function (f) to yield τ, the time to rehospitalization, from the clinical parameters (x_1, ..., x_p) reflecting patient characteristics at the time of discharge.

METHODS

Ethics statement

This study was approved by National Cerebral and Cardiovascular Center Research Ethics Committee. The Committee decided that the acquisition of informed consent from the 151 subjects was not required according to the Japanese Clinical Research Guideline because this was a retrospective observational study. Instead, we made a public announcement in accordance with the request of the Ethics Committee and the Guideline.

Subjects and clinical parameters

A total of 486 patients with acute decompensated heart failure (ADHF) were admitted between May 2006 and December 2009. Because patients who were admitted for ADHF only once were excluded, the remaining 151 patients were included in this study. The oldest hospitalization was adopted regarding repeat patients during this study. The diagnosis of HF was confirmed by an expert team of cardiologists using the Framingham criteria.[7] Careful history-taking, physical examinations, laboratory tests, chest X-rays, electrocardiograms, Doppler echocardiographic studies, coronary angiography and right heart catheterization were performed during the hospitalization. The timing of patient discharge was determined by the expert team of cardiologists in charge of the HF department; discharge was recommended when the patients presented no signs of decompensation, such as NYHA functional class <3, no sign of rales, no galloping rhythm, stable blood pressure and an improvement in renal function due to an optimal treatment that followed international guidelines.[8] Rehospitalization for the enrolled patients was defined as hospitalization for decompensated HF. The primary end point was the first rehospitalization for decompensated HF.

Cardiac catheterization

Left ventricular pressure was recorded with a 5-F pigtail catheter. Left ventricular volume and ejection fraction were determined with left ventriculography with a contrast medium using Kennedy's formula. Right-sided catheterization was performed using a 7 F Swan–Ganz catheter to measure pulmonary capillary wedge pressure, mean pulmonary artery pressure (PAP), right ventricular end-diastolic pressure and mean right atrial pressure. Cardiac output was measured using the estimated Fick principle and the Thermal dilution. Systemic vascular resistance and pulmonary vascular resistance were calculated using the established formulas: systemic vascular resistance $= 80 \times$ (mean pulmonary artery pressure $-$mean right atrial pressure)/cardiac output and pulmonary vascular resistance $= 80 \times$ (mean pulmonary artery pressure $-$ pulmonary capillary wedge pressure)/cardiac output.

Echocardiography

Echocardiographic examinations were performed with a Sonos-5500 (Philips Medical System, Andover, MA, USA), Alpha 10 (Hitachi-Aloka Medical, Tokyo, Japan), Vivid 7 Dimension (GE Healthcare, Buckinghamshire, UK), ACUSON Sequoia C256 (Mochida Simens Medical System, Tokyo, Japan) or Aplio XV (Toshiba Medical Systems, Tochigi, Japan) machine with a 2.5-MHz probe. Patients underwent a Doppler echocardiographic study for HF at admission and before discharge. Standard views were recorded, including the parasternal long-axis, short-axis and apical 4- and 2-chamber views, and cardiac chamber sizes and left atrial dimensions were evaluated according to the recommendations of the American Society of Echocardiography.[9] The severity of valve regurgitation was quantified on a semicontinuous scale from none (0) to severe.[4] Pulsed-wave Doppler examination and Doppler tissue imaging of the mitral annulus was performed. The peak mitral early diastolic inflow and atrial filling (E and A) velocities and the E-wave deceleration time were obtained. The sample volumes of the pulsed Doppler tissue imaging were determined at the septal and lateral margins of the mitral annulus. The peak early mitral annular velocities were measured, and then the average values of the septal and lateral velocities were used as E'.

The mathematical model for the rehospitalization process

To construct a model for future rehospitalization using the basic clinical factors for the patients, we adopted two working assumptions for the practical rehospitalization process.

Assumption 1. A mean elapsed time τ_i from discharge to the rehospitalization of patient i depends on some of the given clinical factors $X^i = \left\{x_1^i, \ldots, x_p^i\right\}$ of the patient, that is, a common subset $X_S^i \subseteq X^i$ over all patients. The dependency is primarily approximated by the following inverse linear relation:

$$\tau_i \cong \frac{1}{\sum_{x_j^i S^i} \beta_j x_j^i + \gamma} \tag{1}$$

where the denominator represents the expected frequency of cardiovascular rehospitalization per day, X_S^i is a set of values of the factors in X_S for patient i, β_j is the contributing weight of the jth factor to the frequency and γ is the intrinsic frequency for any patient.

Assumption 2. The clinical factors X_S^i of patient i are fairly stable between discharge and rehospitalization. Thus, the expectation value of the mean elapsed time τ_i remains nearly constant for patient i. As any event occurring with a constant frequency in a given time period is generated by a Poisson process,[10] rehospitalization also occurs via this process under Assumption 2. Thus, the probability density $p_i(t)$ for the rehospitalization of patient i at an elapsed time t after discharge is represented by the following exponential formula:

$$p_i(t) = \frac{1}{\tau_i} \exp\left(-\frac{t}{\tau_i}\right) \tag{2}$$

The parameter τ_i is given by Equation (1) according to Assumption 1.

We next describe the assumption test. Assumption 1 is limited to the relationship between the parameter τ_i and the clinical factors X_S^i. If the accuracy of the approximation is insufficient, we can easily extend it to a nonlinear relation such as a higher-order polynomial. Assumption 2 essentially characterizes the process of the occurrence of rehospitalization and defines the formula for its probability density $p_i(t)$. Accordingly, before the modeling of the rehospitalization process based on a given data set, a test should be applied to verify that Assumption 2 actually holds true for the given data set.

With n samples in the data set $D = \{(X^i, \tau_i) | i = 1, \ldots, n\}$, where X^i is the set of clinical factor values for patient i, and τ_i is the elapsed time at rehospitalization after discharge, we first compute a histogram of the rehospitalization occurrences over t, that is, the number of rehospitalization occurrences $\hat{m}_k$ in each elapsed time interval $((k-1)\Delta t, k\Delta t)$ $(k = 1, \ldots, q)$ in the data set. The number of equal-width bins q into which to partition the sample range $[0, q\Delta t]$ is appropriately chosen to be $q = \sqrt{n}$. (Venables and Repley)[11] We also expect a certain value of $\hat{m}_k$ by Equation (2) under Assumption 2. The value $\hat{m}_k$ computed from the data set and its value expected by Equation (2), m_k, should be consistent if Assumption 2 holds for the data set. Consistency with m_k and $\hat{m}_k$ is evaluated by the following G-score:[12]

$$G = 2 \sum_{k=1}^{q} \hat{m}_k \ln \frac{\hat{m}_k}{m_k} \tag{3}$$

Because this G-score is known to follow a χ^2 distribution of degree $q-2$, we applied a χ^2-test to the null hypothesis that the histogram of the given data set is consistent with Equation (2), that is, that Assumption 2 holds true for the data set. If the P-value of the test is less than a specific risk level a such as $a = 0.05$, we conclude that Assumption 2 does not hold for the data set. This G-test is known to be more rigorous than the well-known Pearson's χ^2-test.

Thus, our problem was to derive the expectation valuem_k $(k = 1, \ldots, q)$ from Equation (2). We considered that τ_i of the patients in D are sampled from a common population distribution $p_\tau(\tau)$. Therefore, the total probability

distribution of the rehospitalization time $P(t)$ is expected to be a superposition of Equation (2) for various τ sampled from $p_\tau(\tau)$, as follows, where $p(t)$ is $p_i(t)$ in Equation (2) for a general τ:

$$P(t) = \int_0^\infty p_\tau(\tau)p(t)\mathrm{d}\tau = \int_0^\infty p_\tau(\tau)\frac{1}{\tau}\exp\left(-\frac{t}{\tau}\right)\mathrm{d}\tau$$

We use the following natural conjugate prior distribution for the unknown $p_\tau(\tau)$:

$$p_\tau(\tau) = \frac{\tau^{-n}\exp\left(-1/\tau\sum_{i=1}^{n}\tau_i\right)}{\int_0^\infty \tau^{-n}\exp\left(-1/\tau\sum_{i=1}^{n}\tau_i\right)\mathrm{d}\tau}$$

where τ_i is given by the data set D. The selection of this parameter distribution is widely considered to be reasonable in Bayesian statistics because it preserves the exponential shape of the distribution of elapsed times t.[13] After several manipulations, the following $P(t)$ is derived:

$$P(t) = \frac{(n+1)\left(\sum_{i=1}^{n}\tau_i\right)^{n+1}}{\left(\sum_{i=1}^{n}\tau_i + t\right)^{n+2}}$$

Accordingly, the expectation m_k is given by the accumulation of $P(t)$ over $((k-1)\Delta t, k\Delta t]$ as follows:

$$\begin{aligned} m_k &= n\int_{(k-1)\Delta t}^{k\Delta t} P(t)\mathrm{d}t \\ &= n\left(\frac{\sum_{i=1}^{n}\tau_i}{\sum_{i=1}^{n}\tau_i + (k-1)\Delta t}\right)^{n+1} - n\left(\frac{\sum_{i=1}^{n}T_i}{\sum_{i=1}^{n}\tau_i + k\Delta t}\right)^{n+1} \end{aligned} \quad (4)$$

Using Equations (3) and (4), we tested the validity of Assumption 2 for the given data set D.

Finally, we describe the modeling algorithm. First, the value of every factor $x_j^i i$ for all patients $i = 1, \ldots, n$ in D was normalized to fit into the interval [0,1] using the maximum and minimum values. This normalization to eliminate differences in the factor scales was necessary to allow for the measurement of the essential contribution of each factor's variation to τ_i. Subsequently, we applied Equations (1) and (2) to the normalized data set D_N to model the probabilistic rehospitalization process when Assumption 2 holds for the data set. We determined the model parameters β_j and γ in Equation (1) to maximize the following objective function:

$$L(\beta_1, \ldots, \beta_p, \gamma) = \ln\left[\prod_{i=1}^{n}\left(\sum_{j=1}^{p}\beta_j x_j^i + \gamma\right)\exp\left\{-\left(\sum_{j=1}^{p}\beta_j x_j^i + \gamma\right)\tau_i\right\}\right] - \lambda\left(\sum_{j=1}^{p}|\beta_j| + |\gamma|\right) \quad (5)$$

The first term is the log-likelihood of the model consisting of Equations (1) and (2) over D_N. The second term is called an $L1$-regularization term, which penalizes the coefficients of negligible factors by setting them equal to zero when the larger hyper-parameter λ eliminates more factors.[13,14] This term avoids the over-fitting of the model to the data set by selecting a set of effective factors X_S^i from a given X^i. In our study, λ is tuned to be 0.02 to maintain the largest value of Equation(5) similarly to the other parameters β_j and γ.

To seek the optimum parameter values of $\beta_1,\ldots,\beta_p$, γ that maximize the objective function $L(\beta_1,\ldots,\beta_p, \gamma)$, we applied a simple greedy hill-climbing algorithm, in which the parameter values are iteratively modified toward their gradient direction $(\partial L/\beta_1,\ldots,\partial L/\beta_p, \partial L/\gamma)$. When the improvement of L becomes nearly negligible, the resulting parameter values are taken as the optima. Because this process depends on the initial values of the parameters, we repeated this optimization 100 times starting with random initial values and selected the result providing the maximum L.

RESULTS

Patients characteristics

Out of the 151 patients, 36 died of cardiovascular events after rehospitalization during the follow-up period. The remaining 115 patients were readmitted to our hospital at a median time of 296 days after discharge (range, 3–1891). Among these patients, the HF etiologies were valvular heart disease ($n = 38$), dilated cardiomyopathy ($n = 30$), hypertrophic cardiomyopathy ($n = 22$), ischemic heart disease ($n = 20$), hypertensive heart disease ($n = 17$) and others. Their mean age was 68.6 ± 14.6 years (range, 19–93), and 38% of the patients were women. The clinical characteristics of the 151 patients are summarized in Table 1.

Validation of the formula

We hypothesized that the time-to-rehospitalization histogram for all patients (Figure 1) should be distributed exponentially if the mathematically estimated formula for the prognosis of each patient is regarded as a Poisson distribution. We therefore validated the assumptions of the model architecture. The goodness of fit was controlled by a χ^2-test, considering that the incidence rates of rehospitalization or death differ depending on the patients. Thus, the null hypothesis that the observed frequency is a mixed Poisson process was tested, as explained in the Methods section. We chose an elapsed time to rehospitalization of 150 days, which is one-thirteenth of the range of the time interval [1,1,950] according to the measure of $q = \sqrt{n} = \sqrt{151} \cong 13$. As a result, the P-value was 0.29, which was far larger than 0.05, and we confirmed that the null hypothesis was not rejected. Therefore, we concluded that the mathematically derived estimation formula for the rehospitalization of each patient was a mixed Poisson distribution.

Factors in rehospitalization for HF

We collected 402 clinical factors (Figures 2 and 3), and 150 out of 402 factors having small effects on the prognosis were automatically excluded by the regularization method described in the Methods section. Finally, we selected 252 factors for the analysis (Figures 2 and 3). The estimation results for the attribute coefficients are presented in bar graph form and numerically.

Regarding underlying diseases in HF, whereas dilated cardiomyopathy (-4.5), hypertrophic cardiomyopathy (-1.5) and hypertensive heart disease (-1.0) had better outcomes, valvular disease (7.4) and dilated phase hypertrophic cardiomyopathy (2.4) had poor prognoses. Ischemia (4.4) was the worst trigger of HF. Based on laboratory data, whereas elevated inflammatory response values, such as white blood cell counts ($-1.6/5.8$; at admission/at discharge) or C-reactive protein levels ($-2.2/8.1$; at admission/at discharge), did not indicate a poor prognosis at admission, these elevated inflammatory response values at discharge were associated with a poor prognosis. Increases in the levels of aspartate aminotransferase (6.6), alanine aminotransferase (3.2), uric acid (6.6) and BNP (4.8) at discharge also indicated a poor prognosis. Patients who received dopamine (11.9), isosorbide dinitrate (5.0) or diuretic (2.0) infusions in the acute management of HF showed worse prognoses. In contrast, the use of dobutamine (-2.5) or nitroglycerin (-2.5) drip infusions resulted in better prognoses.

Regarding oral medications at discharge, the angiotensin-converting enzyme alacepril (-4.2), the β-blocker carvedilol (-7.1, the best response), the angiotensin receptor blocker telmisartan (-1.6), the diuretic furosemide (-4.2), the lipid-lowering drugs pitavastatin

Table 1 Patient characteristics

	Population (n = 151)
Age (years)*	68.6 ± 14.6
Gender, female, *n* (%)	58 (38)
Medical history	
Frequency of heart failure (time)*	3.2 ± 2.5
Hypertension	73 (48)
Diabetes mellitus	55 (36)
Hyperlipidemia	45 (30)
Signs at admission	
Elevated jugular venous pressure	84 (56)
S_3 gallop	85 (56)
Lower extremity edema	76 (50)
NYHA functional class: II/III/IV	54/44/53
Clinical scenario: 1/2/3/4/5	28/77/34/0/12
Nohria—profile A	2 (1)
Nohria—profile B	108 (72)
Nohria—profile C	28 (19)
Nohria—profile L	13 (9)
Baseline characteristics at admission/at discharge	
Heart rate (beats min^{-1})*	84.4 ± 26.7/73.2 ± 58.3
Systolic BP (mm Hg)*	124.4 ± 31.8/ 111.0 ± 15.8
Diastolic BP (mm Hg)*	68.5 ± 17.5/59.4 ± 8.4
Body weight (kg)*	57.3 ± 13.5/52.3 ± 11.9
Δ Body weight (kg)*	4.6 ± 3.8
Laboratory factors at admission/at discharge	
Hemoglobin ($g\,dl^{-1}$)*	12.4 ± 7.7/11.8 ± 2.0
Leukocytes ($10^9\,l^{-1}$)*	6940 ± 2982/ 5968 ± 2464
Blood urea nitrogen ($mg\,dl^{-1}$)*	28.6 ± 20.7/30.0 ± 19.7
Creatinine ($mg\,dl^{-1}$)*	1.27 ± 0.90/1.24 ± 0.69
Sodium ($mEq\,l^{-1}$)*	137.6 ± 3.9/136.8 ± 4.3
Uric acid ($mg\,dl^{-1}$)*	7.5 ± 2.0/7.4 ± 2.1
T-bil ($mg\,dl^{-1}$)*	0.92 ± 0.67/0.71 ± 0.42
C-reactive protein ($mg\,dl^{-1}$)*	1.3 ± 2.8/0.7 ± 1.8
BNP ($pg\,ml^{-1}$)*	920 ± 956/439 ± 548
Δ BNP ($pg\,ml^{-1}$) (1 month after discharge-at discharge)*	78 ± 226
Echocardiographic factors at admission/at discharge	
Left ventricular end-diastolic dimension (mm)*	58.9 ± 13.3/58.3 ± 11.9
Left ventricular end-systolic dimension (mm)*	47.4 ± 15.2/45.8 ± 14.6
Fractional shortening (%)*	21.2 ± 11.5/23.1 ± 11.4
Ventricular septum thickness (mm)*	9.6 ± 2.9/9.6 ± 2.7
Posterior wall thickness (mm)*	9.8 ± 2.5/9.6 ± 2.0
Left atrial diastolic dimension (mm)*	49.9 ± 8.1/47.8 ± 9.3
Pressure across tricuspid valve (mm Hg)*	37.0 ± 16.3/25.4 ± 10.5
Medication at admission	
Use of dopamine, *n* (%)	10 (6)
Use of dobutamine, *n* (%)	33 (22)
Use of phosphodiesterase inhibitor, *n* (%)	13 (9)
Use of carperitide, *n* (%)	32 (21)
Use of nitroglycerin, *n* (%)	22 (15)
Use of diuretics, *n* (%)	60 (40)

Abbreviations: BNP, B-type natriuretic peptide; BP, blood pressure; NYHA, New York Heart Association; T-bil, total bilirubin.
*Plus or minus values are means ± s.d. Clinical profiles were classified as profile A (dry–warm), B (wet–warm), C (wet–cold) or L (dry–cold).

(−3.3), atorvastatin (−2.9) and ezetimibe (−2.2), the coronary dilator isosorbide dinitrate (−3.1), the antiallergic fexofenadine hydrochloride (−5.1), the sedative-hypnotic triazolam (−3.2), proton pump inhibitor lansoprazole (−0.9) and all antiflatulents, except toughmac, led to better prognoses. However, Ca inhibitor nifedipine (9.4) resulted in the worst outcome, and all diabetes drugs, antiarrhythmic drugs, potassium agents, vitamins and purgatives, excluding senna, were associated with worse prognoses.

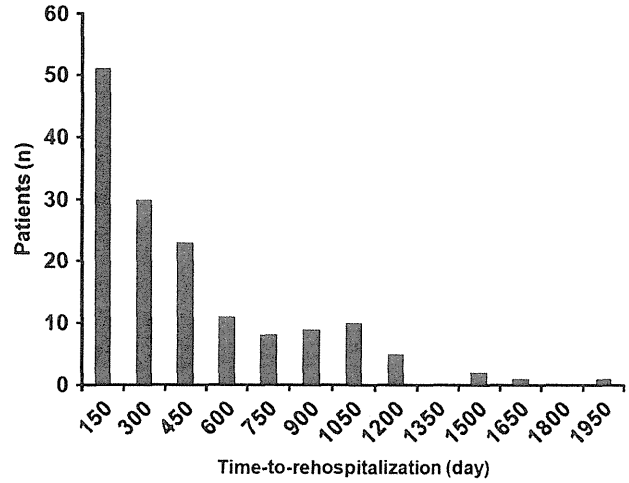


Figure 1 Time-to-rehospitalization histogram for all patients.

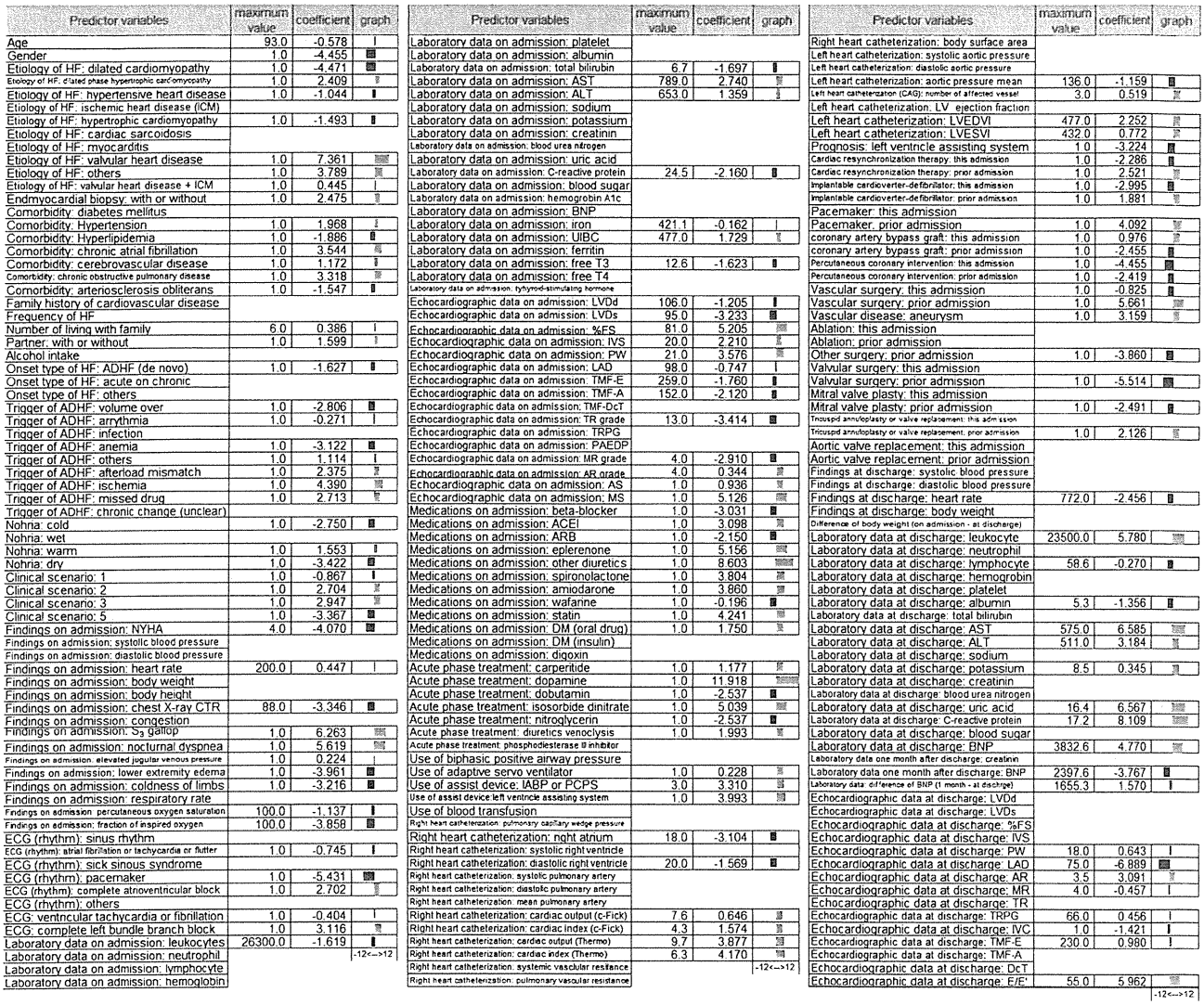
Fitting the model to clinical data

The mean actual value for rehospitalization (X) was 388 ± 377 days, whereas the mean estimated value calculated by the probability model based on a Poisson process (Y) was 398 ± 381 days; X and Y were very tightly correlated (Figure 4). The results showed that the mathematical formula for rehospitalization time is the dependent variable, and the clinical and personal factors before rehospitalization are the independent variables.

DISCUSSION

This study provided evidence that the values of numerous factors, including risk factors at one phase of disease, can be used to construct a mathematical equation to predict clinical outcomes. We were able to derive the equation $\tau = f(x_1, \ldots, x_p)$, where τ is the time to a future clinical event and $x_1, \ldots, x_p$ are clinical factors observed before the event. In this case, τ represents the days until rehospitalization after discharge, and $x_1, \ldots, x_p$ are the clinical and personal factors for patients hospitalized for ADHF. This study provides evidence that the clinical outcome of τ in this context is a function of 252 significant factors such as plasma BNP levels at and soon after discharge. This study presents the time to rehospitalization as the dependent variable and the clinical and personal factors before rehospitalization as the independent variables.

This study suggests the novel idea that the time to clinical events, such as rehospitalization or death, can be mathematically formulated from clinical and personal factors, demonstrating that clinical medicine can engage in physical science. The novelty of this study is based on the fact that clinical outcomes have been thought to be determined mainly from medical knowledge and the experience of the physicians. It can be argued that the known effectiveness of drugs may determine the time course of clinical events. Although this is partially true,[15–17] no one knows how one drug or the combination of several drugs affects patients with different degrees of severity of a given disease. It may also be argued that large-scale trials may better depict clinical outcomes; for example, the patients with BNP levels of <170 pg/ml showed a 20% reduction of rehospitalization compared with the patients with BNP levels greater than 170 pg/ml.[18,19] Evaluating such results by Kaplan–Meier analysis is common in clinical medicine; however, this analysis only provides the average tendency of the average patient to undergo rehospitalization and does not



Predictor variables	maximum value	coefficient	graph
Age	93.0	-0.578	
Gender	1.0	-4.455	
Etiology of HF: dilated cardiomyopathy	1.0	-4.471	
Etiology of HF: dilated phase hypertrophic cardiomyopathy	1.0	2.409	
Etiology of HF: hypertensive heart disease	1.0	-1.044	
Etiology of HF: ischemic heart disease (ICM)			
Etiology of HF: hypertrophic cardiomyopathy	1.0	-1.493	
Etiology of HF: cardiac sarcoidosis			
Etiology of HF: myocarditis			
Etiology of HF: valvular heart disease	1.0	7.361	
Etiology of HF: others	1.0	3.789	
Etiology of HF: valvular heart disease + ICM	1.0	0.445	
Endmyocardial biopsy: with or without	1.0	2.475	
Comorbidity: diabetes mellitus			
Comorbidity: Hypertension	1.0	1.968	
Comorbidity: Hyperlipidemia	1.0	-1.886	
Comorbidity: chronic atrial fibrillation	1.0	3.544	
Comorbidity: cerebrovascular disease	1.0	1.172	
Comorbidity: chronic obstructive pulmonary disease	1.0	3.318	
Comorbidity: arteriosclerosis obliterans	1.0	-1.547	
Family history of cardiovascular disease			
Frequency of HF			
Number of living with family	6.0	0.386	
Partner: with or without	1.0	1.599	
Alcohol intake			
Onset type of HF: ADHF (de novo)	1.0	-1.627	
Onset type of HF: acute on chronic			
Onset type of HF: others			
Trigger of ADHF: volume over	1.0	-2.806	
Trigger of ADHF: arrythmia	1.0	-0.271	
Trigger of ADHF: infection			
Trigger of ADHF: anemia	1.0	-3.122	
Trigger of ADHF: others	1.0	1.114	
Trigger of ADHF: afterload mismatch	1.0	2.375	
Trigger of ADHF: ischemia	1.0	4.390	
Trigger of ADHF: missed drug	1.0	2.713	
Trigger of ADHF: chronic change (unclear)			
Nohria: cold	1.0	-2.750	
Nohria: wet			
Nohria: warm	1.0	1.553	
Nohria: dry	1.0	-3.422	
Clinical scenario: 1	1.0	-0.867	
Clinical scenario: 2	1.0	2.704	
Clinical scenario: 3	1.0	2.947	
Clinical scenario: 5	1.0	-3.367	
Findings on admission: NYHA	4.0	-4.070	
Findings on admission: systolic blood pressure			
Findings on admission: diastolic blood pressure			
Findings on admission: heart rate	200.0	0.447	
Findings on admission: body weight			
Findings on admission: body height			
Findings on admission: chest X-ray CTR	88.0	-3.346	
Findings on admission: congestion			
Findings on admission: S_3 gallop	1.0	6.263	
Findings on admission: nocturnal dyspnea	1.0	5.619	
Findings on admission: elevated jugular venous pressure	1.0	0.224	
Findings on admission: lower extremity edema	1.0	-3.961	
Findings on admission: coldness of limbs	1.0	-3.216	
Findings on admission: respiratory rate			
Findings on admission: percutaneous oxygen saturation	100.0	-1.137	
Findings on admission: fraction of inspired oxygen	100.0	-3.858	
ECG (rhythm): sinus rhythm			
ECG (rhythm): atrial fibrillation or tachycardia or flutter	1.0	-0.745	
ECG (rhythm): sick sinous syndrome			
ECG (rhythm): pacemaker	1.0	-5.431	
ECG (rhythm): complete atrioventricular block	1.0	2.702	
ECG (rhythm): others			
ECG: ventricular tachycardia or fibrillation	1.0	-0.404	
ECG: complete left bundle branch block	1.0	3.116	
Laboratory data on admission: leukocytes	26300.0	-1.619	
Laboratory data on admission: neutrophil			-12<-->12
Laboratory data on admission: lymphocyte			
Laboratory data on admission: hemoglobin			

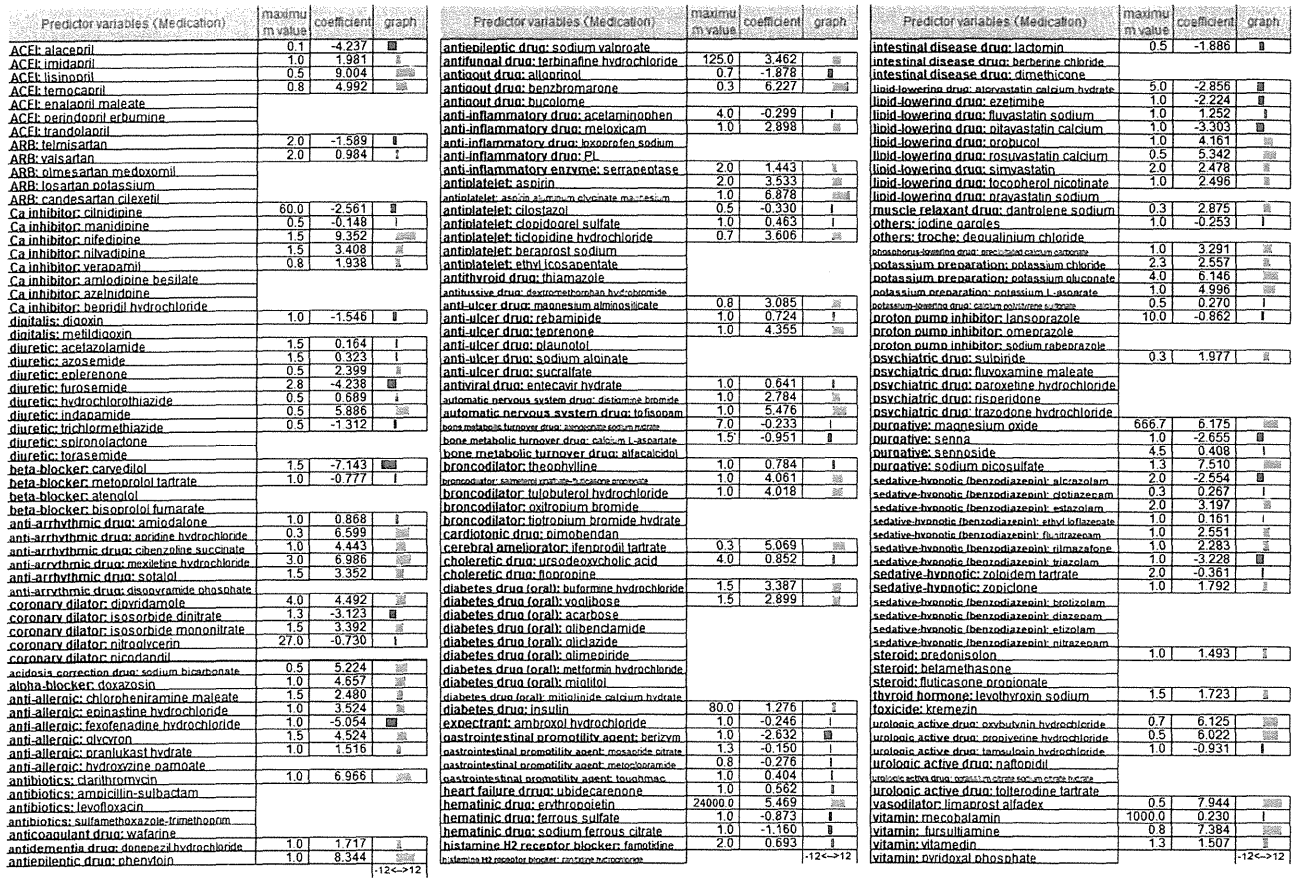
Predictor variables	maximum value	coefficient	graph
Laboratory data on admission: platelet			
Laboratory data on admission: albumin			
Laboratory data on admission: total bilirubin	6.7	-1.697	
Laboratory data on admission: AST	789.0	2.740	
Laboratory data on admission: ALT	653.0	1.359	
Laboratory data on admission: sodium			
Laboratory data on admission: potassium			
Laboratory data on admission: creatinin			
Laboratory data on admission: blood urea nitrogen			
Laboratory data on admission: uric acid			
Laboratory data on admission: C-reactive protein	24.5	-2.160	
Laboratory data on admission: blood sugar			
Laboratory data on admission: hemoglobin A1c			
Laboratory data on admission: BNP			
Laboratory data on admission: iron	421.1	-0.162	
Laboratory data on admission: UIBC	477.0	1.729	
Laboratory data on admission: ferritin			
Laboratory data on admission: free T3	12.6	-1.623	
Laboratory data on admission: free T4			
Laboratory data on admission: tyhyroid-stimulating hormone			
Echocardiographic data on admission: LVDd	106.0	-1.205	
Echocardiographic data on admission: LVDs	95.0	-3.233	
Echocardiographic data on admission: %FS	81.0	5.205	
Echocardiographic data on admission: IVS	20.0	2.210	
Echocardiographic data on admission: PW	21.0	3.576	
Echocardiographic data on admission: LAD	98.0	-0.747	
Echocardiographic data on admission: TMF-E	259.0	-1.760	
Echocardiographic data on admission: TMF-A	152.0	-2.120	
Echocardiographic data on admission: TMF-DcT			
Echocardiographic data on admission: TR grade	13.0	-3.414	
Echocardiographic data on admission: TRPG			
Echocardiographic data on admission: PAEDP			
Echocardiographic data on admission: MR grade	4.0	-2.910	
Echocardiographic data on admission: AR grade	4.0	0.344	
Echocardiographic data on admission: AS	1.0	0.936	
Echocardiographic data on admission: MS	1.0	5.126	
Medications on admission: beta-blocker	1.0	-3.031	
Medications on admission: ACEI	1.0	3.098	
Medications on admission: ARB	1.0	-2.150	
Medications on admission: eplerenone	1.0	5.156	
Medications on admission: other diuretics	1.0	8.603	
Medications on admission: spironolactone	1.0	3.804	
Medications on admission: amiodarone	1.0	3.860	
Medications on admission: wafarine	1.0	-0.196	
Medications on admission: statin	1.0	4.241	
Medications on admission: DM (oral drug)	1.0	1.750	
Medications on admission: DM (insulin)			
Medications on admission: digoxin			
Acute phase treatment: carperitide	1.0	1.177	
Acute phase treatment: dopamine	1.0	11.918	
Acute phase treatment: dobutamin	1.0	-2.537	
Acute phase treatment: isosorbide dinitrate	1.0	5.039	
Acute phase treatment: nitroglycerin	1.0	-2.537	
Acute phase treatment: diuretics venoclysis	1.0	1.993	
Acute phase treatment: phosphodiesterase III inhibitor			
Use of biphasic positive airway pressure			
Use of adaptive servo ventilator	1.0	0.228	
Use of assist device: IABP or PCPS	3.0	3.310	
Use of assist device:left ventricle assisting system	1.0	3.993	
Use of blood transfusion			
Right heart catheterization: pulmonary capillary wedge pressure			
Right heart catheterization: right atrium	18.0	-3.104	
Right heart catheterization: systolic right ventricle			
Right heart catheterization: diastolic right ventricle	20.0	-1.569	
Right heart catheterization: systolic pulmonary artery			
Right heart catheterization: diastolic pulmonary artery			
Right heart catheterization: mean pulmonary artery			
Right heart catheterization: cardiac output (c-Fick)	7.6	0.646	
Right heart catheterization: cardiac index (c-Fick)	4.3	1.574	
Right heart catheterization: cardiac output (Thermo)	9.7	3.877	
Right heart catheterization: cardiac index (Thermo)	6.3	4.170	
Right heart catheterization: systemic vascular resitance			-12<-->12
Right heart catheterization: pulmonary vascular resistance			

Predictor variables	maximum value	coefficient	graph
Right heart catheterization: body surface area			
Left heart catheterization: systolic aortic pressure			
Left heart catheterization: diastolic aortic pressure			
Left heart catheterization: aortic pressure mean	136.0	-1.159	
Left heart catheterization (CAG): number of affected vessel	3.0	0.519	
Left heart catheterization: LV ejection fraction			
Left heart catheterization: LVEDVI	477.0	2.252	
Left heart catheterization: LVESVI	432.0	0.772	
Prognosis: left ventricle assisting system	1.0	-3.224	
Cardiac resynchronization therapy: this admission	1.0	-2.286	
Cardiac resynchronization therapy: prior admission	1.0	2.521	
Implantable cardioverter-defibrillator: this admission	1.0	-2.995	
Implantable cardioverter-defibrillator: prior admission	1.0	1.881	
Pacemaker: this admission			
Pacemaker: prior admission	1.0	4.092	
coronary artery bypass graft: this admission	1.0	0.976	
coronary artery bypass graft: prior admission	1.0	-2.455	
Percutaneous coronary intervention: this admission	1.0	-4.455	
Percutaneous coronary intervention: prior admission	1.0	-2.419	
Vascular surgery: this admission	1.0	-0.825	
Vascular surgery: prior admission	1.0	5.661	
Vascular disease: aneurysm	1.0	3.159	
Ablation: this admission			
Ablation: prior admission			
Other surgery: prior admission	1.0	-3.860	
Valvular surgery: this admission			
Valvular surgery: prior admission	1.0	-5.514	
Mitral valve plasty: this admission			
Mitral valve plasty: prior admission	1.0	-2.491	
Tricuspid annuloplasty or valve replacement: this admission			
Tricuspid annuloplasty or valve replacement: prior admission	1.0	2.126	
Aortic valve replacement: this admission			
Aortic valve replacement: prior admission			
Findings at discharge: systolic blood pressure			
Findings at discharge: diastolic blood pressure			
Findings at discharge: heart rate	772.0	-2.456	
Findings at discharge: body weight			
Difference of body weight (on admission - at discharge)			
Laboratory data at discharge: leukocyte	23500.0	5.780	
Laboratory data at discharge: neutrophil			
Laboratory data at discharge: lymphocyte	58.6	-0.270	
Laboratory data at discharge: hemoglobin			
Laboratory data at discharge: platelet			
Laboratory data at discharge: albumin	5.3	-1.356	
Laboratory data at discharge: total bilirubin			
Laboratory data at discharge: AST	575.0	6.585	
Laboratory data at discharge: ALT	511.0	3.184	
Laboratory data at discharge: sodium			
Laboratory data at discharge: potassium	8.5	0.345	
Laboratory data at discharge: creatinin			
Laboratory data at discharge: blood urea nitrogen			
Laboratory data at discharge: uric acid	16.4	6.567	
Laboratory data at discharge: C-reactive protein	17.2	8.109	
Laboratory data at discharge: blood sugar			
Laboratory data at discharge: BNP	3832.6	4.770	
Laboratory data one month after discharge: creatinin			
Laboratory data one month after discharge: BNP	2397.6	-3.767	
Laboratory data: difference of BNP (1 month - at discharge)	1655.3	1.570	
Echocardiographic data at discharge: LVDd			
Echocardiographic data at discharge: LVDs			
Echocardiographic data at discharge: %FS			
Echocardiographic data at discharge: IVS			
Echocardiographic data at discharge: PW	18.0	0.643	
Echocardiographic data at discharge: LAD	75.0	-6.889	
Echocardiographic data at discharge: AR	3.5	3.091	
Echocardiographic data at discharge: MR	4.0	-0.457	
Echocardiographic data at discharge: TR			
Echocardiographic data at discharge: TRPG	66.0	0.456	
Echocardiographic data at discharge: IVC	1.0	-1.421	
Echocardiographic data at discharge: TMF-E	230.0	0.980	
Echocardiographic data at discharge: TMF-A			
Echocardiographic data at discharge: DcT			
Echocardiographic data at discharge: E/E'	55.0	5.962	
			-12<-->12

Figure 2 Factors influencing the estimation of rehospitalization for HF and the contribution of each parameter. All of the clinical and personal factors for the patients with HF. Predictor variables with coefficient indicate the factors selected after the application of the regularization method. Negative values indicate favorable impact on prognosis, whereas positive values indicate undesirable effect. HF, heart failure; ADHF, acute decompensated heart failure; NYHA, New York Heart Association; CTR, cardiothoracic ratio; ECG, electrocardiogram; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; UIBC, unsaturated iron-binding capacity; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; IVS, interventricular septal thickness; PW, left ventricular posterior thickness; LAD, left atrial dimension; TMF-E, the peak mitral inflow early diastolic velocity; TMF-A, the peak mitral inflow atrial filling; DcT, deceleration time; TR PG, tricuspid regurgitation pressure gradient; PAEDP, pulmonary artery end-diastolic pressure; MR, mitral regurgitation; AR, aortic regurgitation; AS, aortic stenosis; MS, mitral stenosis; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DM, diabetes mellitus; IABP, intraaortic balloon pumping; PCPS, percutaneous cardio pulmonary support; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; IVC, inferior vena cava respiratory change; *E/E'*, ratio of peak mitral *E*-wave velocity to peak mitral annular velocity.

prospectively provide a future clinical outcome for each patient. Indeed, in the epidemiological study, many biomarkers, such as BNP levels or C-reactive protein levels in addition to the classical risk factors, such as hypertension or diabetes mellitus, are known to be related to cardiovascular events and death. However, Wang *et al.*[20] showed that although multiple biomarkers are associated with a high relative risk of adverse events, even in the combination of these factors they add only moderately to the prediction of risk in an individual person. This suggests that the occurrence of cardiovascular events may not be well predictable or mathematically formulated. On the other hand, using the formula developed in this study, we can identify the day of a clinical event to within a small range, suggesting that we need more clinical data to predict the future outcomes or obtain the mathematical formula for the prediction than we expected.

It would be difficult to strictly prove that this mathematical formula is correct because no gold standard or correct answer is available in the medical literature. However, there are hints as to the correctness of this formula. First, we assume that the probability of rehospitalization follows a Poisson distribution; if this is true, a histogram of the day of rehospitalization after discharge should follow a Poisson distribution. We found that the present data for the actual day of rehospitalization are distributed as a Poisson distribution.



Predictor variables (Medication)	maximum value	coefficient	graph
ACEI: alacepril	0.1	-4.237	
ACEI: imidapril	1.0	1.981	
ACEI: lisinopril	0.5	9.004	
ACEI: temocapril	0.8	4.992	
ACEI: enalapril maleate			
ACEI: perindopril erbumine			
ACEI: trandolapril			
ARB: telmisartan	2.0	-1.589	
ARB: valsartan	2.0	0.984	
ARB: olmesartan medoxomil			
ARB: losartan potassium			
ARB: candesartan cilexetil			
Ca inhibitor: cilnidipine	60.0	-2.561	
Ca inhibitor: manidipine	0.5	-0.148	
Ca inhibitor: nifedipine	1.5	9.352	
Ca inhibitor: nilvadipine	1.5	3.408	
Ca inhibitor: verapamil	0.8	1.938	
Ca inhibitor: amlodipine besilate			
Ca inhibitor: azelnidipine			
Ca inhibitor: benidipil hydrochloride			
digitalis: digoxin	1.0	-1.546	
digitalis: metildigoxin			
diuretic: acetazolamide	1.5	0.164	
diuretic: azosemide	1.5	0.323	
diuretic: eplerenone	0.5	2.399	
diuretic: furosemide	2.8	-4.238	
diuretic: hydrochlorothiazide	0.5	0.689	
diuretic: indapamide	0.5	5.886	
diuretic: trichlormethiazide	0.5	-1.312	
diuretic: spironolactone			
diuretic: torasemide			
beta-blocker: carvedilol	1.5	-7.143	
beta-blocker: metoprolol tartrate	1.0	-0.777	
beta-blocker: atenolol			
beta-blocker: bisoprolol fumarate			
anti-arrhythmic drug: amiodalone	1.0	0.868	
anti-arrhythmic drug: aprindine hydrochloride	0.3	6.599	
anti-arrhythmic drug: cibenzoline succinate	1.0	4.443	
anti-arrythmic drug: mexiletine hydrochloride	3.0	6.986	
anti-arrhythmic drug: sotalol	1.5	3.352	
anti-arrythmic drug: disopyramide phosphate			
coronary dilator: dipyridamole	4.0	4.492	
coronary dilator: isosorbide dinitrate	1.3	-3.123	
coronary dilator: isosorbide mononitrate	1.5	3.392	
coronary dilator: nitroglycerin	27.0	-0.730	
coronary dilator: nicorandil			
acidosis correction drug: sodium bicarbonate	0.5	5.224	
alpha-blocker: doxazosin	1.0	4.657	
anti-allergic: chlorpheniramine maleate	1.5	2.480	
anti-allergic: epinastine hydrochloride	1.0	3.524	
anti-allergic: fexofenadine hydrochloride	1.0	-5.054	
anti-allergic: olvcyron	1.5	4.524	
anti-allergic: pranlukast hydrate	1.0	1.516	
anti-allergic: hydroxzine pamoate			
antibiotics: clarithromycin	1.0	6.966	
antibiotics: ampicillin-sulbactam			
antibiotics: levofloxacin			
antibiotics: sulfamethoxazole-trimethoprim			
anticoagulant drug: wafarine			
antidementia drug: donepezil hydrochloride	1.0	1.717	
antiepileptic drug: phenytoin	1.0	8.344	
			-12<->12

Predictor variables (Medication)	maximum value	coefficient	graph
antiepileptic drug: sodium valproate			
antifungal drug: terbinafine hydrochloride	125.0	3.462	
antigout drug: allopurinol	0.7	-1.878	
antigout drug: benzbromarone	0.3	6.227	
antigout drug: bucolome			
anti-inflammatory drug: acetaminophen	4.0	-0.299	
anti-inflammatory drug: meloxicam	1.0	2.898	
anti-inflammatory drug: loxoprofen sodium			
anti-inflammatory drug: PL			
anti-inflammatory enzyme: serrapentase	2.0	1.443	
antiplatelet: aspirin	2.0	3.533	
antiplatelet: aspirin aluminum glycinate magnesium	1.0	6.878	
antiplatelet: cilostazol	0.5	-0.330	
antiplatelet: clopidogrel sulfate	1.0	0.463	
antiplatelet: ticlopidine hydrochloride	0.7	3.606	
antiplatelet: beraprost sodium			
antiplatelet: ethyl icosapentate			
antithyroid drug: thiamazole			
antitussive drug: dextromethorphan hydrobromide			
anti-ulcer drug: magnesium aluminosilicate	0.8	3.085	
anti-ulcer drug: rebamipide	1.0	0.724	
anti-ulcer drug: teprenone	1.0	4.355	
anti-ulcer drug: plaunotol			
anti-ulcer drug: sodium alginate			
anti-ulcer drug: sucralfate			
antiviral drug: entecavir hydrate	1.0	0.641	
automatic nervous system drug: distigmine bromide	1.0	2.784	
automatic nervous system drug: tofisopam	1.0	5.476	
bone metabolic turnover drug: ipriflavone	7.0	-0.233	
bone metabolic turnover drug: calcium L-aspartate	1.5	-0.951	
bone metabolic turnover drug: alfacalcidol			
broncodilator: theophylline	1.0	0.784	
broncodilator: salmeterol xinafoate-fluticasone propionate	1.0	4.061	
broncodilator: tulobuterol hydrochloride	1.0	4.018	
broncodilator: oxitropium bromide			
broncodilator: tiotropium bromide hydrate			
cardiotonic drug: pimobendan			
cerebral ameliorator: ifenprodil tartrate	0.3	5.069	
choleretic drug: ursodeoxycholic acid	4.0	0.852	
choleretic drug: flopropine			
diabetes drug (oral): buformin hydrochloride	1.5	3.387	
diabetes drug (oral): voglibose	1.5	2.899	
diabetes drug (oral): acarbose			
diabetes drug (oral): glibenclamide			
diabetes drug (oral): gliclazide			
diabetes drug (oral): glimepiride			
diabetes drug (oral): metformin hydrochloride			
diabetes drug (oral): miglitol			
diabetes drug (oral): pioglitazone calcium hydrate			
diabetes drug: insulin	80.0	1.276	
expectrant: ambroxol hydrochloride	1.0	-0.246	
gastrointestinal promotility agent: berizym	1.0	-2.632	
gastrointestinal promotility agent: mosapride citrate	1.3	-0.150	
gastrointestinal promotility agent: metoclopramide	0.8	-0.276	
gastrointestinal promotility agent: trimebutine	1.0	0.404	
heart failure drug: ubidecarenone	1.0	0.562	
hematinic drug: erythropoietin	24000.0	5.469	
hematinic drug: ferrous sulfate	1.0	-0.873	
hematinic drug: sodium ferrous citrate	1.0	-1.160	
histamine H2 receptor blocker: famotidine	2.0	0.693	
histamine H2 receptor blocker: ranitidine hydrochloride			-12<->12

Predictor variables (Medication)	maximum value	coefficient	graph
intestinal disease drug: lactomin	0.5	-1.886	
intestinal disease drug: berberine chloride			
intestinal disease drug: dimethicone			
lipid-lowering drug: alcryvastatin calcium hydrate	5.0	-2.856	
lipid-lowering drug: ezetimibe	1.0	-2.224	
lipid-lowering drug: fluvastatin sodium	1.0	1.252	
lipid-lowering drug: pitavastatin calcium	1.0	-3.303	
lipid-lowering drug: probucol	1.0	4.161	
lipid-lowering drug: rosuvastatin calcium	0.5	5.342	
lipid-lowering drug: simvastatin	2.0	2.478	
lipid-lowering drug: tocopherol nicotinate	1.0	2.496	
lipid-lowering drug: pravastatin sodium			
muscle relaxant drug: dantrolene sodium	0.3	2.875	
others: iodine garoles	1.0	-0.253	
others: troche: dequalinium chloride			
phosphorus-lowering drug: precipitated calcium carbonate	1.0	3.291	
potassium preparation: potassium chloride	2.3	2.557	
potassium preparation: potassium gluconate	4.0	6.146	
potassium preparation: potassium L-aspartate	1.0	4.996	
potassium-lowering drug: calcium polystyrene sulfonate	0.5	0.270	
proton pump inhibitor: lansoprazole	10.0	-0.862	
proton pump inhibitor: omeprazole			
proton pump inhibitor: sodium rabeprazole			
psychiatric drug: sulpiride	0.3	1.977	
psychiatric drug: fluvoxamine maleate			
psychiatric drug: paroxetine hydrochloride			
psychiatric drug: risperidone			
psychiatric drug: trazodone hydrochloride			
purgative: magnesium oxide	666.7	6.175	
purgative: senna	1.0	-2.655	
purgative: sennoside	4.5	0.408	
purgative: sodium picosulfate	1.3	7.510	
sedative-hypnotic (benzodiazepin): alprazolam	2.0	-2.554	
sedative-hypnotic (benzodiazepin): clotiazepam	0.3	0.267	
sedative-hypnotic (benzodiazepin): estazolam	2.0	3.197	
sedative-hypnotic (benzodiazepin): ethyl loflazepate	1.0	0.161	
sedative-hypnotic (benzodiazepin): flunitrazepam	1.0	2.551	
sedative-hypnotic (benzodiazepin): flurazepam	1.0	2.283	
sedative-hypnotic (benzodiazepin): triazolam	1.0	-3.228	
sedative-hypnotic: zolpidem tartrate	2.0	-0.361	
sedative-hypnotic: zopiclone	1.0	1.792	
sedative-hypnotic (benzodiazepin): brotizolam			
sedative-hypnotic (benzodiazepin): diazepam			
sedative-hypnotic (benzodiazepin): etizolam			
sedative-hypnotic (benzodiazepin): nitrazepam			
steroid: predonisolon	1.0	1.493	
steroid: belamethasone			
steroid: fluticasone propionate			
thyroid hormone: levothyroxin sodium	1.5	1.723	
toxicide: kremezin			
urologic active drug: oxybutynin hydrochloride	0.7	6.125	
urologic active drug: propiverine hydrochloride	0.5	6.022	
urologic active drug: tamsulosin hydrochloride	1.0	-0.931	
urologic active drug: naftopidil			
urologic active drug: potassium citrate sodium citrate hydrate			
urologic active drug: tolterodine tartrate			
vasodilator: limaprost alfadex	0.5	7.944	
vitamin: mecobalamin	1000.0	0.230	
vitamin: fursultiamine	0.8	7.384	
vitamin: vitamedin	1.3	1.507	
vitamin: pyridoxal phosphate			-12<->12

Figure 3 Factors influencing the estimation of rehospitalization for heart failure and the contribution of each parameter. All of the medications at discharge for the patients with heart failure. Medications were calculated as ratios of their recommended doses. All drugs were divided into 55 groups. Predictor variables with coefficient indicate the factors selected after the application of the regularization method. Negative values indicate favorable impact on prognosis, whereas positive values indicate undesirable effect. HF, heart failure; ADHF, acute decompensated heart failure; NYHA, New York Heart Association; CTR, cardiothoracic ratio; ECG, electrocardiogram; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; UIBC, unsaturated iron-binding capacity; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; IVS, interventricular septal thickness; PW, left ventricular posterior thickness; LAD, left atrial dimension; TMF-E, the peak mitral inflow early diastolic velocity; TMF-A, the peak mitral inflow atrial filling; DcT, deceleration time; TR PG, tricuspid regurgitation pressure gradient; PAEDP, pulmonary artery end-diastolic pressure; MR, mitral regurgitation; AR, aortic regurgitation; AS, aortic stenosis; MS, mitral stenosis; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DM, diabetes mellitus; IABP, intraaortic balloon pumping; PCPS, percutaneous cardio pulmonary support; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; IVC, inferior vena cava respiratory change; E/E', ratio of peak mitral E-wave velocity to peak mitral annular velocity.

Second, when we compared the day of rehospitalization in a clinical setting and the calculated day of rehospitalization obtained by the formula, these two data are well fitted, suggesting that the current formula is likely to be correct. Third, we prevented over-fitting of the clinical data using the free variables, indicating the suitability of the present formula.

We do not believe that this equation is the perfect formula to predict the day of rehospitalization from numerous variables. Although we included 402 factors as the free variables, including factors as diverse as echocardiographic data and marital status, we may have neglected to include other unknown but important factors that may determine the day of rehospitalization. We did not include information on patient genetic backgrounds, such as point mutations in the myosin heavy chain, or social status, such as occupation or annual income, private matters, such as hobbies or personal characteristics, and mental health parameters, such as depression. The inclusion of these issues may improve the formula presented in this study; however, the present formula already provides a good fit with an R^2 value of 0.9879. Most importantly, the importance of the possibility of constituting such a mathematical formula in clinical practice is now clear.

In this study, we assumed that a linear function of each parameter contributes to the formation of the formula for the clinical outcome. One might suggest the use of nonlinear functions of all of the factors to provide a more accurate approximation of the rehospitalization time. In fact, we performed a nonlinear analysis using this data, and surprisingly, the nonlinear method using support vectors yielded no improvement over the present formula using the linear functions of the factors.

LIMITATIONS

First of all, the factors in this study may have confounded each other, and we used the regularization method to eliminate automatically the factors that have weak effects on prognosis. Although the remaining

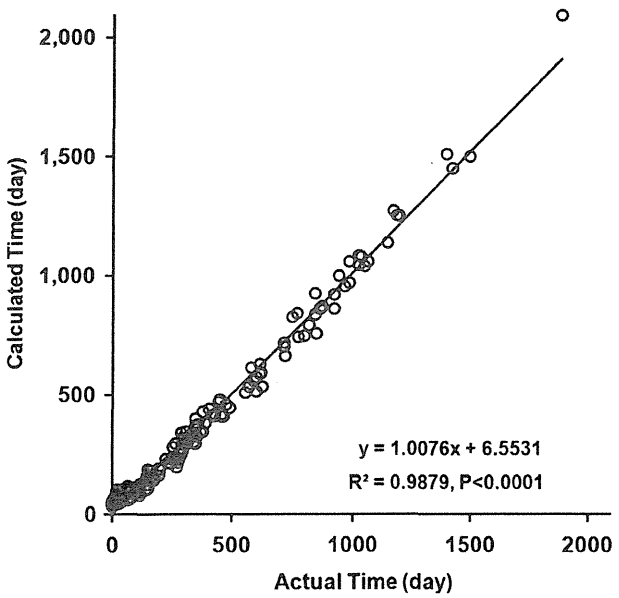


Figure 4 Correlation between the clinical data and the values calculated using the mathematical formula. The clinical data are in excellent agreement with the calculated times.

factors with strong effects on prognosis could have confounded each other, the results of this study are probably not weakened because we obtained a good fitting to the clinical outcome using these factors. When we consider the clinical and pathophysiological meaning of each factor, we need to pay attention to each factor independently.

The other main limitation of this study is that the patient population consists of a retrospective cohort. However, because we enrolled all of the patients who were admitted to our department during the entry period, the selection bias may be small. Furthermore, this is a single-center study, so the formula may be true only in our institute. However, because (1) approximately one-half of the patients who were hospitalized during this time were referred from other hospitals, (2) the nature and treatment of HF did not differ among the hospitals and (3) our hospital sets a high standard for CHF treatment and specializes in receiving CHF patients from all over Japan; we believe that the formula developed in this study may be generalized. We estimated the day of rehospitalization in this study; however, the important issue is the ability to make this prediction, which needs further investigation.

CONCLUSIONS

This study demonstrated that clinical medicine and practice can use a mathematical formula to predict clinical outcomes or events using current data. A prospective study is needed to test whether this formula predicts the day of rehospitalization in CHF patients who are admitted because of ADHF and discharged after treatment. The application of these risk factors to individual CHF patients may distinguish those patients who are at low risk from those who are at high risk and may benefit from closer monitoring and aggressive treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank T Takayama, M Shishikura and Y Miyawaki for assisting in the collection of data. This work is supported by grants-in-aid from the Japanese Ministry of Health, Labor and Welfare (H23-Nanchi-Ippan-22 to MK) and the Japanese Ministry of Education, Culture, Sports, Science and Technology (21390251 to MK), and also by grants from the Japan Heart Foundation (PPAR to MK) and the Japan Cardiovascular Research Foundation (Stacin to MK).

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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Geriatric Nutritional Risk Index Predicts Functional Dependency and Mortality in Patients With Heart Failure With Preserved Ejection Fraction

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Background: The clinical significance of nutritional risk assessment in patients with heart failure with preserved ejection fraction (HFpEF) remains undefined. Geriatric nutritional risk index (GNRI) is a simple nutritional assessment tool for elderly subjects. Its predictive value was evaluated in patients with HFpEF, a common HF phenotype in the elderly population.

Methods and Results: The present study enrolled 152 consecutive patients (mean age, 77±11 years; male, 53.9%) who were hospitalized with HFpEF at the authors' institution. GNRI on admission was calculated as follows: 14.89×serum albumin (g/dl)+41.7×body mass index/22. Characteristics and mortality (median follow-up of 2.1 years) were compared between 2 groups: low GNRI (<92) with moderate or severe nutritional risk; and high GNRI (≥92) with no or low nutritional risk. Patients in the low-GNRI group were more often female, and had lower serum hemoglobin and sodium, but higher serum blood urea nitrogen (BUN), C-reactive protein, and B-type natriuretic peptide (BNP) compared to those in the high-GNRI group ($P<0.05$, respectively). Physical activity at discharge measured by Barthel index was significantly lower in the low-GNRI group than the high-GNRI group ($P<0.05$). On Cox hazard analysis, lower GNRI predicted increased mortality independent of age, gender, prior HF hospitalization, and higher BUN and BNP ($P<0.01$).

Conclusions: GNRI may be useful for predicting functional dependency and mortality in patients with HFpEF. (*Circ J* 2013; **77:** 705–711)

Key Words: Body mass index; Geriatric nutritional risk index; Heart failure with preserved ejection fraction; Hypoalbuminemia

Malnutrition is common, and is associated with increased mortality risk in patients with heart failure (HF).[1,2] Previous studies have shown that several nutritional indicators, including body mass index (BMI), serum albumin, total cholesterol, and total lymphocyte count, predict survival in patients with HF with reduced ejection fraction (HFrEF).[3–6] The clinical significance of nutritional risk assessment in patients with HF with preserved ejection fraction (HFpEF), however, has not been well established.

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Nutritional assessment should be practical, easy to perform, non-invasive, requiring no use of devices, and applicable at the bedside.[7] The geriatric nutritional risk index (GNRI) is a simple and well-established nutritional assessment tool for elderly subjects.[8–12] Recent studies have shown that a similar index (nutritional risk index; NRI) predicts survival in patients with HFrEF.[13,14] The predictive value of GNRI in patients with HFpEF, however, remains undefined.

The aim of the present study was to evaluate the clinical significance of GNRI in patients with HFpEF, a common HF phenotype in the elderly population.[15]

Methods

Subjects

The present study enrolled a total of 194 consecutive patients who were hospitalized in Tottori University Hospital with a primary diagnosis of HFpEF from January 2004 to April 2011.

Received August 22, 2012; revised manuscript received September 19, 2012; accepted October 23, 2012; released online November 25, 2012 Time for primary review: 20 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-1091

Table 1. Baseline Patient Characteristics vs. GNRI

	Overall (n=152)	High GNRI (≥92) (n=79)	Low GNRI (<92) (n=73)	P-value
Age (years)	77±11	76±10	78±11	0.309
Male (%)	53.9	62.0	45.2	0.038
BMI (kg/m²)	21.7±4.0	23.3±3.7	19.9±3.4	<0.001
NYHA class III/IV	83.3	80.0	87.1	0.620
SBP (mmHg)	151±37	152±38	150±37	0.858
Heart rate (beats/min)	90±25	92±28	88±23	0.440
Prior HF hospitalization (%)	14.4	15.2	13.7	0.794
Comorbidity (%)				
Coronary artery disease	32.9	30.4	35.6	0.492
Hypertension	61.8	64.6	58.9	0.474
Atrial fibrillation	53.3	57.0	49.3	0.345
Diabetes	39.5	40.5	38.4	0.786
Dyslipidemia	27.6	32.9	21.9	0.130
COPD	9.2	7.6	11.0	0.474
Cerebrovascular disease	19.7	20.3	19.2	0.868
Laboratory data				
Hemoglobin (g/dl)	11.1±2.4	11.8±2.3	10.3±2.3	<0.001
Sodium (mEq/L)	139±5	140±4	138±5	<0.001
BUN (mg/dl)	25.0 (19.0–39.0)	23.0 (16.5–34.5)	27.0 (20.0–42.0)	0.026
Creatinine (mg/dl)	1.1 (0.8–1.8)	1.1 (0.8–1.5)	1.1 (0.9–1.9)	0.991
eGFR (ml·min⁻¹·1.73m⁻²)	48.0 (27.0–65.9)	49.8 (30.2–64.5)	45.7 (21.1–67.3)	0.189
Total protein (g/dl)	6.7±0.7	6.8±0.5	6.3±0.7	<0.001
Albumin (g/dl)	3.5±0.5	3.8±0.3	3.1±0.4	<0.001
Total cholesterol (mg/dl)†	158±39	169±39	146±35	<0.001
LDL-C (mg/dl)†	91±31	99±31	82±28	0.002
HDL-C (mg/dl)†	49±16	52±15	46±16	0.019
CRP (mg/dl)	0.58 (0.18–2.55)	0.39 (0.16–1.38)	1.12 (0.20–3.66)	0.010
BNP (pg/ml)	434 (243–699)	358 (155–575)	578 (306–1,250)	<0.001
Echocardiography				
LVDdI (mm/m²)	33.2±6.1	32.6±5.1	33.9±7.0	0.193
LVMI (g/m²)	133.8±55.5	136.5±59.8	131.0±50.8	0.539
Relative wall thickness	0.45±0.12	0.44±0.10	0.46±0.14	0.228
LVEF (%)	56.8±11.1	56.4±10.6	57.1±11.6	0.713
Medication prior to admission (%)				
ACEI/ARB	55.9	59.5	52.1	0.356
β-blocker	27.0	27.8	26.0	0.801
Mineralocorticoid blocker	13.2	17.7	8.2	0.083

Data given as mean±SD or median (interquartile range). †Data available for 130 subjects.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVDdI, left ventricular diastolic diameter index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association; SBP, systolic blood pressure.

HFpEF was defined as follows: (1) HF symptoms defined by Framingham criteria; (2) preserved left ventricular ejection fraction (LVEF) ≥40% as previously described;[16] and (3) absence of the following HF etiology: severe valve disease, congenital disease, complete atrial ventricular block, pericardial disease, primary pulmonary hypertension, pulmonary artery embolism, or acute myocardial infarction. Patients with cancer (n=18) or liver cirrhosis (n=2), or on dialysis (n=1) were excluded. Twenty-one patients were also excluded because of lack of body weight or laboratory data. Finally a total of 152 patients were enrolled in the present study. The study was approved by the Institutional Review Board for Human Investigation in Tottori University.

Data Collection

Medical records were retrospectively reviewed with regard to demography, medical history, comorbidity, laboratory data, echocardiograms, medication, and clinical course. All measurements except for Barthel index were taken at the time of hospital admission. BMI was calculated as weight in kilograms divided by height² (m²). Estimated glomerular filtration rate (eGFR) was determined by using a previously described formula.[17] Left ventricular (LV) end-diastolic diameter was indexed to body surface area (LV end-diastolic diameter index:

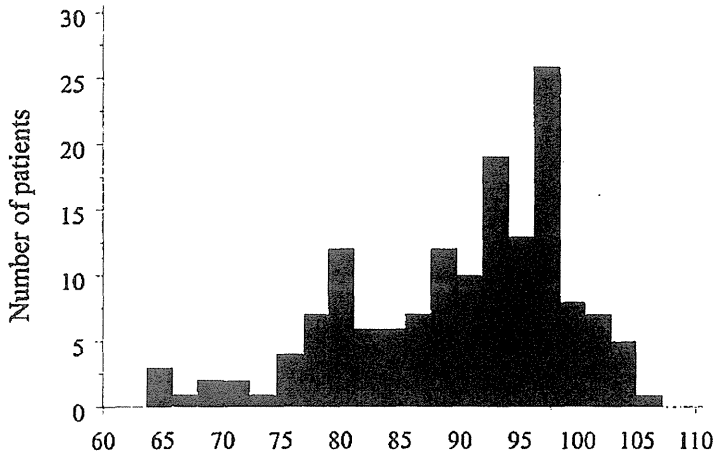

Figure 1. Distribution of geriatric nutritional risk index (GNRI).

LVDdI). LVEF, relative wall thickness, and LV mass index were calculated as previously described.[18,19] Follow-up data were obtained from medical records or telephone interview (median follow-up of 2.1 years after hospital admission; interquartile range [IQR], 1.2–3.6).

GNRI

Baseline GNRI was calculated from serum albumin and BMI obtained on hospital admission as previously described:[10]

$$\text{GNRI}=14.89\times\text{serum albumin (g/dl)}+41.7\times\text{present body weight/[(height)}^2\text{(m}^2\text{)}\times 22]$$
$$=14.89\times\text{serum albumin (g/dl)}+41.7\times\text{BMI/22}$$

Clinical characteristics and mortality were compared between 2 groups: low GNRI (<92) with moderate or severe nutritional risk; and high GNRI (≥92) with low or no nutritional risk according to the previous report.[8]

Activities of Daily Living

The Barthel index was measured by well-trained nurses at hospital discharge, except for 5 patients who died in hospital. The Barthel index measures a patient's functional status for basic daily activities, with scores ranging from 0 (total dependence) to 100 points (independence) as previously described.[20,21]

Clinical Outcomes

We evaluated both all-cause mortality and HF re-hospitalization during the follow-up period. The cause of death was classified as cardiovascular and non-cardiovascular based on the clinical information. Death from a cardiovascular cause was defined as death due to HF, sudden death, and vascular events (myocardial infarction, stroke, or other vascular diseases). Other causes of death were defined as non-cardiovascular cause death.

Statistical Analysis

Continuous variables are expressed as mean±SD for normally distributed variables, and median and IQR for non-normally distributed variables. Categorical variables are expressed as percentages. Differences in continuous variables are compared using t-test for normally distributed variables, and Mann-Whitney U-test for non-normally distributed variables. Categorical variables are compared using chi-square test. Event-free survival curve after hospital admission was estimated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model, which was performed as stepwise regression with forward selection, was used to assess independent predictors of all-cause mortality in the subjects. Age, sex, and all baseline variables associated with mortality on univariate analysis ($P<0.10$) were entered into the model; BMI and serum albumin level used in the calculation of GNRI were excluded. Age and sex were forced into the model to adjust for age and gender effects. The area under the receiver operating characteristic curves (AUC) was used to compare the predictive value of BMI, serum albumin level, and GNRI for predicting all-cause mortality. To adjust for age and gender effect, we developed each risk score model including age and gender based on the regression coefficient as previously described.[18] $P<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 20 and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0).

Results

Baseline Patient Characteristics

Baseline patient characteristics are listed in Table 1. The mean age of the overall cohort was 77±11 years, and 53.9% were male; elderly patients aged over 65 years comprised 86.2%. The mean LVEF was 56.8±11.1%. New York Heart Association (NYHA) functional class III or IV was found in 83.4% of patients on hospital admission. Coronary artery disease was prevalent in 32.9% of patients. Hypertension (61.8%) was the most common comorbidity, followed by atrial fibrillation (53.3%) and diabetes (39.5%). Moderate or severe impaired renal function (eGFR $<30\,\text{ml}\cdot\text{min}^{-1}\cdot 1.73\,\text{m}^{-2}$) was found in 30.9% of patients. Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs), β-blocker, and mineralocorticoid blocker were prescribed to 55.9%, 27.0%, and 13.2% of patients prior to hospital admission, respectively.

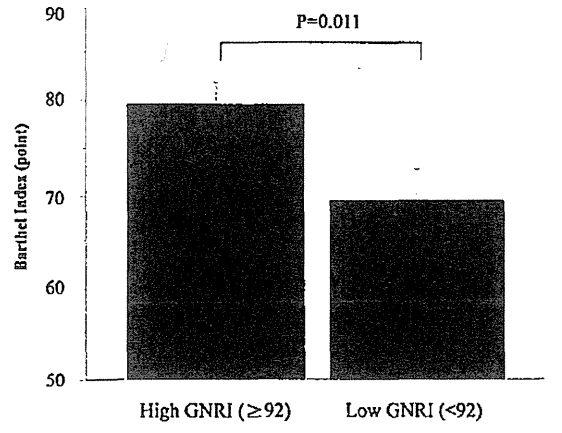

Figure 2. Barthel index at discharge vs. geriatric nutritional risk index (GNRI).

Patient Characteristics According to GNRI

Figure 1 shows the distribution of GNRI. The mean GNRI was 90.0±9.3. Patients in the low-GNRI group were more often female. BMI and serum hemoglobin, sodium, total protein, albumin, total cholesterol, and low-density and high-density lipoprotein cholesterol were significantly lower, whereas serum blood urea nitrogen (BUN), C-reactive protein, and B-type natriuretic peptide (BNP) were significantly higher in the low-GNRI group than the high-GNRI group. There were no significant differences of age, NYHA class, the prevalence of comorbidities, LVEF, LV geometry, and pre-hospital medications between the 2 groups. The 2 groups (except for 5 patients who died in hospital) had no significant difference in medication at discharge (low GNRI, n=68 vs. high GNRI, n=79: ACEI/ARB, 77.9% vs. 83.5%, P=0.388; β-blocker, 44.1% vs. 46.8%, P=0.742; mineralocorticoid blocker, 29.4% vs. 20.3%, P=0.198, respectively).

GNRI and Activities of Daily Living

Figure 2 shows Barthel index at discharge between the 2 groups. Patients in the low-GNRI group had significantly lower Barthel index than those in the high-GNRI group.

GNRI and Mortality

During the median follow-up of 2.1 years (IQR, 1.2–3.6 years), 55 patients died. Of these, 39 patients (70.9%) had cardiovascular cause death: HF death (n=22, 40.0%), vascular death (n=11, 20.0%), and sudden death (n=6, 10.9%). Sixteen patients (29.1%) had non-cardiovascular cause death: infectious disease (n=7, 12.7%), respiratory disease (n=3, 5.5%), gastrointestinal disease (n=2, 3.6%), and others (n=4, 7.3%).

Kaplan-Meier survival analysis for all-cause mortality is given in **Figure 3**. Patients in the low-GNRI group had significantly higher mortality compared to those in the high-GNRI group (hazard ratio [HR], 2.667; 95% confidence interval [CI]: 1.527–4.651, P<0.001). The increased mortality risk was found in both cardiovascular (HR, 2.469; 95% CI: 248–4.902, P<0.001) and non-cardiovascular disease (HR, 3.086; 95% CI: 1.172–8.130, P=0.023). On stepwise Cox hazard analysis, lower GNRI as a continuous variable was an independent predictor of all-cause mortality as well as advanced age, previous history of HF hospitalization, and higher BUN and BNP (**Table 2**). In contrast, there was no significant difference in HF re-hospitalization between the 2 groups (HR, 0.962; 95% CI: 0.517–1.795, P=0.905).

Predictive Value of GNRI

Figure 4 shows the receiver operating characteristics curve of 3 risk score models based on BMI, serum albumin, and GNRI for predicting all-cause mortality. The AUC of GNRI, but not albumin, was significantly higher compared to that of BMI,

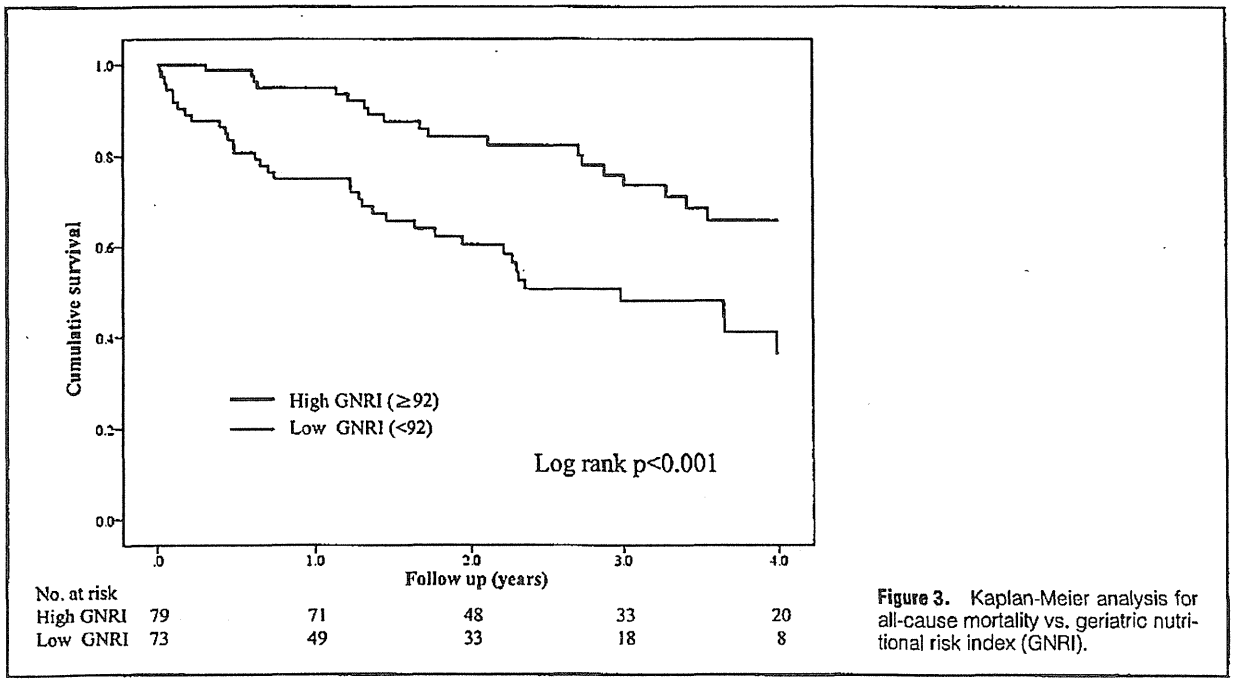

Figure 3. Kaplan-Meier analysis for all-cause mortality vs. geriatric nutritional risk index (GNRI).

Table 2. Independent Predictors of All-Cause Mortality in HFpEF

	Univariate analysis		Stepwise multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.066 (1.031–1.101)	<0.001	1.062 (1.026–1.100)	<0.001
Male	0.872 (0.513–1.481)	0.612	0.877 (0.510–1.543)	0.672
Prior HF hospitalization	2.857 (1.590–5.128)	<0.001	2.364 (1.230–4.545)	0.010
Coronary artery disease	1.695 (0.976–2.941)	0.0610		
GNRI	0.950 (0.926–0.974)	<0.001	0.947 (0.920–0.975)	<0.001
Hemoglobin (g/dl)	0.906 (0.816–1.006)	0.0650		
Sodium (mEq/L)	0.939 (0.888–0.994)	0.0293		
BUN (mg/dl)	1.024 (1.013–1.035)	<0.001	1.018 (1.006–1.030)	0.003
eGFR (ml·min^{-1}·1.73 m^{-2})	0.979 (0.968–0.991)	<0.001		
BNP (per 100 pg/ml)	1.031 (1.010–1.051)	0.003	1.028 (1.005–1.052)	0.016

CI, confidence interval; HFpEF, HF with preserved ejection fraction; HR, hazard ratio. Other abbreviations as in Table 1.

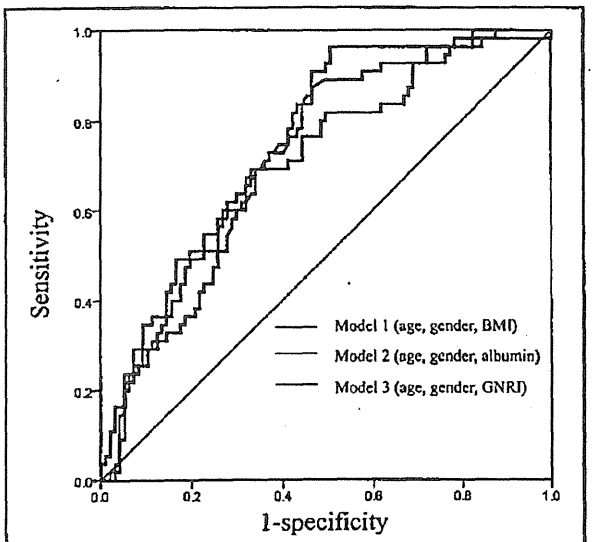

Figure 4. Area under the receiver operating characteristics curve of risk score model for predicting all-cause mortality. BMI, body mass index; GNRI, geriatric nutritional risk index.

Table 3. AUC of Risk Score Model for Predicting All-Cause Mortality

	AUC (95% CI)	P-value
Model 1 (age, gender, BMI)	0.696 (0.611–0.781)	(Reference)
Model 2 (age, gender, albumin)	0.731 (0.650–0.811)	0.302
Model 3 (age, gender, GNRI)	0.752 (0.676–0.829)	0.049

Model 1, 0.057×age+0.157×male (1)/female (0)−0.117×BMI; model 2, 0.064×age+0.064×male (1)/female (0)−0.750×albumin; model 3, 0.061×age+0.153×male (1)/female (0)−0.052×GNRI. AUC, area under the receiver operating characteristics curve. Other abbreviations as in Tables 1,2.

indicating that GNRI had the highest predictive value for predicting mortality (Table 3).

Discussion

The present study has demonstrated the clinical significance of nutritional risk assessment using GNRI in patients with HFpEF. We found that low GNRI was significantly associated with decreased activities of daily living (ADL), and increased mortality independent of age, gender, and well-known prognostic factors (previous history of HF hospitalization, BUN, and BNP). These results suggest that GNRI is a useful index to stratify the risk of morbidity and mortality in patients hospitalized with HFpEF.

GNRI was first described by Bouillanne et al to predict malnutrition-related complications (bedsores and infections) and mortality in hospitalized elderly patients.[8] It was developed by modifying the NRI for elderly subjects, and has been reported to be significantly correlated with biochemical and anthropometric markers of nutritional status.[8–12]

There are a few previous reports about the relationship between NRI and mortality risk in patients with HFrEF. Aziz et al reported that NRI was associated with the composite endpoints all-cause mortality and HF readmission in patients with acute decompensated HF.[13] Al-Najjar and Clark have also shown that NRI predicts mortality in outpatients with HFrEF.[14] We have further extended previous findings by demonstrating the clinical significance of the GNRI, a modified NRI, in HFpEF patients for the first time.

Serum albumin level and BMI are often used as indicators of nutritional status in routine clinical practice, and recent studies have shown that these indicators predict survival in both HFrEF and HFpEF patients.[3,4,22,23] In patients with HF, however, serum albumin level is influenced by several non-nutritional factors including fluid status, hepatic congestion, renal dysfunction (albuminemia), and inflammation.[4,18,23] Similarly, BMI is influenced by fluid status,[3,22] indicating that the measurement of albumin or BMI alone is insufficient as a nutritional risk assessment. In contrast, GNRI measured using both serum albumin and BMI may overcome the shortcomings of each indicator. We found that the predictive value of GNRI tended to be higher than that of BMI or serum albumin alone. For one thing, increased extracellular fluid volume decreases serum albumin, whereas it increases BMI. Considering such a counteracting effect, GNRI as a combined index of albumin and BMI may lead to minimization of the effect of fluid status, and identify nutritional risk better than each of them.[13]

Several other nutritional screening tools such as Subjective Global Assessment (SGA), Mini Nutritional Assessment-Screening Form (MNA-SF), Malnutrition Universal Screening Tool (MUST), and Nutritional Risk Screening 2002 (NRS 2002) are available for nutritional risk assessment in elderly subjects.[11] These indexes require subjective assessment, which may be affected by the examiner's experience. In addition, they require body weight change, which is affected by fluid status in patients hospitalized with HF. In contrast, GNRI consists of simple objective measurements, BMI and serum albumin, which can be easily obtained on admission in patients with HF. Therefore, GNRI may be more easily used in HF patients than other indexes, although further investigations are necessary to evaluate which nutritional index is more specific to patients with HF.

HF is characterized by limited exercise tolerance, which is mainly determined by decreased cardiac output, abnormal respiratory response, and skeletal muscle dysfunction.[24] Exercise intolerance and symptoms may lead to activity restriction, and recent studies have shown that low physical activity level predicts poor outcome in patients with HF.[21,24] The relationship between low GNRI and decline in ADL may be involved with reduced exercise capacity, reflecting HF severity. In addition, patients in the low-GNRI group required intensive care such as inotropic support and prolonged hospital stay (data not shown), which may lead to bed-rest deconditioning, and result in decreased ADL. Impaired muscle strength with malnutrition and cachexia may affect the decreased physical activity of patients with low GNRI.[12,25] Cognitive impairment and motor dysfunction caused by cerebrovascular or orthopedic disease are also important factors associated with decreased ADL in elderly subjects.[26] Because these factors were not taken into account in this study, further investigations are required to clarify the relationship between GNRI and precise functional assessment in patients with HFpEF.

There are several potential explanations for the relationship between low GNRI and cardiovascular/non-cardiovascular mortality in patients with HFpEF. Low GNRI is accompanied by low BMI and hypoalbuminemia, reflecting malnutrition and inflammation, which are associated with worse HF outcome.[3,4,18,22,23] Hypoalbuminemia is associated with increased mortality in several non-cardiac comorbidities such as end-stage renal disease, infection, and pulmonary disease.[18] This may explain the increased non-cardiovascular mortality of patients in the low-GNRI group. In contrast, there was no significant difference in HF re-hospitalization between the 2 groups. One potential reason is that the cause of HF re-hospitalization is multifactorial, and is related not only to the severity of HF, but also patient self-care and socioenvironmental factors.[27]

In patients with HFpEF, morbidity and mortality still remain high.[15,28] Unfortunately, there is currently no particular pharmacological treatment for these patients.[15] Thus, additional management strategies with involvement of non-pharmacological approaches urgently need to be developed to improve outcome. Nutritional intervention may be a potential management strategy for these patients. Several small studies have shown that nutritional supplementation has a beneficial effect on cardiac metabolism, resulting in improved cardiac function and exercise capacity.[29–31] Malnutrition, however, is often present in cachexia, which is a complex metabolic syndrome characterized by anorexia, weight loss, inflammation, insulin resistance, and increased muscle protein breakdown.[25] An ongoing loss of muscle mass cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[25,32] Thus, it may be necessary to apply comprehensive intervention, including nutritional supplementation, muscle anabolic therapy, and anti-inflammatory or anti-cytokine agents along with appropriate physical training.[2,25,32] Further investigations are required to evaluate the effect of comprehensive nutritional intervention on morbidity and mortality in malnourished HFpEF patients as assessed using GNRI.

This study had several limitations. The present study evaluated GNRI at a single time point and did not asses the changes in GNRI. This study was retrospective, and the sample size was relatively small. Further prospective investigations are necessary to confirm the present findings in another large cohort.

In conclusion, GNRI may be a simple and useful index for predicting functional dependency and mortality in patients with HFpEF.

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