmonary embolism, or CV procedural death. HF hospitalization was defined as an unexpected hospitalization with at least one of the following symptoms: increasing dyspnea on exertion, worsening orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue/worsening exercise tolerance, or altered mental status, and at least two of the following symptoms: peripheral edema, elevated jugular venous pressure, radiologic signs of HF, increasing abdominal distension or ascites, pulmonary edema or crackles, rapid weight gain, hepatojugular reflux, S3 gallop, or elevated BNP. These endpoints were evaluated by retrospective medical record review.

Statistical analysis

Normally distributed continuous variables were described as mean ± standard deviation, and non-normally distributed data were expressed as medians and interquartile ranges. Categorical variables were described as percentages. Missing values (not more than 20%) were imputed by multivariate imputation method.

Pearson’s correlation analysis was conducted to investigate the association between the nutritional indexes (CONUT score and GNRI) and hemodynamic correlates, including pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), RAP, cardiac index, and RVSWI.

Receiver operating characteristic (ROC) curves were generated to investigate the prognostic accuracy of CONUT score and GNRI for the endpoints. The optimal cut-off point for death or HF hospitalization within 12 months was determined using ROC curve analysis. Patients were divided to malnourished group defined as CONUT ≥ cut-off point and well-nourished group defined as CONUT < cut-off point. They were also divided to malnourished group defined as GNRI < cut-off point and well-nourished group defined as GNRI ≥ cut-off point. To compare the characteristics of the malnourished and well-nourished patients, we used Student’s t-test for continuous variables and chi-square test for categorical variables. Kaplan–Meier curves and 12-month event-free rates were estimated. The log-rank test was also used to compare the two groups. A p-value < 0.05 was considered statistically significant.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
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<tbody>
<tr>
<td>Serum albumin (g/ml)</td>
<td>0, 2, 4, 6</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>Lymphocytes (count/ml)</td>
<td>0, 1, 2, 3</td>
</tr>
</tbody>
</table>

CONUT, controlling nutritional.
Logistic regression analysis was performed to investigate whether hemodynamic correlates were associated with malnutrition, which was defined based on CONUT score or GNRI. Factors with a p-value < 0.05 by univariate analysis were included in the multivariate analysis. All statistical analyses were performed using JMP version 13.0.1 for Windows (SAS, Cary, NC, USA).

Results

Study population

During the study period, 479 patients without ACS or hemodialysis underwent RHC in our institution. Twelve patients without BNP data and 115 patients with BNP < 100 pg/ml were excluded. We also excluded 36 patients without echocardiography data. Of the remaining 316 patients, a total of 139 patients with reduced EF were included in the final analysis (Fig. 1). Mean age was 66 ± 13 years, ischemic etiology was 47%, and EF was 27 ± 7.7%. Mean CONUT score was 2.5 ± 1.8 and mean GNRI was 101 ± 12.

CONUT score showed a weak but significant correlation with PCWP, PASP, and RAP (PCWP, r = 0.241, p = 0.004; PASP, r = 0.216, p = 0.011; RAP, r = 0.342, p < 0.001). GNRI weakly correlated with PADP and RAP (PADP, r = 0.173, p = 0.041; RAP, r = 0.191, p = 0.025) (Table 2).

Area under the ROC curve (AUC) for the composite endpoint was significantly higher in CONUT score (0.746, 95% CI 0.648–0.824) than in GNRI (0.576, 95% CI 0.455–0.688) (p = 0.006; Fig. 2A). AUC for HF hospitalization was also significantly higher in CONUT score (0.687, 95% CI 0.583–0.775) than in GNRI (0.506, 95% CI 0.387–0.624) (p = 0.041; Fig. 2C). The optimal cut-off points for the composite endpoint were 3 for CONUT score and 95 for GNRI, respectively.

Table 3 shows the characteristics of malnourished and well-nourished patients according to CONUT score. Malnourished patients (CONUT score ≥ 3) had lower heart rate, higher creatinine, lower hemoglobin, lower alanine aminotransferase, and higher C-reactive protein (CRP) levels than well-nourished patients (CONUT score < 3). Malnourished patients were less likely to be treated with ACE-I or ARB compared with well-nourished patients. Regarding hemodynamic parameters, malnourished patients had higher PCWP, PASP, PADP, and RAP than well-nourished patients.

Table 3 also shows the characteristics of well-nourished and malnourished patients according to GNRI. Malnourished patients (GNRI < 95) were less likely to be male and to have dyslipidemia compared with well-nourished patients (GNRI ≥ 95). Malnourished patients had lower body mass index and higher creatinine, lower hemoglobin, higher CRP, and higher BNP levels than well-nourished patients. ACE-I or ARB and mineralocorticoid receptor antagonist were less likely to be used in malnourished patients compared with well-nourished patients. Contrary to CONUT score, higher right side pressures were observed in well-nourished patients rather than malnourished patients, although these relationships did not reach statistical significance.

The composite endpoint of death or HF hospitalization occurred more frequently in patients with CONUT score ≥ 3 than in those
with CONUT score < 3 [40% (24 patients) vs. 11% (9 patients), log-rank p < 0.001; Fig. 3A, Table 4]. This relationship was also investigated with GNRI [40% (16 patients) in those with GNRI < 95 and 17% (17 patients) in those with GNRI ≥ 95, log-rank p = 0.002; Fig. 3B, Table 4].

Multivariate logistic regression analysis revealed that higher creatinine level, absence of ACE-I or ARB, and higher RAP were significantly associated with CONUT score ≥ 3 (Table 5A). For GNRI, absence of dyslipidemia, lower hemoglobin level, higher log BNP level, and absence of mineralocorticoid receptor antagonist were significantly associated with GNRI < 95 (Table 5B).

**Discussion**

The main findings of the study were as follows: 1) higher right side pressures were observed in the malnourished status of CONUT score, while these were observed in well-nourished status of GNRI, 2) both CONUT score and GNRI were useful in predicting prognosis. The prognostic values of CONUT score were better than those of GNRI, and 3) in the multivariate analysis, ACE-I or ARB, creatinine, and RAP were associated with CONUT score, while dyslipidemia, hemoglobin, log BNP, and mineralocorticoid receptor antagonist were associated with GNRI.
CONUT score and right side HF

CONUT score showed a significant correlation with right side pressures, and right side pressures were higher in malnourished patients (CONUT score ≥3) than in well-nourished patients (CONUT score <3). Moreover, RAP was significantly associated with CONUT score ≥3 after adjusting for possible confounding factors. Cardiac cachexia is commonly observed in right side HF [25,26], in which elevated RAP plays a more vital role than right ventricular (RV) functions. A previous study investigated relationships between cardiac cachexia and echocardiographic parameters including left ventricular diastolic diameter, left atrial area, EF, E/ e', PASP, tricuspid annular plane systolic excursion (TAPSE), RAP, and moderate to severe tricuspid regurgitation [12]. Among these parameters, only RAP remained significantly associated with cachexia after multivariate adjustment. In addition, elevated RAP was positively correlated with bowel wall thickness. The results of the current study were consistent with the evidence that elevated RAP and intestinal congestion are the most essential hemodynamic factors for malnutrition in HF [27].

GNRI and right side HF

In contrast to CONUT score, higher right side pressures, such as PADP and RAP, were weak but significantly correlated with better nutritional status according to GNRI. Higher right side pressures were observed not in the malnourished patients.
Table 5A
Predictors for CONUT ≥ 3.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Heart rate</td>
<td>0.96</td>
<td>0.93–0.99</td>
<td>0.020</td>
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<tr>
<td>Creatinine</td>
<td>4.93</td>
<td>2.25–12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.75</td>
<td>0.63–0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT</td>
<td>0.98</td>
<td>0.96–1.00</td>
<td>0.023</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.24</td>
<td>0.10–0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCWP</td>
<td>1.05</td>
<td>1.01–1.09</td>
<td>0.018</td>
</tr>
<tr>
<td>PAWP</td>
<td>1.03</td>
<td>1.01–1.06</td>
<td>0.012</td>
</tr>
<tr>
<td>RAP</td>
<td>1.17</td>
<td>1.07–1.29</td>
<td>&lt;0.001</td>
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</table>

<table>
<thead>
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<th>Variables</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
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<tr>
<td>Nutritional parameters</td>
<td>ACE-I</td>
<td>0.96</td>
<td>0.92–1.00</td>
</tr>
<tr>
<td>Nutritional parameters</td>
<td>Creatinine</td>
<td>3.33</td>
<td>1.53–8.90</td>
</tr>
<tr>
<td>Nutritional parameters</td>
<td>Hemoglobin</td>
<td>0.92</td>
<td>0.74–1.15</td>
</tr>
<tr>
<td>Nutritional parameters</td>
<td>ALT</td>
<td>1.00</td>
<td>0.97–1.01</td>
</tr>
<tr>
<td>Nutritional parameters</td>
<td>ACE-I or ARB</td>
<td>0.24</td>
<td>0.08–0.68</td>
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<tr>
<td>Nutritional parameters</td>
<td>PCWP</td>
<td>1.01</td>
<td>0.92–1.12</td>
</tr>
<tr>
<td>Nutritional parameters</td>
<td>PAWP</td>
<td>1.01</td>
<td>0.95–1.07</td>
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<tr>
<td>Nutritional parameters</td>
<td>RAP</td>
<td>1.16</td>
<td>1.02–1.34</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; BNP, b-type natriuretic peptide; CI, confidence interval; CONUT, controlling nutritional status; CRP, C-reactive protein; GNRI, geriatric nutritional risk index; OR, odds ratio; PASP, pulmonary artery systemic pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

Table 5B
Predictors for GNRI < 95.

<table>
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<tr>
<th>Variables</th>
<th>OR</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>0.36</td>
<td>0.17–0.75</td>
<td>0.007</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.61</td>
<td>1.56–2.46</td>
<td>0.004</td>
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<tr>
<td>Hemoglobin</td>
<td>0.77</td>
<td>0.54–0.91</td>
<td>0.002</td>
</tr>
<tr>
<td>CRP</td>
<td>2.88</td>
<td>1.45–7.49</td>
<td>0.025</td>
</tr>
<tr>
<td>Log BNP</td>
<td>3.36</td>
<td>1.97–6.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.25</td>
<td>0.10–0.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Mineralocorticoid</td>
<td>0.42</td>
<td>0.19–0.89</td>
<td>0.023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>0.29</td>
<td>0.10–0.80</td>
<td>0.016</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.79</td>
<td>0.48–1.40</td>
<td>0.399</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.69</td>
<td>0.53–0.89</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP</td>
<td>1.63</td>
<td>0.91–3.15</td>
<td>0.403</td>
</tr>
<tr>
<td>Log BNP</td>
<td>3.38</td>
<td>1.81–6.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.42</td>
<td>0.13–1.35</td>
<td>0.145</td>
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<tr>
<td>Mineralocorticoid</td>
<td>0.30</td>
<td>0.10–0.83</td>
<td>0.020</td>
</tr>
</tbody>
</table>

(GNRI < 95) but in the well-nourished patients (GNRI ≥ 95). This pathophysiologically inverse relationship suggests that GNRI could be affected by congestion. Calculation of GNRI includes body weight, which could fail in differentiating between true body mass and fluid retention. It is also contradictory that not invasive hemodynamic parameters but BNP, which is a surrogate for hemodynamics, was a predictor for GNRI. The results could be attributed to the inverse relationship of BNP and obesity [28]. Therefore, GNRI could not appropriately reflect the underlying hemodynamic mechanism of malnutrition in HF. Although GNRI was useful in predicting prognosis, its prognostic values were lower than those of CONUT score.

Intestinal congestion and inflammation

CRP was higher in the malnourished group according to CONUT score or GNRI. However, it was not significantly associated with malnourished status in the multivariate analysis.

Intestinal congestion could lead to cardiac cachexia in multiple ways. For instance, bowel edema is associated with appetite loss and postprandial fullness [12]. It also relates to increased permeability and higher concentrations of adherent bacteria [29,12]. Augmented bacterial biofilm can precipitate translocation of lipopolysaccharide (LPS) to the systemic circulation [30,31]. Modified intestinal morphology and function may contribute to chronic inflammation and, therefore, malnutrition.

In the present study, higher CRP was significantly associated with malnutrition, however, this finding was not observed after adjusting for confounding factors. Because malnutrition in HF is multifactorial, simple pathway of intestinal congestion, increased adherent bacteria, and inflammation cannot explain all the mechanism. Appetite loss or malabsorption may also contribute to malnutrition in HF. Elevated RAP, which was significantly associated with malnutrition according to CONUT after adjustment for other confounding factors, can be the basis of these complicated pathways.

Neurohormonal activation and renin–angiotensin–aldosterone system inhibitors

In the current analysis, the use of ACE-I or ARB was associated with well-nourished patients according to CONUT score, and the use of mineralocorticoid receptor antagonist was associated with well-nourished patients according to GNRI.

In patients with HF, sympathetic nerve and neurohormonal activities are elevated, which contributes to the redistribution of organ perfusion away from the splanchnic circulation [8]. Consequently, the pre-capillary resistance vessels and post-capillary capacitance vessels are constricted, thereby reducing intestinal perfusion [32,33]. Intestinal ischemia was demonstrated to cause bacterial translocation by increasing bowel permeability [8,9]. In this study, the use of renin–angiotensin–aldosterone system inhibitors was associated with better nutritional status, suggesting that these agents can ameliorate neurohormonal activation, inappropriate blood flow redistribution, and intestinal perfusion [34]. In the present study, cardiac index was not related to nutritional indexes. Considering organ flow redistribution in HF, this finding does not necessarily indicate that intestinal hypoperfusion does not affect malnutrition.

Clinical perspective

Although inflammatory mediators and malnutrition may play a role in the pathophysiology of HF, the usefulness of anti-inflammatory agents has not been determined [35–38]. In this study, higher RAP was associated with higher CONUT score and was a significant predictor for malnutrition. A simple treatment strategy for right side congestion, such as appropriate dose adjustment of diuretic therapy to maintain a low RAP, could improve inflammation and nutritional status. In addition, guideline-oriented medical therapy with renin–angiotensin–aldosterone inhibitors is strongly recommended from the view point of preserving appropriate intestinal perfusion.
Limitations

This study was a retrospective analysis of a prospective registry. Several values are missing, such as physical findings, nutrition intakes, tumor necrotic factor-α, and LPS. Moreover, whether appropriate right side decongestion therapy can improve nutritional status and patient outcomes should be prospectively investigated. Referring to prior studies, we investigated patients with reduced EF in the current analysis. However, nutritional indexes also have prognostic implications in HF patients with preserved EF. In the future, mechanism of malnutrition in these patients needs to be investigated especially in terms of inflammation, intestinal function, and hemodynamic correlates.

Conclusions

Higher right side pressures, especially RAP, were associated with malnutrition according to CONUT score. However, with GNRI, higher right side pressures were observed in patients with better nutritional status. GNRI could be affected by congestion, because its calculation includes body weight. Although both CONUT score and GNRI were useful in predicting prognosis, the prognostic values of CONUT score were better than those of GNRI.

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Conflict of interest

Kengo Tanabe has received honoraria for lectures from Daichisankyo, Tanabemitsubishi, Bayer, Sanofi, and Bristol-Myers Squibb. The remaining authors have nothing to disclose.

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References