研究の進捗

	総患者	心不全再入院なし	心不全再入院あり	p値
入院時及び退院時心エコー図データ				
左室拡張末期経（mm）	58	57	60	NS
左室収縮末期経（mm）	46	44	49	NS
左室短縮率（mm）	22	23	20	NS
左室中隔壁厚（mm）	10	10	9	NS
2度以上の大動脈弁逆流（%）	11	12	10	NS
2度以上の僧帽弁逆流（%）	44	41	54	NS
2度以上の三尖弁逆流（%）	25	21	37	NS
採血データ				
白血球数（/mm^3）	5582	5619	5490	NS
AST（IU/L）	25	24	26	NS
尿素窒素（mg/dL）	30	27	39	0.0012
尿酸（mg/dL）	6.6	6.4	7.2	NS
CRP（mg/dL）	0.63	0.69	0.49	NS
BNP（pg/mL）	388	388	565	NS
退院時処方の種類				
ジギタリス（%）	22	18	32	NS
β遮断薬（%）	75	72	80	NS
利尿薬（%）	85	80	95	0.0259
強心薬（%）	18	6	46	<0.0001
抗血小板薬（%）	9	11	5	NS
抗甲状腺薬（%）	1	2	0	NS
気管支拡張薬（%）	0	0	0	NS
抗アレルギー薬（%）	4	6	0	NS
抗ヒスタミン薬（%）	6	7	5	NS
抗炎症薬（%）	27	30	22	NS
利胆薬（%）	5	6	2	NS
整腸剤（%）	10	13	26	NS
高脂血症治療薬（%）	39	38	41	NS
プロトンポンプ阻害薬（%）	54	51	61	NS
下剤（%）	27	23	37	NS
抗精神病薬（%）	6	7	5	NS
ビタミン薬（%）	4	4	2	NS

まとめ

- 慢性心不全患者の退院時の臨床データを使用して，心不全にて再入院するまでの日数を予測する関数式を作成した。

- 本関数式の臨床的有用性を検討するための前向き介入研究を行う体制を整備している。本研究にて関数式の有用性が示されれば，プライマリーケア医の心不全診療ガイドとなるのみならず，早期に慢性心不全治療に介入することが可能となることで入院回数を減らし，医療費削減に寄与すると考えられる。

- 本関数式の妥当性を検討するための前向き観察研究が進行中であり，141名の心不全患者が登録されて，平均255日の観察機関で41名の再入院を認めた。今後も，登録患者を増やして5年間の観察期間における心不全再入院の有無を見る。

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ORIGINAL ARTICLE

Derivation of a mathematical expression for predicting the time to cardiac events in patients with heart failure: a retrospective clinical study

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The prognoses for patients with certain diseases are estimated by averaging the results of clinical trials. To investigate the possibility of deriving a mathematical formula for the estimation of prognosis, we formulated the equation $\tau = f(x_1, \ldots, x_p)$, where $x_1, \ldots, x_p$ are clinical features and τ represents the clinical outcome for heart failure (HF). We attempted to determine the function to mathematically formulate the relationship between clinical features and outcomes for these patients. We followed 151 patients (mean age: 68.6 ± 14.6 years; men: 61.6%) who were consecutively hospitalized and discharged as a result of acute decompensated HF (ADHF) between May 2006 and December 2009. The mathematical analysis was performed through a probabilistic modeling of the relational data by assuming a Poisson process for rehospitalization owing to HF and by linearly approximating the relationship between the clinical factors and the mean elapsed time to rehospitalization. The former assumption was validated by a statistical test of the data, and the contribution of each parameter was assessed based on the coefficients of the linear relation. Using a regularization method to analyze 402 clinical parameters, we identified 252 factors that substantially influenced the elapsed time until rehospitalization. With the probability model based on the Poisson process, the actual (X; 388 ± 377 days) and estimated (Y; 398 ± 381 days) elapsed times to rehospitalization were tightly correlated ($Y = 1.0076X + 6.5531$, $R^2 = 0.9879$, $P < 0.0001$). We established a mathematical formula that closely predicts the clinical outcomes of patients who are hospitalized with ADHF and discharged after appropriate treatment.
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Keywords: heart failure; mathematical model; prognosis; rehospitalization

INTRODUCTION

Studies show that numerous factors, including disease severity, treatment protocols and the environment, independently determine patients' prognoses. For example, in patients with chronic heart failure (CHF), many studies have shown that various independent indices of the severity of CHF, such as plasma B-type natriuretic peptide (BNP) level, left ventricular function, exercise tolerance or New York Heart Association (NYHA) functional class affect the time to hospitalization or cardiac death.[1–5] However, because we could not identify the elapsed time until hospitalization in certain patients with CHF, we estimated this time using knowledge of the pathophysiology of CHF, our experience with previous comparable patients and Kaplan–Meier plots of their hospitalization in the clinical studies; we then explained our estimation to each patient. This procedure led us to conclude that estimating the elapsed time to rehospitalization is a type of problem that is specific to clinical medical science because the results and outcomes of biology or basic medical sciences can be derived from mathematically formulated equations. Furthermore, other fields of basic science, such as physics and mathematics or applied sciences, such as mechanics, thermodynamics and fluid dynamics, are mathematically formulated; the observational phenomena in applied sciences other than medical science can be predicted by mathematical equations, for example, the law of universal gravitation.[6] The most important issue in deriving a mathematical expression for relationships among two or more factors is the prediction of the future value of one variable based on the other factor(s). All phenomena, such as the severity of CHF and the patients' characteristics before the occurrence of clinical events, may therefore provide a mathematical equation for the clinical outcome if we can relate factors in the patient's clinical status to clinical outcomes such as rehospitalization.

To investigate this possibility, we sought to solve the equation $\tau = f(x_1, \ldots, x_p)$, where $x_1, \ldots, x_p$ represent clinical features affecting the clinical outcome for CHF. We attempted to determine the

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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 × (mean pulmonary artery pressure − mean right atrial pressure)/cardiac output and pulmonary vascular resistance = 80 × (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 $X^i = \{x_1^i, \ldots, x_p^i\}$ 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:

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

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:

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

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.

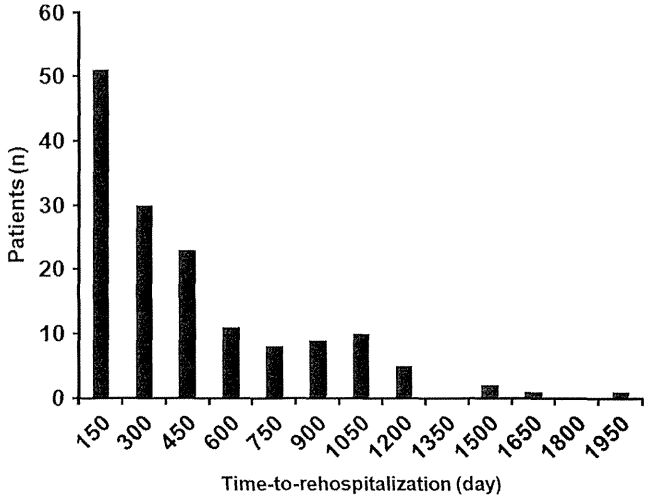

Figure 1 Time-to-rehospitalization histogram for all patients.

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: hemogrobin 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: hemogrobin			
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.

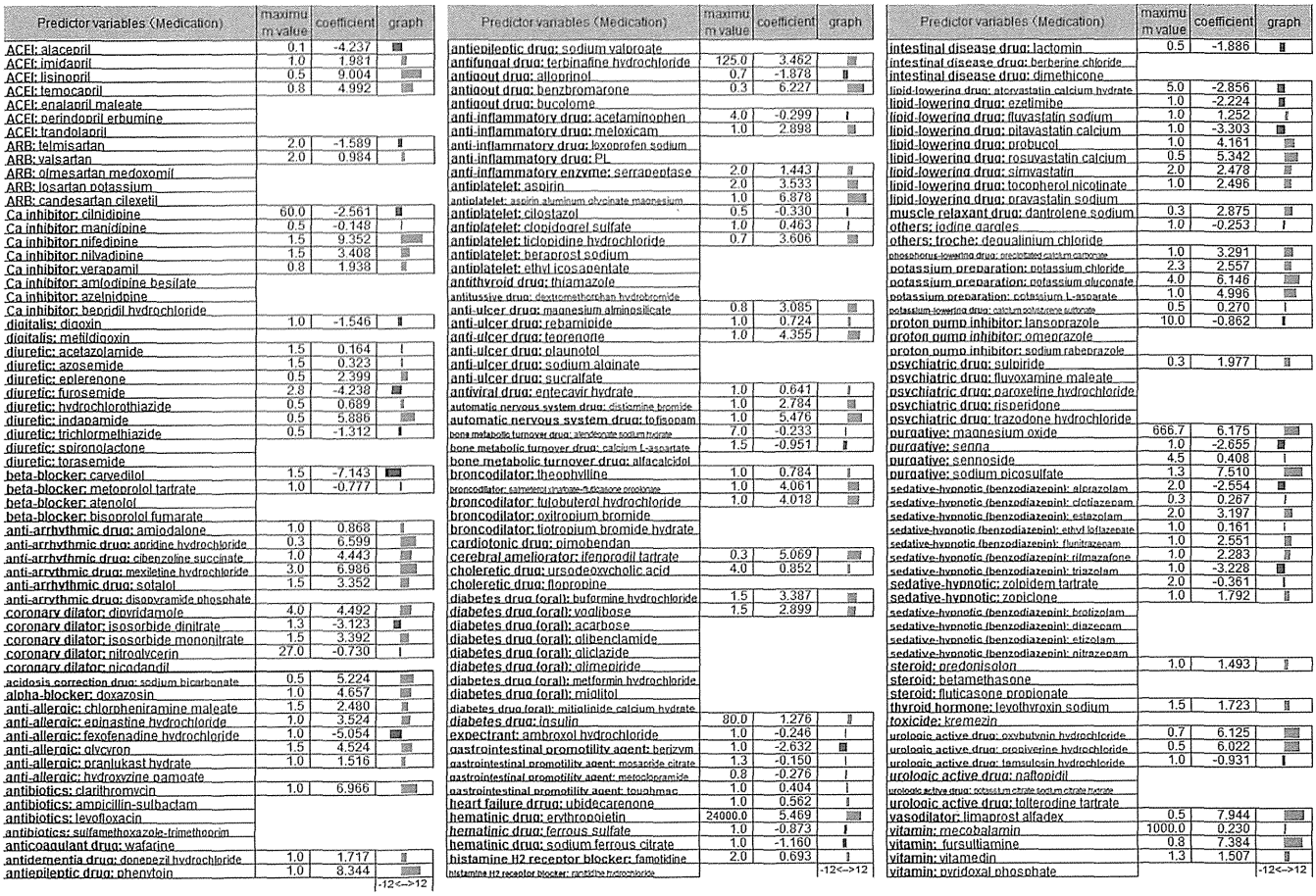

Figure 3 Factors influencing the estimation of rehospitalization for heart failure and the contribution of each parameter. All of the medications at discharge for the patients with heart failure. Medications were calculated as ratios of their recommended doses. All drugs were divided into 55 groups. 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

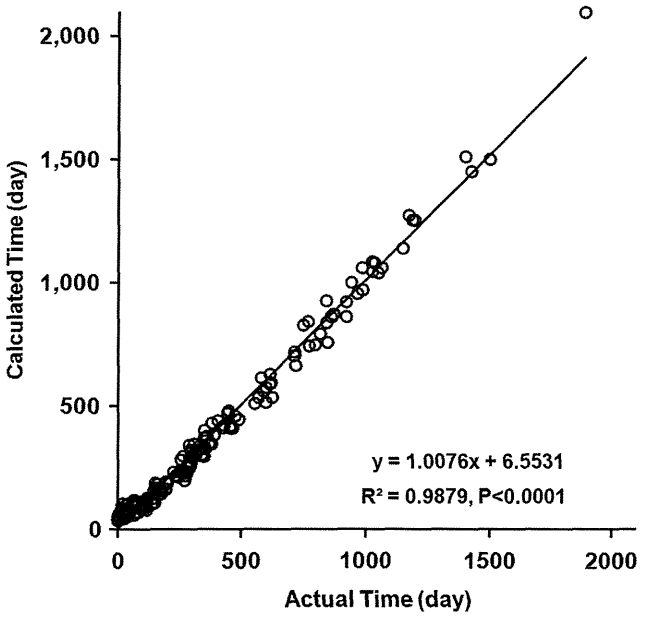

Figure 4 Correlation between the clinical data and the values calculated using the mathematical formula. The clinical data are in excellent agreement with the calculated times.

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.

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Pathophysiological impact of serum fibroblast growth factor 23 in patients with nonischemic cardiac disease and early chronic kidney disease

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Imazu M, Takahama H, Asanuma H, Funada A, Sugano Y, Ohara T, Hasegawa T, Asakura M, Kanzaki H, Anzai T, Kitakaze M. Pathophysiological impact of serum fibroblast growth factor 23 in patients with nonischemic cardiac disease and early chronic kidney disease. *Am J Physiol Heart Circ Physiol* 307: H1504–H1511, 2014. First published September 12, 2014; doi:10.1152/ajpheart.00331.2014.—Although the important role of fibroblast growth factor (FGF)23 on cardiac remodeling has been suggested in advanced chronic kidney disease (CKD), little is known about serum (s)FGF23 levels in patients with heart failure (HF) due to nonischemic cardiac disease (NICD) and early CKD. The present study aimed to investigate sFGF23 levels in NICD patients and identify the responsible factors for the elevation of sFGF23 levels. We prospectively measured sFGF23 levels in consecutive hospitalized NICD patients with early CKD (estimated glomerular filtration rate ≥ 40 ml·min^{-1}·1.73 m^{-2}) and analyzed the data of both echocardiography and right heart catheterization. Of the 156 NICD patients (estimated glomerular filtration rate range: 41–128 ml·min^{-1}·1.73 m^{-2}), the most severe HF symptom (New York Heart Association class III-IV, 53% vs. 33%, $P = 0.015$) was found in the above median sFGF23 (39.1 pg/ml) group compared with the below median sFGF23 group. sFGF23 levels were higher in patients with HF hospitalization history compared with those without HF [median: 46.8 (interquartile range: 38.8–62.7) vs. 34.7 (interquartile range: 29.6–42.4) pg/ml, $P < 0.0001$]. In the multivariate analysis, HF hospitalization was independently related to elevated sFGF23 levels ($P = 0.022$). Both systolic dysfunction and high plasma aldosterone concentration were identified as predictors of high sFGF23 levels ($P < 0.05$). Among the neurohormonal parameters, elevated sFGF23 levels were the only factor to predict a declining left ventricular ejection fraction ($P = 0.001$). These findings suggest that the progression of HF per se contributes to the elevation of sFGF23 levels even in the early stages of CKD, which leads to further myocardial dysfunction, potentially creating a vicious cycle.

fibroblast growth factor 23; heart failure; chronic kidney disease

FIBROBLAST GROWTH FACTOR (FGF)23, a phosphate-regulating hormone secreted from osteoblasts, promotes urinary phosphorus excretion and inhibits the activation of vitamin D in the presence of its cofactor, Klotho (1, 11, 21). Recent studies have suggested that an elevated circulating FGF23 level is an independent risk factor for mortality and morbidity in patients with chronic kidney disease (CKD) (8, 12) and a potential risk factor for cardiovascular events in a community-based population (10). Furthermore, a recent experimental study (4) has demonstrated that FGF23 directly promotes cardiomyocyte hypertrophy. Several clinical studies have also suggested the relationship of serum FGF23 levels with both cardiac dysfunction (25) and hypertrophy in CKD patients (7) and the association between serum FGF23 levels and clinical outcomes in outpatients with stable heart failure (HF) (20). Interestingly, the previous studies have suggested no relationship of FGF23 levels with the prevalence of coronary artery disease (CAD) (25) and coronary artery calcification (24). These clinical and experimental findings have the significant implication that FGF23 can directly influence cardiac function and structure other than the ischemic mechanisms. These findings facilitated us to hypothesize that FGF23 plays a role on the progression of cardiac dysfunction in patients with nonischemic cardiac disease (NICD). In addition, other studies (6, 28) have also reported that circulating FGF23 levels are elevated before the development of overt hyperphosphatemia in the early stages of CKD. These lines of evidence promoted us to test the idea that serum FGF23 levels are elevated even in early stages of CKD and affect the pathophysiology in HF patients. Furthermore, it is also crucial to identify the risk factor to elevated FGF23 levels in HF patients, although the determinants of serum FGF23 levels in NICD patients have not yet been completely identified in the clinical setting.

Accordingly, we measured serum FGF23 levels in NICD patients without advanced renal impairment, surveyed the relationship of serum FGF23 levels with cardiac structure, function, and the hemodynamic state, and sought to identify the determinants of serum FGF23 levels in NICD patients.

METHODS

Study design. This study was a prospective cross-sectional study of serum FGF23 levels in hospitalized patients with NICD at a single center.

NICD patients. Since previous studies have suggested that serum FGF23 levels increased marginally with declining renal function below 30–40 ml/min of glomerular filtration rate (GFR) (13, 28), we set the inclusion criteria for renal function as an estimated GFR (eGFR) of ≥40 ml·min^{-1}·1.73 m^{-2}. We could obtain written informed consents from a total of 181 consecutive patients admitted to our department between January and December 2012 (male patients: $n = 93$, 51.4%; female patients: $n = 88$, 48.6%). Patients with CAD were excluded from this study. All patients received coronary angiography or coronary computed tomography. CAD was defined by ≥75% narrowing in one or more coronary arteries or clinical history of myocardial infarction or coronary artery bypass surgery or percutaneous coronary intervention. Of the included patients, whether the HF episode met Framingham criteria was reviewed by two investigators

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(M. Imazu and H. Takahama) via medical records and confirmed that all patients met the criteria. Patients with cardiomyopathy underwent either myocardial biopsy or cardiac MRI for diagnosis. Diagnosis for cardiomyopathy was based on the definition of the World Health Organization/International Society and Federation Cardiology Task Force (23).

Biomarker measurements. Patients underwent a blood test for measurements of serum levels of FGF23, creatinine, calcium, phosphate, intact parathoroid hormone, troponin T, IL-6, TNF-α, plasma renin activity, and plasma levels of aldosterone in the present study before being discharged from the hospital. Blood sampled from the patients was placed in tubes with EDTA, and the serum was separated and frozen in plastic tubes at −80°C until analysis. The serum FGF23 level was measured with a chemiluminescence enzyme immunoassay (Kyowa Medex, Tokyo, Japan) as previously described (26). Both serum concentrations of IL-6 and TNF-α were measured with immu-

Table 1. *Baseline characteristics in NICD patients*

Characteristics	Below Median Group	Above Median Group	*P* Value
n	78	78	
Demographic data			
Age, yr	66 (IQR: 55–74)	57 (IQR: 43–69)	0.011
Women/men, %	60/40	40/60	0.010
New York Heart Association class III-IV, %	33	53	0.015
History			
HF hospitalization, %	23	60	<0.0001
Hypertension, %	50	37	0.106
Diabetes mellitus, %	21	27	0.324
Stroke, %	12	10	0.797
Atrial fibrillation, %	22	40	0.015
Etiology of NICD			<0.0001
Primary cardiomyopathy, *n*	19	38	0.235
Idiopathic dilated cardiomyopathy, *n*	9	24	
Hypertrophic cardiomyopathy, *n*	9	14	
Arrhythmogenic right ventricular cardiomyopathy, *n*	1	0	
Secondary cardiomyopathy, *n*	5	11	0.036
Amyloidosis, *n*	0	4	
Myocarditis, *n*	3	1	
Cardiac sarcoidosis, *n*	1	0	
Other, *n*	1	6	
Valvular disease, *n*	51	21	0.070
Aortic stenosis, *n*	21	4	
Aortic regurgitation, *n*	7	1	
Mitral stenosis, *n*	6	1	
Mitral regurgitation, *n*	10	8	
Tricuspid regurgitation, *n*	0	1	
Postvalve replacement, *n*	7	6	
Hypertensive heart disease with HF, *n*	3	8	
Physical findings			
Systolic blood pressure, mmHg	116 (IQR: 107–126)	104 (IQR: 93–118)	<0.0001
Heart rate, beats/min	65 (IQR: 58–76)	70 (IQR: 62–77)	0.081
Body mass index, kg/m^2	22.5 (IQR: 20.0–25.7)	22.1 (IQR: 19.9–25.3)	0.970
Medications			
β-Blockers, %	41	69	0.0004
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, %	46	64	0.024
Loop diuretics, %	22	62	<0.0001
Aldosterone antagonists, %	9	58	<0.0001
Statins, %	32	23	0.210
Laboratory data			
Phosphate, mg/dl	3.6 (IQR: 3.2–3.9)	3.7 (IQR: 3.3–4.1)	0.258
Intact parathyroid hormone, pg/dl	52 (IQR: 40–68)	56 (IQR: 41–80)	0.137
eGFR, ml·min^{-1}·1.73 m^{-2}	73 (IQR: 63–83)	69 (IQR: 55–80)	0.060
Troponin T, ng/ml	0.010 (IQR: 0.008–0.014)	0.015 (IQR: 0.009–0.023)	0.027
TNF-α, pg/ml	0.81 (IQR: 0.40–1.61)	1.36 (IQR: 0.85–2.05)	0.008
IL-6, pg/ml	1.51 (IQR: 0.92–2.66)	2.16 (IQR:1.29–3.19)	0.024
Plasma renin activity, ng·ml^{-1}·h^{-1}	1.4 (IQR: 0.4–3.8)	6.5 (IQR: 1.2–13.6)	0.0003
Plasma aldosterone concentration, ng/dl	12.6 (IQR: 8.5–16.3)	14.4 (IQR: 8.7–29.9)	0.032
Brain natriuretic peptide, pg/ml	81 (IQR: 41–162)	154 (IQR: 55–289)	0.007
TmP/GFR, mg/dl	3.29 (IQR: 2.90–3.55)	3.19 (IQR: 2.66–3.81)	0.797
FGF23, pg/ml	31.1 (IQR: 27.6–35.3)	51.3 (IQR: 43.2–61.5)	
Echocardiography data			
LVEDV index, ml/m^2	103 (IQR: 84–139)	128 (IQR: 90–165)	0.098
LVEF, %	63 (IQR: 45–68)	38 (IQR: 23–60)	<0.0001
Relative wall thickness	0.37 (IQR: 0.29–0.48)	0.33 (IQR: 0.25–0.41)	0.101
Left atrial volume index, ml/m^2	51 (IQR: 38–69)	57 (IQR: 49–71)	0.109

Values are numbers of patients (*n*), medians with interquartile ranges (IQRs), or percentages. The below median group comprised patients with a less than median value of serum fibroblast growth factor (FGF)23 level (39.1 pg/ml); the above median group comprised patients with a greater than median value of serum FGF23 level. NICD, nonischemic cardiac disease; HF, heart failure; eGFR, estimated glomerular filtration rate (eGFR); TmP/GFR, tubular maximal reabsorption rate of phosphate to GFR; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction.

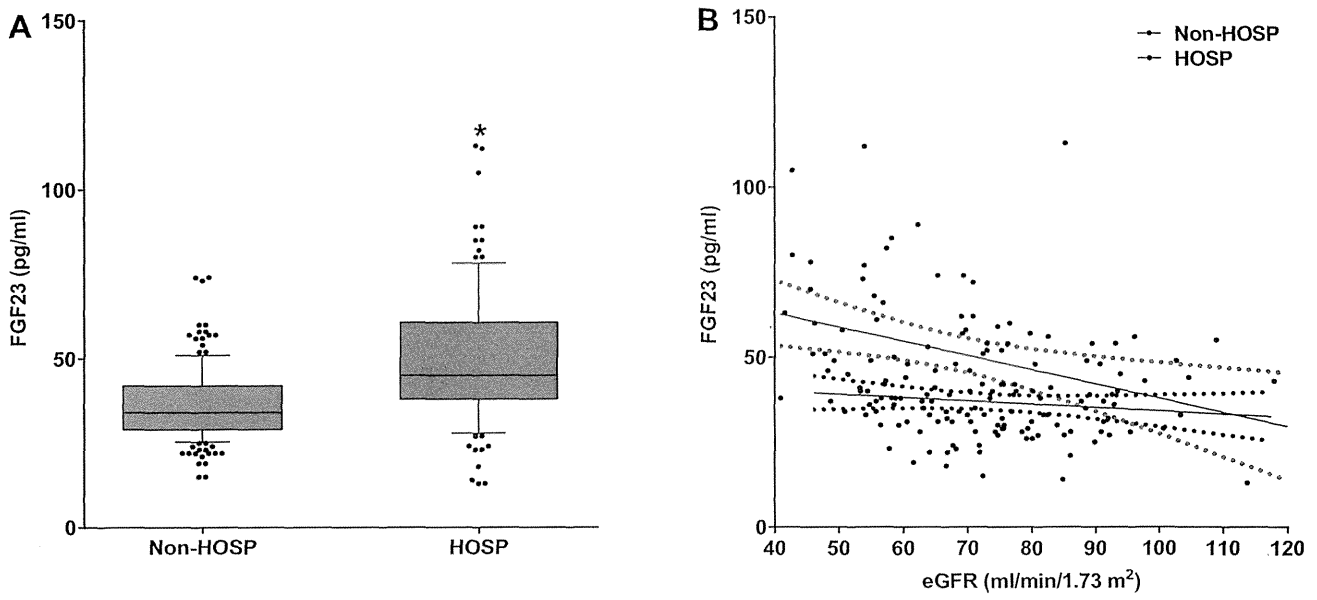

Fig. 1. Serum fibroblast growth factor (FGF)23 levels in patients with nonischemic cardiac disease (NICD). *A*: serum FGF23 levels in NICD patients. Red and blue squares show patients with a history of heart failure hospitalization (HOSP group) and without any history of HF hospitalization (non-HOSP group), respectively. $*P < 0.0001$, non-HOSP group vs. HOSP group. Values are shown as medians and 5–95% distribution. *B*: relationships between estimated glomerular filtration rate (eGFR) and serum FGF23 levels in NICD patients with and without a history of heart failure hospitalization. Graphs indicate the correlations between serum FGF23 levels and eGFR. Red and blue plots and lines show patients in the HOSP and non-HOSP groups, respectively. There was no difference in the relationship between eGFR and serum FGF23 levels in the non-HOSP group ($r = 0.129$, $P = 0.224$). In contrast, a steeper relationship between eGFR and serum FGF23 levels was found in patients in the HOSP group ($r = 0.342$, $P = 0.005$ in the HOSP group, group difference, $P = 0.042$).

noassays (R&D Systems). The plasma intact parathoroid hormone level was measured by an electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan). eGFR (in $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) was calculated according to the following published equation for Japanese individuals: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for women) (18). Both plasma renin activity and aldosterone concentration were measured by radioimmunoassays (Fujirebio, Tokyo, Japan). Urinary creatinine and phosphate concentrations were obtained via medical records. As previously described (2), the tubular reabsorption of phosphate (TRP) was calculated using the following equation: $1 - (U_P/P_P) \times (P_{Cr}/U_{Cr})$, where U_P and P_P are urine and plasma phosphate concentrations, respectively, and P_{Cr} and U_{Cr} are urine and plasma creatinine concentrations, respectively. The renal tubular maximum reabsorption rate of phosphate to GFR (TmP/GFR) was calculated according to the following equation: $TRP \times P_P$ (if $TRP \leq 0.86$) or $0.3 \times TRP/[1 - (0.8 \times TRP)] \times P_P$ (if $TRP > 0.86$).

Echocardiography. We retrospectively reviewed the data of echocardiography of the enrolled patients via their medical records. Left ventricular (LV) dimensions, left atrium volume, and wall thickness were measured according to American Society of Echocardiography guidelines (16). LV ejection fraction (LVEF) was measured using the Simpson biplane method or the semiquantitative two-dimensional visual estimate method as previously described (22). LV end-diastolic volume and mass were calculated using the Teichholz and Devereux formula (3, 27), respectively.

Right heart catheterization. The indication of right heart catheterization (RHC) was determined by the need of disease managements for an assessment for the HF severity for hospitalized patients. We collected the data from all enrolled patients who underwent RHC. Standard RHC was performed using a Swan-Ganz catheter (Goodman, Tokyo, Japan). Cardiac output was calculated with the direct Fick method as O_2 consumption divided by the arteriovenous O_2 difference, as previously described (15). Briefly, O_2 consumption was obtained by a respiratory gas analyzer (Aeromonitor AE-300S, Minato Medical Science, Osaka, Japan). Levels of hemoglobin, O_2 saturation, and Po_2 (arterial and venous Po_2) were measured by a blood gas analyzer (OSM3, Radiometer, Copenhagen, Denmark). Blood from a vein was sampled from the pulmonary artery.

Clinical outcomes. After the enrollment in this study, we investigated cardiovascular death, heart transplantation, implantation of a LV assist device, and rehospitalization for HF over 1 yr through medical chart review or a letter. Cardiovascular events were defined as a composite of cardiovascular death, implantation of a LV assist device, or rehospitalization for HF.

Ethics. Written informed consent was obtained from all subjects. This study was approved by our institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis. Data are expressed as medians and interquartile ranges (IQRs). Between-group differences were compared with a χ^2-test for categorical variables. Student's *t*-test (normalized distributed data) or Wilcoxon's rank sum test (non-normalized distributed data) was used for the comparison of continuous variables between two groups. Pearson's correlation coefficient analysis or Spearman's rank correlation coefficient analysis and linear regression were used to assess the relationships between FGF23 levels and other variables. The multiple linear regression model was used to test multiple covariates. All variables with $P < 0.10$ in univariate analysis were selected and performed into the multivariable models. All tests were

Table 2. *Comparison of serum FGF23 levels in non-HF and HF patients*

Nonhospitalized group versus hospitalized group	Adjusted Mean Difference	95% Confidence Interval	*P* Value
Model 1	−7.260	−9.877, −4.642	<0.0001
Model 2	−6.190	−8.802, −3.578	<0.0001
Model 3	−3.989	−6.771, −1.206	0.005

Model 1 was adjusted for age and sex, *model 2* was adjusted for age, sex, and eGFR, and *model 3* was adjusted for age, sex, eGFR, and use of loop diuretics (yes = 1).

Table 3. *Univariate and multivariate analyses of serum FGF23 levels in laboratory data*

	Univariate Analysis			Multivariate Analysis		
Variables	Regression coefficient, pg/ml	95% confidence interval	*P* value	Regression coefficient, pg/ml	95% confidence interval	*P* value
eGFR	−0.329	−0.495, −0.163	0.0001	0.237	−0.510, 0.037	0.089
Troponin T	235.8	2.741, 468.9	0.047	70.40	−185.9, 326.7	0.587
TNF-α	2.227	0.260, 4.194	0.027	2.715	−0.538, 5.968	0.101
IL-6	0.628	−0.580, 1.837	0.306			
White blood cell count	0.0003	−0.0013, 0.0019	0.747			
C-reactive protein	2.579	−5.967, 11.13	0.552			
Plasma aldosterone concentration	0.384	0.194, 0.573	0.0001	0.345	0.122, 0.567	0.003

n = 156 patients total. In the multivariate model, age and sex were adjusted.

two-tailed, and P values of <0.05 were considered significant. These analyses were performed with JMP 10 (SAS Institute, Cary, NC).

RESULTS

Relationship between clinical features of NICD-induced HF patients and serum FGF23 levels. We excluded 25 CAD patients from this study according to the aim of this study and the criteria. Of the remaining 156 patients, we divided the patients into above and below median FGF23 levels (39.1 pg/ml), as shown in Table 1 (above or below median groups). Between these two groups, higher prevalence of New York Heart Association (NYHA) class III-IV at admission (53% vs. 33%, P = 0.015) and HF hospitalization (60% vs. 23%, P < 0.0001) were frequently observed in the above median group. We also observed a higher proportion of patients with cardiomyopathy (62% vs. 28%, P < 0.0001) and atrial fibrillation (40% vs. 22%, P = 0.015) and a lower systolic blood pressure [104 (IQR: 93–118) vs. 116 (IQR: 107–126) mmHg, P < 0.0001] in the above median group. Loop diuretics were frequently used in the above median group compared with the below median group (62% vs. 22%, P < 0.0001). Aldosterone antagonists were frequently used in the above median group compared with the below median group (58% vs. 9%, P < 0.0001). eGFR was on the statistical border between the two groups (P = 0.060). Blood levels of troponin T, TNF-α, IL-6, and aldosterone were higher in the above median group than in the below median group (Table 1). Echocardiography revealed a lower degree of LVEF in the above median group [38 (IQR: 23–60)% vs. 63 (45–68)%, P < 0.0001]. There were no significant differences regarding the LV end-diastolic volume index, relative wall thickness, and left atrial volume index between the groups. The subtype of cardiac disease is shown in Table. 1. There was no patient with a history of kidney transplant or kidney disease. TmP/GFR was measured in 104 patients, and we found no differences between the above and below median FGF23 groups (Table 1). In the analysis between serum FGF23 levels and physiological variables, serum FGF23 levels were related to mean blood pressure (r = −0.281, P = 0.003) but were not related to heart rate (r = 0.090, P = 0.267) and body mass index (r = −0.017, P = 0.830).

Serum FGF23 levels in NICD-induced HF patients. We investigated serum FGF23 levels in patients with or without a history of HF hospitalization (hospitalized or nonhospitalized groups, respectively). Serum FGF23 levels were higher in the hospitalized group compared with the nonhospitalized group [34.7 (IQR: 29.6–42.4) vs. 46.8 (IQR: 38.8–62.7), P < 0.0001; Fig. 1*A*]. Figure 1*B* shows the relationship between eGFR and FGF23 levels in the hospitalized and nonhospitalized groups. There were no differences in the relationship between eGFR and serum FGF23 levels in the nonhospitalized group (r = 0.129, P = 0.224). In contrast, as eGFR decreased, serum FGF23 levels were elevated at a higher rate for the hospitalized group than for the nonhospitalized group (r = 0.342, P = 0.005 in the hospitalized group, group difference, P = 0.042). Table 2 shows the multivariate linear model of serum FGF23 levels in these groups. Serum FGF23 levels were higher in the hospitalized group even after adjustments of age, sex, eGFR, and the use of loop diuretics. TmP/GFR did not differ between the hospitalized and nonhospitalized groups.

Predictor of serum FGF23 levels in NICD-induced HF patients. Table 3 shows the relationships between serum FGF23 levels and other laboratory markers. eGFR, troponin T, TNF-α, and plasma aldosterone concentration were related to FGF23 levels in the univariate analysis. In the multivariate analysis, plasma aldosterone concentration was the only factor related to serum FGF23 levels (P = 0.003). Table 4 shows the relationship of serum FGF23 levels with ventricular structural and functional values as assessed by echocardiography. In the multivariate analysis, LVEF was the only factor related to serum FGF23 levels (P = 0.020). Table 5 shows the multivariate analysis for the relationship of serum FGF23 levels with history of HF hospitalization, plasma aldosterone concentration, LVEF, and use of diuretics after adjusting for age, sex,

Table 4. *Univariate and multivariate analyses of FGF23 in echocardiography data*

	Univariate Analysis			Multivariate Analysis		
Variables	Regression coefficient, pg/ml	95% confidence interval	*P* value	Regression coefficient, pg/ml	95% confidence interval	*P* value
LVEDV index	0.083	0.030, 0.136	0.003	0.032	−0.054, 0.118	0.462
LVEF	−0.348	−0.500, −0.197	<0.0001	−0.251	−0.461, −0.040	0.020
Relative wall thickness	−15.66	−33.82, 2.496	0.090	11.35	−11.84, 34.54	0.334

In the multivariate model, age, sex, and eGFR were adjusted.

Table 5. *Multivariate analysis of FGF23*

Variables	Multivariate Analysis		
	Regression coefficient, pg/ml	95% confidence interval	*P* value
History of HF hospitalization	−4.330	−8.250, −0.411	0.031
Plasma aldosterone concentration	0.236	0.041, 0.431	0.018
LVEF	−0.141	−0.344, 0.063	0.174
Use of loop diuretics	−3.042	−0.629, 0.201	0.066

n = 156 patients total. In the multivariate model, age, sex, and eGFR were adjusted.

and eGFR. The history of HF hospitalization (P = 0.031) and plasma aldosterone concentration (P = 0.018) were independently related to serum FGF23 levels in this model.

Relationships of systolic function with serum FGF23 levels and other laboratory markers. To test the correlation of LVEF with the laboratory data, including serum FGF23 levels, we performed multivariate regression analyses. The results are shown in Table 6. In the multivariate model, after adjusting for age and sex, serum FGF23 levels were correlated with LVEF (P = 0.001), whereas no relationships with LVEF were found in eGFR, TNF-α, and plasma aldosterone concentration.

Relationship between serum FGF23 levels and the hemodynamic state. Table 7 shows the central hemodynamic data obtained through RHC in 127 patients. In the above median FGF23 group, the cardiac index was significantly lower compared with the below median group [2.4 (IQR: 1.9–2.7) vs. 2.7 (IQR: 2.4–3.1) $l \cdot min^{-1} \cdot m^{-2}$, P = 0.001]. Table 8 shows the relationship between serum FGF23 levels and hemodynamic values as assessed by RHC. In the multivariate analysis, the cardiac index was the only factor related to serum FGF23 levels (P = 0.018).

Predictive value of serum FGF23 levels for clinical outcomes. During the 1-yr followup term, cardiovascular events occurred in 15 patients (cardiac death: 1 patient, implantation of a LV assist device: 2 patients, and rehospitalization for HF: 12 patients). Kaplan-Meier analysis showed that the frequency of cardiovascular events were higher in the above median FGF23 group than in the below median FGF23 group (P = 0.005; Fig. 2). Even after adjustments for age, sex, and eGFR, the predictability of serum FGF23 levels for cardiovascular events persisted (Table 9).

DISCUSSION

The present study showed that serum FGF23 levels were elevated in NICD patients who had a HF hospitalization history compared with patients without any HF hospitalization history. Although it is known that the circulating FGF23 level is influenced by other variables, such as renal function (28), we prospectively measured serum FGF23 levels in patients without advanced renal impairment and confirmed the pathophysiological importance of serum FGF23 levels in patients with HF history even in the early stages of CKD. The multivariate analysis in the present study revealed that HF hospitalization history was the strongest predictor for the elevation of serum FGF23 levels in NICD. The present study also revealed that serum FGF23 levels are tightly related to plasma aldosterone levels and that systolic dysfunction and low cardiac output are tightly related to serum FGF23 levels. Taken together, we raise the possibility that such pathogenesis and risk factors for the development of HF are the determinants of serum FGF23 levels in NICD patients. In addition, among the neurohormonal parameters measured in the present study, an elevated serum FGF23 level was the only factor to predict a declining LVEF level. Furthermore, even after adjustments for age, sex, and eGFR, the serum FGF23 level was a strong predictor for future cardiovascular events in the present study. Consistent with previous studies reporting that circulating FGF23 levels can affect cardiac structure and function, our findings suggest that the progression of HF contributes to the elevation of circulating FGF23 levels, which leads to further myocardial dysfunction, potentially creating a vicious cycle.

Serum FGF23 levels in NICD-induced HF patients. There has been less evidence of circulating FGF23 levels in HF patients with preserved renal function. This study confirmed that in NICD patients, even in the early stages of CKD, serum FGF23 levels are elevated in those with a history of HF hospitalization compared with those without HF hospitalization history (Fig. 1). We also confirmed higher serum FGF23 levels in HF patients even accounting for age, sex, eGFR, and the use of diuretics (Table 2). The determinants of serum FGF23 levels have not been completely clarified in previous studies of HF patients. Our findings suggest that NICD-induced HF hospitalization itself is one of the strong determinants of serum FGF23 levels even in a population with relatively preserved renal function. Figure 1*B* shows that there was a steeper negative slope between serum FGF23 levels and eGFR in the hospitalized group compared with the nonhospitalized group, suggesting that serum FGF23 levels are elevated in HF patients even in the early stages of CKD. Although the responsible factors for the elevation of serum FGF23 levels in HF patients have been remained uncertain in previous studies, we identified high plasma aldosterone concentration (Table 3), low LVEF (Table 4), and low cardiac index (Table 8) as predictors for the elevation of serum FGF23 levels even after accounting for eGFR. Whether low cardiac output itself independently contributes to the elevation of serum FGF23 levels from renal function still remains controversial. Interestingly, we also found that in the above median FGF23 group, the percentage of patients who took a loop diuretics was higher than in the below median group (P < 0.0001; Table 1), and we can raise the possibility that decreased renal perfusion by diuretics affects serum FGF23 levels. Consisted with these findings, a previous study (9) has suggested the relationship between the use of diuretics and circulating FGF23 levels. As a speculation, we also suggest that decreasing renal perfusion

Table 6. *Multivariate linear model of LVEF in laboratory data*

Variables	Multivariate Analysis		
	Regression coefficient, pg/ml	95% confidence interval	*P* value
eGFR	0.116	−0.109, 0.341	0.308
TNF-α	0.664	−1.308, 2.635	0.506
Plasma aldosterone concentration	−0.145	−0.359, 0.070	0.184
FGF23	−0.340	−0.531, −0.150	0.001

In the multivariate model, age and sex were adjusted.

Table 7. *Right heart catheterization data*

	Below Median Group	Above Median Group	*P* Value
Right atrial pressure, mmHg	4 (IQR: 2–5)	4 (IQR: 2–5)	0.553
Mean pulmonary artery pressure, mmHg	17 (IQR: 14–20)	18 (IQR: 13–25)	0.207
Pulmonary capillary wedge pressure, mmHg	10 (IQR: 7–12)	11 (IQR: 6–17)	0.345
Cardiac index, $l \cdot min^{-1} \cdot m^{-2}$	2.7 (IQR: 2.4–3.1)	2.4 (IQR: 1.9–2.7)	0.001

Values are medians with IQRs; n = 67 patients in the below median group and 60 patients in the above median group.

induced by a low cardiac output state is one of the key factors affecting serum FGF23 levels. Although eGFR in the present study was relatively preserved (median eGFR: 73 and 69 $ml \cdot min^{-1} \cdot m^{-2}$ in below and above median FGF23 groups, respectively), the findings of steeper correlation between serum FGF23 levels and eGFR in the hospitalized group also support the hypothesis. Our findings also suggest a positive relationship between serum FGF23 levels and neurohormone activation or inflammatory markers, such as TNF-α. These findings are consistent with those of previous study (1) with the respect to the relationship between inflammatory markers and FGF23 levels in CKD patients, suggesting that inflammation is associated with an elevation of circulating FGF23 levels in HF patients. Our findings also demonstrate that there was no longer a relationship between TNF-α and serum FGF23 levels in multivariate analysis (Table 3), with a possible explanation that there might be an interplay between several factors, such as neurohormonal activation and inflammation, for elevating serum FGF23 levels. Interestingly, a more recent study (17) has raised the possibility of endogenous Klotho expression in arteries. Inflammatory cytokines, such as TNF-α, downregulate Klotho expression in the kidney through NF-κB (19) or suppress the expression of both Klotho and FGF receptor in an in vitro study (17). It is worth considering the interplay among neurohormonal activation, inflammatory cytokines, vascular Klotho, and circulating FGF23 levels in patients with HF, and further investigation will be necessary to solve it. Taken together, our results could not explain the mechanism of elevating serum FGF23 levels by a single factor. Indeed, in multivariate analysis (Table 5), LVEF was not correlated with serum FGF23 levels. In addition, we found that aldosterone antagonists were frequently used in the above median group compared with the below median group (58% vs. 9%, $P < 0.001$). This might also influence the higher plasma aldosterone concentration in the above median group. We suggest that such complex interaction or underlying conditions predisposing to the development of HF contribute to the elevation of serum FGF23 levels in NICD patients.

Between the hospitalized and nonhospitalized groups, the differences of serum FGF23 levels were statistically significant, but small. Because of such low circulating levels of FGF23, it is worth to consider whether FGF23 is a "pure" endocrine factor to play a role on cardiac remodeling. Interestingly, some studies (5, 14) have suggested the presence of circulating progenitor cells, which are capable of differentiating into osteoblasts. These findings facilitated us to the further investigation to elucidate the relationship between circulating progenitor cells and serum FGF23 levels. The relationships between such a low level of circulating FGF23 and FGF23 signaling in cardiomyocytes or the endothelium and the interaction with vascular Klotho have also remained uncertain; further investigation will be needed to determine their relationships.

In addition, a clinical study (7) has suggested that circulating FGF23 levels are associated with the degree of LV hypertrophy in patients with CKD. In this study, we determined that serum FGF23 levels were significantly correlated with LV systolic function and cardiac output but were not related to the degree of cardiac hypertrophy. Because the stages of CKD in our patients were relatively early, these differences from previous studies also raise the possibilities that CKD stages and serum FGF23 levels are correlated with the cardiac phenotype. In accordance with this finding, the phosphate reabsorption, as indicated by TmP/GFR, did not differ between the above and below median groups in the present study. This finding suggests that serum FGF23 levels were relatively lower than advanced CKD patients because of our focus on NICD patients with early stages of CKD.

Limitations. We acknowledge that our study has some limitations that merit noting. First, this study was a single-center study, which poses a possible bias risk regarding HF severity and etiologies. Second, although differences in the etiologies of NICD were found between the below and above median FGF23 groups, the present study included valvular disease patients with milder HF symptoms, who hospitalized for an elective catheter test. These variances influence the differences of HF etiologies between the below and above median FGF23 groups. Age differences were observed between the above and below median FGF23 groups. Even after accounting for the age differences in the multivariate models, we confirmed that

Table 8. *Univariate and multivariate analyses of FGF23 in right heart catheterization data*

	Univariate Analysis			Multivariate Analysis		
Variables	Regression coefficient, pg/ml	95% confidence interval	*P* value	Regression coefficient, pg/ml	95% confidence interval	*P* value
Right atrial pressure	1.547	0.494, 2.601	0.004	0.612	−0.594, 1.820	0.317
Mean pulmonary artery pressure	0.503	0.120, 0.885	0.010	0.501	−0.095, 1.097	0.098
Pulmonary capillary wedge pressure	0.612	0.083, 1.142	0.024	−0.551	−1.450, 0.347	0.227
Cardiac index	−6.697	−10.73, −2.669	0.001	−4.532	−0.894, −0.126	0.044

n = 127 patients total. In the multivariate model, age, sex, and eGFR were adjusted.

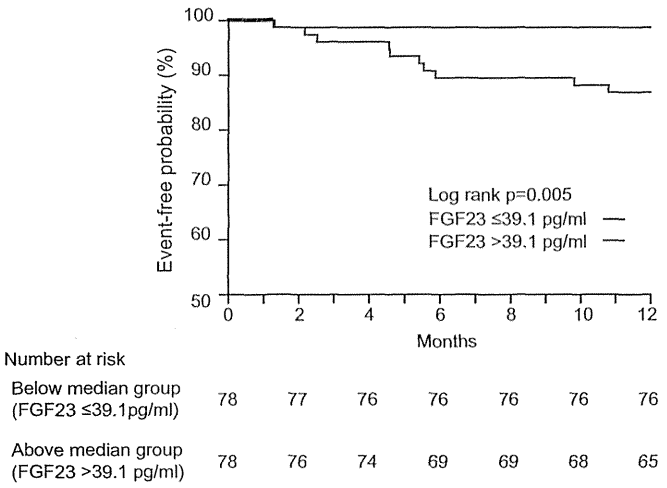

Fig. 2. Kaplan-Meier analysis for cardiovascular events in the below and above median FGF23 groups. Red and blue lines show the below and above median FGF23 groups, respectively. Kaplan-Meier analysis showed that the frequency of cardiovascular events was higher in the above median FGF23 group than in the below median FGF23 group ($P = 0.005$).

serum FGF23 levels were higher in patients with HF hospitalization history. We also demonstrated the predictive value of serum FGF23 levels for clinical outcome even after accounting for age differences in the multivariate models. There were a few patients with extreme outlier values, as shown in Fig. 1*B*. No confounding factor for the elevation of serum FGF23 levels, such as a past history of bone metabolic disease, was found in patients. However, after the exclusion of patients with outlier values, a similar tendency was found ($r = 0.411$, $P = 0.0008$). Urine tests were not performed in all enrolled patients, because the results of urine tests were taken from a part of clinical routine tests. Nevertheless, the subanalysis for TmP/GFR might provide us some information regarding relative levels of serum FGF23 levels.

Conclusions. Serum FGF23 levels were elevated in NICD patients with a history of HF hospitalization even though their renal function was relatively preserved. We demonstrated that the underlying substrates of HF, such as cardiac dysfunction and neurohormonal activation, are associated with an elevation of serum FGF23 levels in our patients and suggest that the progression of HF itself contributes to the elevation of circulating FGF23 levels even in early CKD, which leads to further myocardial dysfunction, potentially creating a vicious cycle.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.I., H.T., A.F., Y.S., T.O., T.H., and M.A. analyzed data; M.I., H.T., A.F., Y.S., T.O., T.H., and M.A. interpreted results of experiments; M.I. and H.T. prepared figures; M.I., H.T., and M.K. drafted manuscript; H.T. and M.K. conception and design of research; H.A., T.H., H.K., T.A., and M.K. edited and revised manuscript; M.K. approved final version of manuscript.

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Table 9. *Predictive value of serum FGF23 levels for cardiovascular events*

Above Median Value Versus Below Median Value	Hazard Ratios	95% Confidence Interval	*P* Value
Unadjusted	1.05	1.03, 1.07	<0.0001
Model 1	1.05	1.03, 1.08	<0.0001
Model 2	1.06	1.03, 1.09	<0.0001

Model 1 was adjusted for age and sex, and *model 2* was adjusted for age, sex, and eGFR.

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Original article

Hyponatremia is an independent predictor of adverse clinical outcomes in hospitalized patients due to worsening heart failure

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ABSTRACT

Background and purpose: Hyponatremia is common and is associated with poor in-hospital outcomes in patients hospitalized with heart failure (HF). However, it is unknown whether hyponatremia is associated with long-term adverse outcomes. The purpose of this study was to clarify the characteristics, clinical status on admission, and management during hospitalization according to the serum sodium concentration on admission, and determine whether hyponatremia was associated with in-hospital as well as long-term outcomes in 1677 patients hospitalized with worsening HF on index hospitalization registered in the database of the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD).

Methods and subjects: We studied the characteristics and in-hospital treatment in 1659 patients hospitalized with worsening HF by using the JCARE-CARD database. Patients were divided into 2 groups according to serum sodium concentration on admission <135 mEq/mL (n = 176; 10.6%) or ≥135 mEq/mL (n = 1483; 89.4%).

Results: The mean age was 70.7 years and 59.2% were male. Etiology was ischemic in 33.9% and mean left ventricular ejection fraction was 42.4%. After adjustment for covariates, hyponatremia was independently associated with in-hospital death [adjusted odds ratio (OR) 2.453, 95% confidence interval (CI) 1.265–4.755, p = 0.008]. It was significantly associated also with adverse long-term (mean 2.1 ± 0.8 years) outcomes including all-cause death (OR 1.952, 95% CI 1.433–2.657), cardiac death (OR 2.053, 95% CI 1.413–2.983), and rehospitalization due to worsening HF (OR 1.488, 95% CI 1.134–1.953).

Conclusions: Hyponatremia was independently associated with not only in-hospital but also long-term adverse outcomes in patients hospitalized with worsening HF.

Introduction

Hyponatremia, usually defined as a serum sodium concentration <135 mEq/L, has been observed in ~20% and consistently an independent risk for all-cause mortality as well as longer length of stay in hospitalized patients with worsening heart failure (HF) [1–4]. However, most of these studies have been focused on short-term outcome with up to 90 days of follow-up. A recent study using a large individual patient data meta-analysis demonstrated that hyponatremia is a determinant of all-cause death during the follow-up of 3 years [3]. This study analyzed only all-cause death and could not include cardiac death or hospitalization due to worsening HF for an inherent limitation of meta-analysis using the incorporated data from both randomized trials and observational studies [3]. Therefore, little information has been available regarding the relationship between serum sodium concentration and adverse outcomes including cardiac death and hospitalization due to worsening HF. Moreover, most of these previous studies were performed mainly in the USA and Europe. Therefore, the impact of hyponatremia on outcomes has not been assessed in a broad cohort of HF patients encountered in routine clinical practice in Japan.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) studied the characteristics, management, and the outcomes including death and rehospitalization in a broad sample of patients hospitalized with worsening HF in Japan [5–13]. The

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JCARE-CARD prospectively enrolled patients admitted with worsening HF in a web-based registry at 164 participating hospitals.

The objectives of this study were to clarify the characteristics of patients, clinical status on admission, and management during hospitalization according to the serum sodium concentration on admission, and determine whether hyponatremia was associated with in-hospital as well as long-term outcomes in 1677 patients hospitalized with worsening HF on index hospitalization registered in the JCARE-CARD database [14,15].

Materials and methods

The details of the JCARE-CARD have been described previously [5,8–10,14,15]. Briefly, it registered the patients hospitalized due to worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) laboratory data; and (9) treatments including discharge medications. The data were entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp).

Using the database of 1677 patients registered in JCARE-CARD [14,15], the present study analyzed the data of (1) patient demographics, clinical characteristics, vital signs, and laboratory data on admission [age, sex, cause of HF, medical history, prior hospitalization due to HF, New York Heart Association (NYHA) functional class, symptoms and signs, vital signs, laboratory data including serum sodium concentration, and echocardiographic parameters], (2) medication use before admission [angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), βblocker, diuretics, digitalis, Ca channel blocker, nitrate, antiarrhythmics, aspirin, warfarin, and statin], (3) in-hospital management (diuretics, inotropic agents, vasodilator agents, and non-pharmacological procedures), (4) clinical status during index hospitalization [admission from emergency room, stay at coronary care unit (CCU), length of CCU stay, length of stay, and in-hospital death], and (5) long-term outcomes (all-cause death, cardiac death, and rehospitalization due to HF). Eighteen (1.1%) patients were excluded with missing data of serum sodium concentration on admission, resulting in 1659 patients included in this analysis. Hyponatremia was defined as a serum sodium concentration on admission <135 mEq/L.

Statistical analysis

Patient characteristics and treatments were compared using Pearson chi-square test for categorical variables, Student's *t*-test for normally distributed continuous variables, and Mann–Whitney *U* test for continuous variables not normally distributed. Multivariable logistic regression was performed to determine the odds of in-hospital mortality. The covariates including medical history [hypertension, diabetes mellitus, ventricular tachycardia/ventricular fibrillation (VT/VF)], NYHA functional class on admission, medication use before hospitalization (ACE inhibitor, diuretics, aldosterone antagonist, and warfarin), laboratory data on admission [estimated glomerular filtration rate (eGFR), hemoglobin, and plasma B-type natriuretic peptide (BNP)] were used in developing the multivariable logistic regression model. The relationship between serum sodium concentration and long-term outcomes was evaluated among patients with the post-discharge Cox proportional hazard models. Relative risk was calculated after adjustment with covariables including age, ischemic etiology, medical history (hypertension, diabetes mellitus, sustained VT/VF, and prior stroke), NYHA functional class on admission, medication use on admission (ACE-inhibitor or ARB, βblocker, diuretics, aldosterone antagonist, and warfarin), and laboratory data on admission (eGFR, hemoglobin, and plasma BNP). SPSS version 16.0 J for Windows (Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics

The distribution of serum sodium concentration on admission in the total cohort of study patients is shown in Fig. 1. The mean and median serum sodium concentrations on admission were 139.6 ± 4.5 mEq/L and 140.0 mEq/L, respectively, ranging from 114.0 to 156.0 mEq/L. Out of 1659 patients, 176 patients (10.6%) had hyponatremia, defined as serum sodium concentration on admission <135 mEq/L.

Clinical characteristics for the total cohort of patients and those classified into 2 groups according to the presence or absence of hyponatremia are shown in Table 1. The mean age was 70.7 ± 13.5 years and 59.3% were men. The causes of HF were ischemic heart disease in 33.9%, valvular heart disease in 28.1%, hypertensive heart disease in 26.4%, and dilated cardiomyopathy in 16.9%. As expected, mean serum sodium concentration was 130.4 mEq/L in patients with hyponatremia and 140.7 mEq/L without it.

The mean age and causes of HF were comparable between 2 groups. Patients with hyponatremia more frequently had diabetes mellitus, prior stroke, sustained VT/VF, and prior hospitalization due to HF, but less hypertension. They had worse NYHA functional class and lower blood pressure on admission. eGFR and hemoglobin concentration were significantly lower in these patients and plasma BNP levels were significantly higher. Echocardiographic parameters including left ventricular ejection fraction (LVEF) were comparable between groups.

Medication use before hospitalization was compared between groups of patients (Table 2). The use of ACE inhibitor, ARB, and βblocker was comparable between groups. The use of loop diuretics, aldosterone antagonist, antiarrhythmics, and warfarin was significantly higher in patients with hyponatremia.

In-hospital management

The use of thiazide and spironolactone was significantly higher in patients with hyponatremia. Patients with hyponatremia were more often treated with catecholamines, PDE III inhibitor, and carperitide. Mechanical ventilation, PCI, and hemodialysis were also more frequently used in them (Table 3).

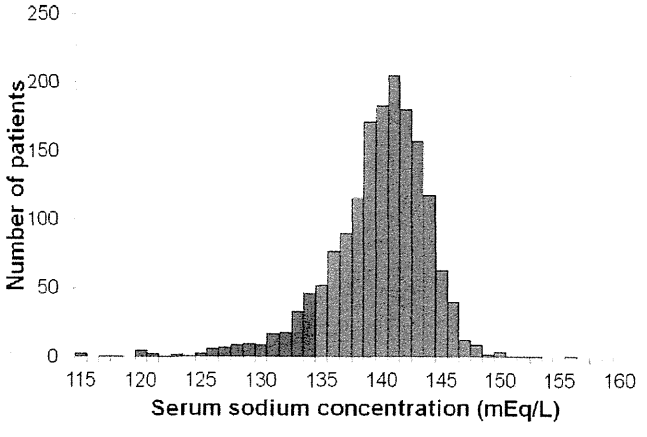

Fig. 1. Distribution of serum sodium concentration on admission in patients hospitalized with worsening heart failure.

Table 1
Patient characteristics according to the presence or absence of hyponatremia.

Characteristics	Total $n=1659$	Hyponatremia $n=176$	No hyponatremia $n=1483$	p-Value
Na, mEq/L	139.7 ± 4.5	130.4 ± 4.4	140.7 ± 2.9	<0.001
Age, yrs (mean ± SD)	70.7 ± 13.5	69.2 ± 14.9	70.9 ± 13.4	0.200
Male, %	59.3	62.0	58.9	0.441
Causes of heart failure, %				
Ischemic	33.9	37.3	33.5	0.327
Valvular	28.1	24.1	28.5	0.229
Hypertensive	26.4	25.3	26.5	0.737
Dilated cardiomyopathy	16.9	12.7	17.4	0.122
Medical history, %				
Hypertension	52.1	43.3	53.2	0.017
Diabetes mellitus	30.0	40.0	28.8	0.003
Dyslipidemia	25.9	22.8	26.2	0.350
Hyperuricemia	49.1	50.3	49.0	0.745
Prior stroke	16.4	21.8	15.8	0.047
COPD	5.9	3.0	6.2	0.098
Smoking	37.5	33.5	38.0	0.270
Prior myocardial infarction	28.2	31.7	27.8	0.297
Atrial fibrillation	34.9	33.9	35.0	0.780
Sustained VT/VF	6.8	15.7	5.8	<0.001
Prior hospitalization, %	49.8	62.4	48.4	0.001
NYHA functional class, %				
1	0.9	0.0	1.0	0.033
2	10.5	6.6	11.0	
3	45.8	41.6	46.3	
4	42.7	51.8	41.7	
Symptoms, %				
Dyspnea on effort	85.8	81.2	86.4	0.031
Dyspnea at rest	68.9	70.3	68.8	0.671
Fatigue	58.2	58.5	58.1	0.848
Signs, %				
Jugular venous distension	33.6	29.7	34.1	0.456
III sound	24.3	21.0	24.7	0.563
Rale	51.5	48.3	51.9	0.424
Edema	53.2	51.1	53.5	0.448
Lung congestion	79.4	81.1	79.2	0.707
Pleural effusion	56.5	52.6	57.0	0.266
Hemodynamics				
Heart rate, bpm	87.9 ± 24.4	84.7 ± 22.1	88.2 ± 24.6	0.165
SBP, mmHg	134.3 ± 30.3	123.0 ± 29.5	135.6 ± 30.1	<0.001
DBP, mmHg	75.4 ± 18.2	68.6 ± 17.8	76.2 ± 18.1	<0.001
Laboratory data				
eGFR, mL/min/1.73 m^2	52.5 ± 24.6	47.7 ± 28.9	53.1 ± 24.0	<0.001
Hemoglobin, g/dL	12.4 ± 4.5	11.5 ± 2.3	12.5 ± 4.7	<0.001
Plasma BNP, pg/mL	880 ± 932	1078 ± 1035	856 ± 916	0.013
Echocardiographic parameters				
LV EDD, mm	55.8 ± 10.6	54.8 ± 10.2	55.9 ± 10.6	0.174
LV ESD, mm	44.0 ± 12.5	43.3 ± 13.4	44.0 ± 12.4	0.549
LVEF, %	42.4 ± 17.9	42.0 ± 19.4	42.5 ± 17.7	0.532

COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction. Data are shown as percent or means ± SD.

Table 2
Medication use before hospitalization according to the presence or absence of hyponatremia.

	Total $n=1659$	Hyponatremia $n=176$	No hyponatremia $n=1483$	p-Value
ACE inhibitor, %	26.5	32.4	25.8	0.062
ARB, %	28.7	25.6	29.1	0.333
ACE inhibitor or ARB, %	51.0	51.1	51.0	0.968
βblocker, %	22.1	23.9	21.9	0.556
Diuretics, %	61.5	67.6	60.8	0.077
Loop diuretics, %	54.3	61.4	53.5	0.047
Aldosterone antagonist, %	24.1	36.9	22.6	<0.001
Digitalis, %	26.4	27.8	26.3	0.651
Ca channel blocker, %	24.4	21.6	24.7	0.367
Nitrates, %	22.3	23.3	22.2	0.743
Antiarrhythmics, %	13.9	20.5	13.1	0.007
Aspirin, %	34.3	35.8	34.1	0.661
Warfarin, %	27.5	37.5	26.3	0.002
Statin, %	16.2	17.0	16.1	0.752

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.