than other drugs for acute rate-control therapy in patients with AF/AFL and LV dysfunction because it is faster-acting and shows greater selectivity for β1 receptors than esmolol, propranolol or amiodarone. In addition, this study was intended to test the usefulness of landiolol in acute rate-control therapy with up to 5 days of follow-up. Therefore, the medium- and long-term prognosis of these patients after treatment with landiolol should be studied in future.

Conclusions

In the treatment of AF/AFL in patients with LV dysfunction, landiolol rapidly decreased the HR in approximately 50% of the patients, and was more effective for urgent HR control than digoxin, without an increase in the incidence of adverse events. Landiolol is an ultra-short-acting, highly cardioselective intravenous β-blocker that could be a promising drug for controlling rapid HR in patients with AF/AFL and LV dysfunction.

Acknowledgments

The authors thank all of the investigators and site staff who participated in this clinical trial.

Disclosures

This study was funded by Ono Pharmaceutical Co Ltd (Osaka, Japan). R.N., K.K., H.I., H.A., Y.S., T.Y., W.S., T.A., M.K., A.S., T.I., Y.I., T.D., and M.H. have received consulting fees from Ono Pharmaceutical. K.F., T.N., and T.O. are employees of Ono Pharmaceutical.

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Appendix

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Supplementary Files

Supplementary File 1

Table S1. Subjective Symptoms and Objective Findings in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

Figure S1. Distribution of levels of B-type natriuretic peptide (BNP).

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-12-1618

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2013) 15, 166–175
doi:10.1093/eurjhf/hfs206

Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure

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Received 19 July 2012; revised 11 September 2012; accepted 30 November 2012

Aims The diagnostic performance of cardiac magnetic resonance (CMR) has not been compared with that of other imaging modalities. Therefore, this study investigated the diagnostic capabilities of CMR and endomyocardial biopsy (EMB) in patients with heart failure (HF).

Methods and results We studied 136 patients with cardiomyopathy who underwent both CMR and EMB. Independent diagnoses were made according to the results of (i) CMR alone; (ii) EMB alone; (iii) clinical data plus echocardiogram; (iv) clinical data, echocardiogram, plus CMR; and (v) clinical data, echocardiogram, plus EMB. These diagnoses were then compared with the final diagnosis (gold standard) that was made using the complete clinical data, including EMB and CMR. The sensitivities of the diagnosis strategies of (i–v) relative to the final diagnosis were 67, 79, 86, 97, and 100%, respectively. CMR alone demonstrated better sensitivity for cardiac sarcoidosis and greater specificity for dilated cardiomyopathy than EMB alone. CMR also tended to show better sensitivity for hypertensive heart disease. There was no difference between the diagnostic capability of CMR and EMB for hypertrophic cardiomyopathy (HCM). However, CMR showed excellent sensitivity (100%) for apical and obstructive HCM, whereas EMB displayed better sensitivity for dilated HCM. Moreover, combined diagnosis with clinical data, echocardiogram, plus CMR achieved superior agreement with the final diagnosis in comparison with EMB alone.

Conclusion Non-invasive CMR demonstrated excellent diagnostic capability for patients with HF and was as effective as or superior to EMB. In particular, the use of CMR in combination with clinical data unrelated to EMB may provide excellent diagnostic accuracy for HF.

Keywords Heart failure • CMR • Endomyocardial biopsy • Diagnosis • Aetiology • Cardiomyopathy

Introduction

Heart failure (HF) is a common clinical syndrome caused by various cardiovascular diseases.[1] Despite the discovery, development, and adoption of novel therapies for HF, the mortality and morbidity resulting from this condition have remained high and are currently increasing. Accordingly, accurate diagnosis of the underlying aetiology of HF is important for appropriate management and treatment. In addition to conventional clinical methods, gadolinium-enhanced cardiac magnetic resonance (CMR) and endomyocardial biopsy (EMB) are useful diagnostic modalities for identifying the aetiology of HF. EMB is considered

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to be the gold standard for diagnosing myocarditis as well as certain infiltrative cardiac diseases, such as amyloidosis, sarcoidosis, and haemochromatosis. In contrast, CMR is also required to identify patients with cardiomyopathy accurately, according to the Consensus Panel Report.[2] CMR is a non-invasive, accurate, and reproducible imaging technique that can be used to evaluate cardiac morphology and function, and provide valuable information for tissue characterization. In addition, several studies have suggested that CMR techniques using late-gadolinium enhancement (LGE) are useful for diagnosing various types of cardiomyopathies. Indeed, both CMR and EMB have demonstrated good performance in patients with troponin-positive acute chest pain but without coronary artery disease.[3] However, there have been no reports directly comparing the diagnostic utility of CMR and EMB in patients with HF.

Therefore, we compared the diagnostic capability of CMR and EMB in HF patients and also assessed the diagnostic performance of the combined use of CMR and all clinical data in comparison with EMB alone.

Methods

Selection of patients

A total of 1034 consecutive patients with HF of unknown aetiology were evaluated between January 2007 and July 2009. Patients who were admitted to our institution for the management of HF, who had LV hypertrophy and/or LV dysfunction, and who had received EMB and LGE CMR were included in this study. Patients were excluded if they had one or more of the following conditions: substantial valvular or ischaemic heart disease; congenital heart disease; constrictive pericarditis; idiopathic restrictive cardiomyopathy; an ambiguous final diagnosis; dilated cardiomyopathy (DCM) with an LVEF > 55%; poor-quality CMR; or an inadequate myocardial biopsy. Of the patients examined, 25 were given an ambiguous final diagnosis for the following reasons: 17 patients did not receive sufficient detailed investigations to reach the final diagnosis; 3 patients were suspected as having arrhythmogenic right ventricular cardiomyopathy (ARVC) but they did not fulfil the Task Force Criteria;[4] 3 patients were suspected as having dilated hypertrophic cardiomyopathy (HCM) but hypertrophic stage was not detected; and 2 patients were diagnosed as LV non-compaction and we excluded these patients because EMB cannot diagnose this condition. As a result, we enrolled 136 patients in this study (*Figure 1*).

For all patients, a careful medical history was collected and physical examinations, laboratory tests, echocardiography, coronary angiography, and right heart catheterization were performed. EMB and CMR were also performed in all patients to evaluate evidence of HF. We identified the aetiology of HF using all possible diagnostic approaches in addition to EMB and CMR.

This study was approved by our Institutional Research Ethics Committee. The Committee decided that informed consent from the 136 subjects was not required according to the Japanese Clinical Research Guidelines because this was a retrospective, observational study. Instead, we made a public announcement as per the request of the Ethics Committee.

Aetiology of cardiomyopathy

According to the clinical data, echocardiogram, CMR, and EMB, six diagnoses were made for each patient, including (i) CMR diagnosis; (ii) EMB diagnosis; (iii) the combined diagnosis with clinical data

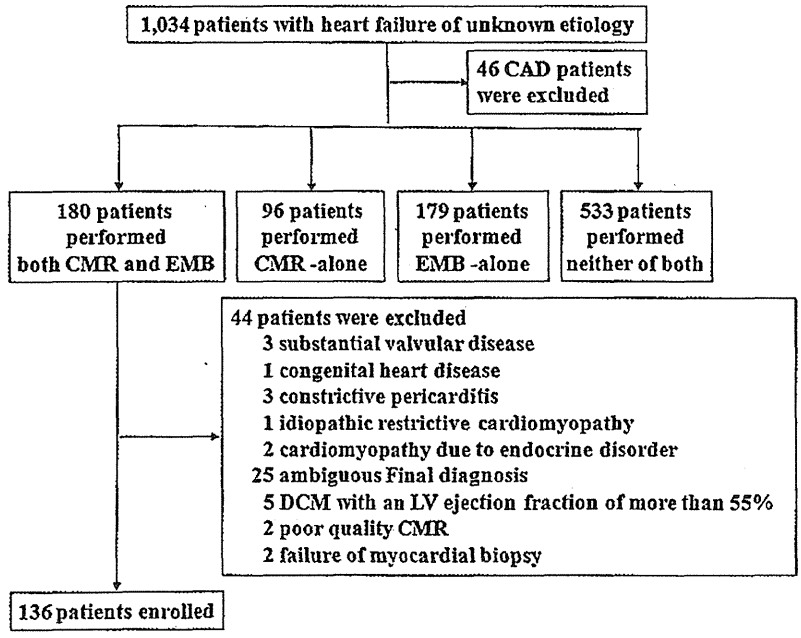

Figure 1 Study profile. Flow chart of the 1034 consecutive patients with heart failure of unknown aetiology admitted to our institution. The chart shows the immediate exclusion of cardiomyopathy due to significant coronary artery disease (CAD) and the further management of these patients. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy.

plus echocardiogram; (iv) the combined diagnosis with clinical data, echocardiogram, plus CMR; (v) the combined diagnosis with clinical data, echocardiogram, plus EMB; and (vi) the final diagnosis. The CMR and EMB diagnoses (i and ii) were established according to the results of CMR or EMB alone, and the investigators were blinded to all of the other data. Clinical data were defined as any method that could be used to diagnose HF other than echocardiography, CMR, or EMB, such as the collection of a patient's medical history, laboratory tests, scintigraphy, and coronary angiography. The final diagnosis (vi) was made prior to patient discharge by an expert team of cardiologists using all of the available data, including the results of EMB, CMR, and other diagnostic modalities. In addition, an expert team of cardiologists, who were not specialists in either CMR or EMB but could interpret these studies, was recruited. The final diagnoses were based on the recommendations of the 2008 European Society of Cardiology (ESC) report for the classification of cardiomyopathies.[5] In patients with several causes of HF, the most significant cause was associated with the diagnosis.

Each diagnosis was assigned according to one of the following categories: DCM, HCM, hypertensive heart disease (HHD), ARVC, muscular dystrophy, infiltrative myocardial disease (i.e. amyloidosis and sarcoidosis), myocarditis, or other causes.

Cardiac magnetic resonance images and analysis

Images were acquired using a 1.5 T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). The CMR protocol consisted of a cardiac functional study, spin-echo imaging, and LGE imaging, as previously described.[6] For the cardiac functional study, three standard long-axis slices and a stack of contiguous short-axis slices (slice thickness, 6 mm; slice gap, 4 mm) were acquired as ECG-gated steady-state free-precession cine images with radial scans and breath-holding. T2-weighted spin-echo images were acquired using half-Fourier acquisition single shot turbo spin-echo (HASTE) before contrast injection with an echo time of 82 ms and fat saturation in the same position as the cine images. LGE images were acquired in the same positions as the cine images at 2, 5, 10, and 20 min after i.v. injection of 0.15 mmol/kg of gadolinium-diethyltriaminepentaacetic acid. The inversion delay time was 300 ms.

The cine and LGE images were evaluated by several observers who were blinded to the clinical data. The EF and volumes were measured quantitatively for the left and right ventricles according to the end-diastolic and end-systolic endocardial contours from a stack of short-axis cine images using ARGUS software. The LV mass (LVM) was calculated as the total myocardial volume multiplied by the specific gravity of the myocardium (1.05 g/mL). The ventricular end-diastolic and end-systolic volumes (EDV and ESV, respectively) and the LVM were standardized according to the body surface area (m^2). The presence, location, and extent of LGE were determined using a standard 17 segment LV model.[7] We classified the pattern of enhancement as subendocardial, midwall (longitudinal stripes), subepicardial, or transmural, as well as patchy (focal enhancement not following the coronary vascular territories) or diffuse.

Endomyocardial biopsy and analysis

Biopsy specimens were taken from the endocardium at the right interventricular septum using Technowood disposable biopsy forceps (TONOKURA IKA KOGYO CO., LTD, Tokyo, Japan) via the right internal jugular vein or right femoral vein, as described elsewhere.[8] Three to five specimens were obtained from each patient. No complications related to EMB were observed. Biopsy specimens were immediately fixed in 15% formalin for 24 h, embedded in paraffin, and cut into 4 μm thick sections. The sections were stained with haematoxylin and eosin and Masson's trichrome. Some of the EMB specimens were frozen for polymerase chain reaction (PCR) analysis for the detection of enterovirus when myocarditis was suspected. Congo red staining was added when amyloidosis was suspected. Immunohistochemistry was performed in ARVC, myocarditis, amyloidosis, dystrophic cardiomyopathy, and some cases of HCM, as appropriate.

While EMB analysis at final diagnosis was made as above using all of the other data, EMB diagnosis was evaluated using only haematoxylin and eosin and Masson's trichrome stains by several cardiac pathologists who were not aware of the clinical features of the patients in this study.

Diagnosis of cardiomyopathy by cardiac magnetic resonance or endomyocardial biopsy

The diagnosis of cardiomyopathy by CMR and EMB was based on well-established and widely accepted definitions.[9,10] A CMR diagnosis was made according to the dimensions, regional and global wall motion, wall thickness, and the presence and pattern of LGE,[11–14] whereas an EMB diagnosis was made according to the report for classification of cardiomyopathies.[4,5,15,16]

A histological diagnosis of DCM was performed by examining the following criteria: interstitial fibrosis, replacement fibrosis, inflammatory cell infiltrates, cellular hypertrophy, and myocardial cell degeneration.[17] Histopathological criteria for HCM included severe myocyte hypertrophy, myocyte disarray > 10%, plexiform fibrosis, and nuclear hypertrophy. The diagnosis of HHD was made according to the presence of moderate myocyte hypertrophy,[18] interstitial fibrosis, and the lack of myocyte disarray. The presence of non-caseating epithelioid granulomas with giant cells was considered indicative of cardiac sarcoidosis (CS).[16] The diagnosis of myocarditis was based on the Dallas criteria modified by the Japanese Circulation Society Guidelines.[19] Based on this modified version of the Dallas criteria, the immunohistochemistry was used to characterize the inflammatory infiltrates. The cut-off for mononuclear cell infiltrates was an inflammatory infiltrate count of at least 5/high power field. We confirmed the diagnoses of cardiac amyloidosis by electron microscopy and performed immunohistochemistry for amyloid typing. The histology diagnosis for ARVC was made according to the Task Force Criteria.[4]

The characteristics of DCM for CMR included dilation and impaired contraction of one or both ventricles and an LVEF <55%.[20] Moreover, the wall thickness is normal or decreased. HCM is characterized by hypertrophy of the left ventricle and occasionally the right ventricle, normal or reduced LV volume, and normal LV contraction or hypercontraction. Apical HCM was regarded as hypertrophy of the apex, and hypertrophic obstructive cardiomyopathy (HOCM) was regarded as an obstruction to the LV outflow tract. We defined dilated HCM as an LVEF ≤ 50%[21,22] and evidence of wall thickening prior to the study. Generally, dilated HCM is characterized by a relative wall thickness with a dilated LV cavity. LV hypertrophy is common in HHD, and additional common findings include a relative wall thickness with or without a dilated LV cavity. The use of CMR for CS can demonstrate certain characteristic features, such as septal thinning, ventricular dilatation, segmental systolic dysfunction, global systolic dysfunction, or ventricular aneurysm. We referred to the typical LGE pattern for diagnosis of DCM, HCM, HHD, and CS. The typical LGE pattern regarded a DCM LGE pattern as patchy or longitudinal midwall enhancement, a HCM LGE pattern as patchy and located at the LV–RV junction, a CS LGE pattern as a non-ischaemic pattern with enhancement of the midwall or epicardium at various sites, especially the anteroseptal

and inferolateral walls, and a HHD LGE pattern as similar to the DCM LGE pattern based upon a previous report.[10] Myocarditis was diagnosed when subepicardial and midwall areas demonstrated an increased signal in the T2-weighted image or when the lateral and inferolateral walls demonstrated an LGE distribution in the epicardium toward the mid myocardial wall. ARVC is characterized by regional or global dysfunction, dilatation, and focal aneurysm of the right ventricle noted in the 2010 guideline,[4] whereas amyloidosis is characterized by concentric hypertrophy with normal or reduced contractility, a thickened interatrial septum, bi-atrial dilation, and a circumferential pattern of LGE, preferentially involving the subendocardium but occasionally demonstrating a patchy transmural pattern. Dystrophic cardiomyopathy in LGE preserves the subendocardium and is more frequently located in the LV lateral wall.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD), whereas categorical variables were expressed as numbers and percentages. Comparisons between groups were performed using a two-sample *t*-test for normally distributed continuous variables and the Wilcoxon test for variables that did not demonstrate a normal distribution. For categorical variables, we used the χ^2 test and Fisher's exact test, as appropriate. For each type of cardiomyopathy, the sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence interval (CI) for the CMR diagnosis, EMB diagnosis, and combined diagnosis with clinical data, echocardiogram, plus CMR were calculated in comparison with the final diagnosis, which served as the gold standard. The PPV and NPV were computed using the following formulae: PPV = true positive/(true positive + false positive); and NPV = true negative/(true negative + false negative). Diagnostic accuracy was calculated using the following formulae: diagnostic accuracy = (true positive + true negative)/total. A comparison of the diagnostic methods was performed using McNemar's test. The analyses were performed using JMP version 7 statistical software. All of the presented 95% CI are two.

Results

Study population and patient characteristics

A total of 136 patients were studied (Supplementary material, *Table S1*). The mean age of these patients was 52 ± 17 years (range 16–81 years): 83 of the patients were male, and 18 patients suffered from AF. EMB and CMR with LGE were performed in all patients, and none of the 136 patients was diagnosed with significant coronary artery disease. The most common diagnosis was DCM (54 patients, 40%), which was followed by HCM (36 patients, 26%). The remaining 46 patients were diagnosed with a secondary cardiomyopathy or HHD. The HCM patients included 4 cases of apical hypertrophy, 11 cases of HOCM, and 15 cases of HCM in the dilated phase.

The CMR results revealed asymmetric septal hypertrophy (septal/free wall thickness ratio ≥ 1.3) in 25 patients (18%), most of whom had either HCM (84%) or HHD (12%) detailed in the Supplementary material, *Table S1*.

The median patient follow-up period was 655 days (range 243–1143 days), and no diagnoses were changed during this time.

Comparison between cardiac magnetic resonance, endomyocardial biopsy, and the combined diagnosis

The sensitivity of EMB, CMR, and the combined diagnosis with clinical data plus echocardiogram, with clinical data, echocardiogram, plus CMR, and with clinical data, echocardiogram, plus EMB was 67, 79, 86, 97, and 100% relative to the final diagnosis, respectively. *Table 1* shows the diagnostic performance of CMR, EMB, and the combined diagnosis with clinical data, echocardiogram, plus CMR. The use of CMR demonstrated a diagnostic capability comparable with EMB for all causes of HF. The highest level of sensitivity of EMB was for DCM (89%) followed by HCM (75%) and HHD (36%) (*Table 2*), whereas the greatest sensitivity of CMR was observed for DCM (83%) followed by HCM (81%) and CS (76%). Furthermore, to explore the relative merits of CMR vs. EMB, we investigated indications of EMB noted in the 2007 guidelines.[23] EMB demonstrated a better diagnostic yield for DCM and dilated HCM, whereas CMR demonstrated better diagnostic performance for cases of CS and HHD even when the indication for EMB was a class I. The diagnostic analysis is listed in *Table 3*. We gave six patients with dilated HCM an incorrect diagnosis of CS and also gave five patients with HHD an incorrect diagnosis of DCM using CMR. In contrast, we tended to misdiagnose CS and HHD as DCM and HCM as HHD when using EMB. Specifically, the six patients with HCM who were misdiagnosed for HHD by EMB included three patients with HOCM diagnoses, two with apical HCM diagnoses, and one with a diagnosis of dilated HCM. *Table 2* shows the sensitivity and specificity for the use of EMB, CMR, and the combined diagnosis with clinical data, echocardiogram, plus CMR. Overall, CMR demonstrated increased specificity for DCM compared with EMB, and CMR also tended to be more sensitive for the diagnosis of CS and HHD. In contrast, EMB demonstrated lower sensitivity than CMR for most diagnoses, with the exception of DCM.

We also examined the diagnostic accuracy of CMR, EMB, and the combined diagnosis with clinical data, echocardiogram, plus CMR (*Table 2*). The sensitivity of the combined diagnosis with clinical data, echocardiogram, plus CMR was greater than that of EMB for the detection of HCM, CS, and HHD. The agreement of both CMR and EMB with a final diagnosis of DCM, HCM, CS, and HHD was noted to be 72, 58, 23, and 21%, respectively (*Figure 2*). Conversely, both CMR and EMB misdiagnosed 6, 3, 12, and 21% of patients with DCM, HCM, CS, and HHD, respectively. Importantly, all of the patients who received accurate diagnoses with EMB alone were also correctly diagnosed using the combined diagnosis with clinical data, echocardiogram, plus CMR.

Characteristics and details of cardiac magnetic resonance

We analysed the frequency of the use of the typical LGE pattern only in cases in which we diagnosed DCM, HCM, CS, and HHD. The CMR results revealed a DCM LGE pattern, HCM LGE pattern, CS LGE pattern, or HHD LGE pattern in 78, 53, 82, and 79% of the patients with DCM, HCM, CS, and HHD, respectively (*Figure 3*). In addition, the patients with typical LGE patterns were more likely to receive an accurate diagnosis. LGE in the papillary

Table 1 Agreement of endomyocardial biopsy, cardiac magnetic resonance, or combined diagnosis with clinical data, echocardiogram, plus cardiac magnetic resonance with final diagnosis in 136 patients based on endomyocardial biopsy indication

Final diagnoses, *n*	Number		EMB diagnosis, *n* (%)		CMR diagnosis, *n* (%)		Combined diagnosis, *n* (%)
EMB indication (class)	I	IIa/IIb	I	IIa/IIb	I	IIa/IIb	
DCM, 54	30	24	26 (87)	22 (92)	24 (80)	21 (88)	51 (94)
HCM, 36	11	25	7 (64)	20 (80)	6 (55)	23 (92)	35 (97)
Dilated HCM, 15	9	6	7 (78)	5 (83)	4 (44)	5 (83)	15 (100)
Obstructive HCM, 11	0	11	0 (0)	9 (82)	0 (0)	11 (100)	11 (100)
Apical HCM, 4	0	4	0 (0)	2 (50)	0 (0)	4 (100)	4 (100)
Sarcoidosis, 17	8	9	2 (25)	4 (44)	6 (75)	7 (78)	17 (100)
HHD, 14	5	9	2 (40)	3 (33)	5 (100)	4 (44)	14 (100)
Others							
ARVC, 5	1	4	0 (0)	0 (0)	1 (100)	4 (100)	5 (100)
Myocarditis, 4	4	0	3 (75)	0 (0)	1 (25)	0 (0)	4 (100)
Amyloidosis, 3	0	3	0 (0)	2 (67)	0 (0)	3 (100)	3 (100)
Dystrophic cardiomyopathy, 3	1	2	0 (0)	0 (0)	1 (100)	2 (100)	3 (100)
Total	60	76	40 (67)	51 (67)	44 (73)	64 (84)	132 (97)

ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB; endomyocardial biopsy HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease.

muscle was frequently found in patients with HCM or sarcoidosis, while it was rarely or never seen in patients with DCM or HHD.

Discussion

This was the first study to compare the diagnostic performance of EMB and CMR in patients with HF. Non-invasive CMR, especially when combined with clinical data and echocardiogram, may provide an excellent diagnostic capacity for identifying the underlying aetiology in patients with HF, equal to or better than invasive EMB. Moreover, CMR is a powerful modality which in combination with clinical data including echocardiogram is sufficient for defining the pathophysiology of HF.

Although it is important to compare the diagnostic potential of EMB and CMR across a large number of patients with HF, comparisons using a large population have not been possible because it is extremely difficult to perform both EMB and CMR with LGE in sufficient patients. Our findings revealed that both the invasive EMB technique ,and the non-invasive CMR technique demonstrated good diagnostic performance (67% vs. 79%), whereas the use of CMR in combination with clinical data including echocardiogram unrelated to the EMB findings demonstrated excellent diagnostic performance (97%). Importantly, CMR alone could not surpass the diagnostic accuracy of EMB, which underscores the importance of EMB. However, the combined diagnosis was more accurate, which suggests that the use of CMR in combination with clinical data plus echocardiogram is the most reliable, non-invasive method for the diagnosis of HF in a routine clinical setting. Thus, we concluded that CMR is equal to or possibly superior to the use of EMB for the diagnosis of the underlying aetiology of HF, especially in patients with sarcoidosis, HHD, others, and those with a class II indication for EMB.

These results suggest that CMR should be used more often than EMB for the initial diagnosis of HF. In addition, the cost of EMB is approximately three times greater than that of delayed enhancement CMR, and most patients can receive CMR at a clinic but would require a hospital stay to undergo EMB and perform EMB with right heart catheterization (which also contributes to the high cost of EMB). Indeed, the 2009 American College of Cardiology (ACC)/American Heart Association (AHA) chronic HF guidelines proposed that EMB should not be performed for the routine evaluation of patients with HF,[24] as EMB is often associated with sampling errors and complications. Therefore, although we do not deny the usefulness of EMB for the diagnosis of the underlying aetiology of HF, we suggest that CMR should be used more frequently for this type of diagnosis.

Diagnostic performance of cardiac magnetic resonance and endomyocardial biopsy

Although EMB provides suggestive findings in patients with DCM, HHD, and dystrophic cardiomyopathy, these findings are non-specific, and a definitive diagnosis cannot be made by EMB *per se*. In contrast, cardiac amyloidosis, CS, HCM, and myocarditis have specific histological characteristics and can be conclusively diagnosed using EMB alone if myocardial biopsy specimens contain these lesions (*Figure 4*). In our study, an accurate and conclusive diagnosis of such conditions could be reached using EMB alone in 38 out of 60 patients (*Table 1*), and we tended to misdiagnose CS and HHD as DCM, and HCM as HHD by EMB (*Table 3*).

Table 2 Sensitivity, specificity, positive predictive value, negative predictive value, accuracy of cardiac magnetic resonance diagnosis, and combined diagnoses with clinical data, echocardiogram, plus cardiac magnetic resonance vs. endomyocardial biopsy diagnosis

A. Cardiac magnetic resonance vs. endomyocardial biopsy

	n	Sensitivity		rTPF	95% CI	*n*	Specificity		rFPF	95% CI
		CMR	EMB				CMR	EMB		
DCM	54	83%	**89%**	1.07	0.89–1.28	82	**93%**	69%	**4.3**	**1.72–10.7**
HCM	36	**81%**	75%	0.93	0.69–1.26	100	**98%**	94%	3	0.48–18.64
CS	17	**76%**	35%	0.46	0.20–1.07	119	92%	**100%**	**0**	–
HHD	14	**64%**	36%	0.56	0.22–1.43	122	**96%**	92%	2	0.59–6.81

B. Cardiac magnetic resonance vs. endomyocardial biopsy

	n	PPV		rPPV	95% CI	*n*	NPV		rNPV	95% CI	Accuracy	
		CMR	EMB				CMR	EMB			CMR	EMB
DCM	54	**88%**	66%	**0.75**	**0.60–0.93**	82	89%	**90%**	1.01	0.89–1.15	**89%**	75%
HCM	36	**94%**	82%	0.87	0.71–1.08	100	**93%**	91%	0.98	0.89–1.07	**93%**	89%
CS	17	57%	**100%**	**1.77**	**1.18–2.66**	119	**96%**	92%	0.95	0.88–1.02	90%	**92%**
HHD	14	**64%**	33%	0.52	0.20–1.31	122	**96%**	93%	0.97	0.90–1.04	**93%**	86%

C. Combined procedure using clinical data with echocardiogram plus cardiac magnetic resonance vs. endomyocardial biopsy

	n	Sensitivity		rTPF	95% CI	*n*	Specificity		rFPF	95% CI
		Combined	EMB				Combined	EMB		
DCM	54	**94%**	89%	0.94	0.82–1.08	82	**100%**	69%	–	–
HCM	36	**97%**	75%	**0.77**	**0.61–0.97**	100	**99%**	94%	6	0.54–67.19
CS	17	**100%**	35%	**0.35**	**0.17–0.74**	119	99%	**100%**	0	–
HHD	14	**100%**	36%	**0.36**	**0.16–0.80**	122	**98%**	92%	5	0.88–28.27

D. Combined procedure using clinical data with echocardiogram plus cardiac magnetic resonance vs. endomyocardial biopsy

	n	PPV		rPPV	95% CI	*n*	NPV		rNPV	95% CI	Accuracy	
		Combined	EMB				Combined	EMB			Combined	EMB
DCM	54	100%	66%	**0.65**	**0.52–0.81**	82	**96%**	90%	0.94	0.85–1.03	**98%**	75%
HCM	36	**97%**	82%	0.84	0.69–1.02	100	**99%**	91%	**0.92**	**0.86–0.99**	**99%**	89%
CS	17	**94%**	100%	1.06	0.93–1.20	119	**100%**	92%	**0.92**	**0.86–0.97**	**99%**	92%
HHD	14	**88%**	33%	**0.38**	**0.16–0.89**	122	**100%**	93%	**0.93**	**0.87–0.98**	**99%**	86%

CI, confidence interval; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; DCM, idiopathic dilated cardiomyopathy; EMB, endomyocardial biopsy; FPF, false positive fraction; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; NPV, negative predictive value; PPV, positive predictive value; TPF, true positive fraction. 95% CIs were calculated according to the ratio of CMR diagnosis and combined diagnosis to EMB diagnosis. The bold values indicate a significant difference.

These misdiagnoses were attributed to non-specific changes in the biopsy specimens or the inappropriate sampling of sites separate from the lesions due to the patchy distribution of the lesions.[17,25–27] However, there are merits in the classification of infiltrating inflammatory cells by either immunohistochemistry or a PCR method to guide treatment. The ESC 2012 guidelines also stated that the use of EMB may be needed to confirm the diagnosis in patients with suspected myocarditis, sarcoidosis, and amyloidosis.[1]

Cardiac magnetic resonance is a safe procedure, and images of diagnostic quality can be obtained in ≥ 98% of patients.[28] The use of CMR also allowed us to obtain detailed images of not only functional and morphological abnormalities but also tissue pathology. In this study, EMB was superior to CMR for diagnoses of DCM and dilated HCM, whereas CMR demonstrated an improved diagnostic yield over EMB in cases of non-dilated HCM, CS, HHD, and other rare diseases (with the exception of myocarditis). Moreover, this tendency was the same independent of the EMB indication. In contrast to previous studies demonstrating a high level of sensitivity and specificity within only a limited study population, our study observed lower diagnostic agreement between methods. Because CMR was used to differentiate between a broad spectrum of diagnostic characteristics in HF patients, which resembles the clinical setting, CMR alone could

Table 3 Comparison of cardiac magnetic resonance diagnosis or endomyocardial biopsy diagnosis with final diagnosis

Final diagnosis CMR diagnosis	DCM (n = 54)	HCM (n = 36)	CS (n = 17)	HHD (n = 14)	Others (n = 15)
DCM, n (%)	**45 (83)**	0	1	5 (36)	0
HCM, n (%)	1	**29 (81)**	1	0	0
CS, n (%)	2 (4)	6 (17)	**13 (76)**	0	2 (13)
HHD, n (%)	3 (5)	1	0	**9 (64)**	0
Others, n (%)	3 (5)	0	2 (12)	0	**12 (80)**
Final diagnosis EMB diagnosis	**DCM (n = 54)**	**HCM (n = 36)**	**CS (n = 17)**	**HHD (n = 14)**	**Others (n = 15)**
DCM, n (%)	**48 (89)**	3 (8)	10 (59)	7 (50)	6 (40)
HCM, n (%)	3 (6)	**27 (75)**	0	2 (14)	1 (7)
CS, n (%)	0	0	**6 (35)**	0	0
HHD, n (%)	2 (4)	6 (17)	0	**5 (36)**	2 (13)
Others, n (%)	1	0	1	0	**5 (33)**

The bold values indicate diagnostic concordance between cardiac magnetic resonance diagnosis or endomyocardial biopsy diagnosis and final diagnosis.

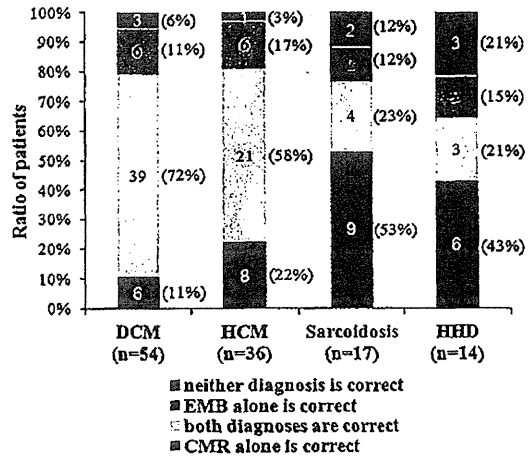

Figure 2 Diagnostic capabilities of endomyocardial biopsy (EMB), cardiac magnetic resonance (CMR), and the combined diagnosis with CMR and EMB. DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; CS, cardiac sarcoidosis; HHD, hypertensive heart disease. The ratio between EMB and CMR for the diagnosis of DCM, HCM, CS, and HHD.

not assign a correct diagnosis for 28 patients (21%) (*Table 1*). The use of CMR tended to misdiagnose HCM as CS, and HHD as DCM. Additionally, six HCM patients who were misdiagnosed with CS all had dilated HCM. A study by Hansen et al. suggested that the use of CMR in CS patients demonstrates similar results to those obtained in patients with HCM or idiopathic cardiomyopathy,[29] which is consistent with the present data (*Table 3*). In the five cases where HHD was misdiagnosed, they were consistently misdiagnosed as DCM due to the similarity of the images.[10] However, in HCM patients, CMR demonstrated excellent diagnostic performance (100%) for apical HCM and HOCM, which suggests that CMR has the ability to evaluate the heterogeneous appearance of HCM better than any other imaging modality,[30,31] and this represents the main difference between CMR and EMB. We could not refer to the diagnostic accuracy of CMR in patients with myocarditis in our study because the number with myocarditis was too small. On the other hand, Marvorogeni *et al.* importantly concluded that both CMR and PCR prove useful for the detection of myocarditis, while CMR is important to detect the development of HF.[32] Our data are consistent with the previous study[32] showing that CMR and EMB have equivalent ability to reach the diagnosis and judge the pathophysiology.

Although the merits and demerits of CMR differ from those of EMB, its diagnostic capability was shown to be equivalent or even superior to that of EMB.

Superiority of the combined diagnosis

The combined diagnosis with non-invasive clinical data provides a sharp impact on an accurate diagnosis of HF.[33] Likewise, the combined diagnosis with clinical data, echocardiogram, plus CMR was shown to be very effective in the current study. Out of 54 DCM patients, 9 were misdiagnosed by CMR, but 6 of these 9 patients were correctly diagnosed using the combined diagnostic technique. Of 36 HCM patients, 7 were misdiagnosed by CMR, although 6 of these 7 patients were correctly assessed using the combined diagnosis (*Tables 2* and *3*). Moreover, the other misdiagnosed patients were also correctly assessed using the combined diagnosis.

Regarding the combined diagnosis with echocardiogram, the present study suggests that even the use of only clinical characteristics including echocardiogram can provide relatively high diagnostic performance compared with that in a previous report,[33] since our Department is specialized in diagnosing patients with non-ischaemic HF. However, the addition of CMR and EMB on top of the clinical information with echocardiogram increases the accuracy to 97% and 100%, respectively. Our original conclusion

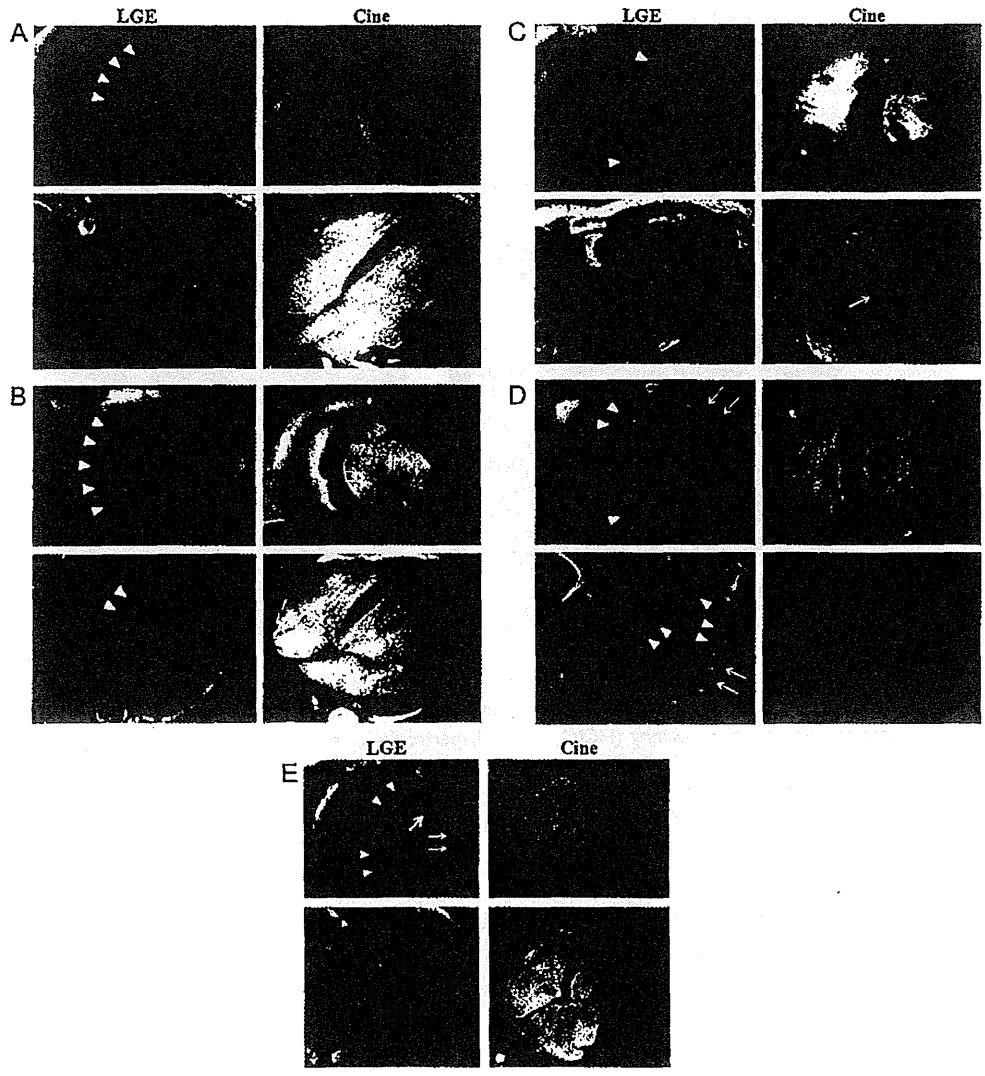

Figure 3 Representative cardiac magnetic resonance (CMR) findings. (*A*) Dilated cardiomyopathy (DCM): midwall longitudinal thin late-gadolinium enhancement (LGE) in the anteroseptum wall without wall thickening (arrowheads). (*B*) Hypertensive heart disease (HHD): broad, ill-defined, and mild LGE in the midwall of the septum (arrowheads) with LV concentric hypertrophy. (*C*) Hypertrophic obstructive cardiomyopathy (HOCM): LGE in the LV–RV junctions of the anteroseptum and inferoseptum (arrowheads). Note: left atrial dilatation, LV asymmetric hypertrophy, papillary muscle hypertrophy, and LV outflow tract obstruction (arrow). (*D*) Dilated phase HCM: midwall patchy LGE in the anteroseptum and inferoseptum (arrowheads) and epicardial LGE in the anterior and posterior regions (arrow). (*E*) Cardiac sarcoidosis: subepicardial LGE of the anteroseptum with wall thinning and inferoseptum (arrowheads), subendocardial LGE of the lateral region (thin arrow), and LGE in the papillary muscle (thick arrow).

that CMR provides a diagnostic capability comparable with EMB seems to be true even with the clinical information including echocardiogram. Furthermore, all of the patients who were correctly diagnosed by EMB were correctly diagnosed using the combined technique, which indicates that the combined method was superior to the use of EMB in this study. Previous studies performed in populations with only one clinically suspected disease reported high diagnostic accuracy,[11,12,34] and our results indicate that CMR would probably be available for a broad spectrum of HF patients, particularly those with a class II indication for EMB, for differentiation between unknown aetiologies. Furthermore, the knowledge of diseases that are prone to misdiagnosis would increase the diagnostic performance for determining the aetiology of HF in a routine clinical setting. Although CMR is a non-invasive method, as is an echocardiogram, it is equal or superior to an echocardiogram because it can provide specific tissue characterization in addition to cardiac morphology and function. Accordingly, we suggest that it would be better initially to perform CMR in all patients, especially those with a class II indication for EMB, and diagnose the underlying aetiology of HF through the use of

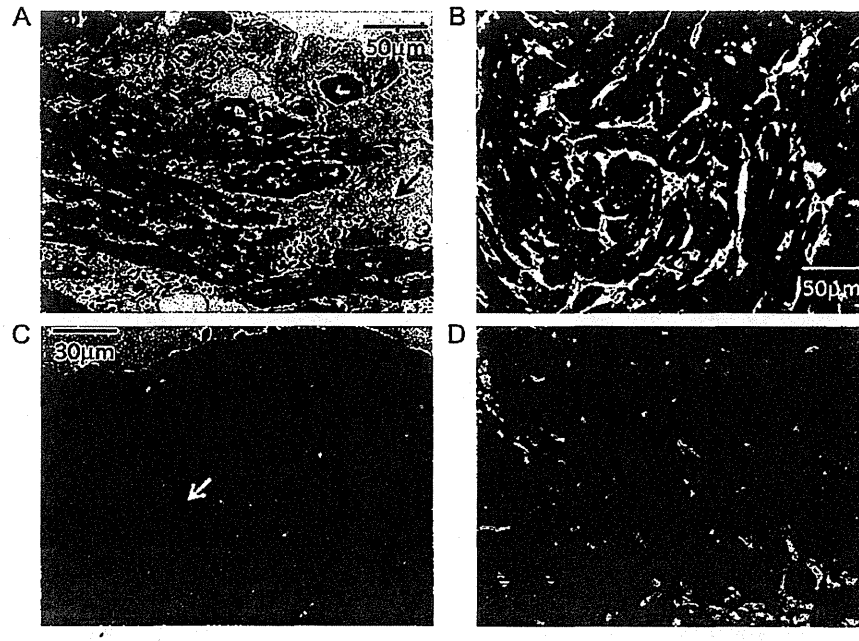

Figure 4 Representative examples of histological findings from endomyocardial biopsies. (*A*) Dilated cardiomyopathy (DCM): the photomicrograph demonstrates replacement fibrosis (blue areas, black arrow) and moderate myocyte hypertrophy (Masson trichrome stain, bar = 50 μm). (*B*) Hypertrophic cardiomyopathy (HCM): severe hypertrophy of myocytes, myocyte disarray, and bizarre nuclei are shown (Masson trichrome stain, bar = 50 μm). (*C*) Cardiac sarcoidosis: non-caseating epithelioid granulomas with giant cells (white arrow) are shown (haematoxylin and eosin stain, bar = 30 μm). (*D*) Cardiac amyloidosis: amorphous amyloid deposits (blue-grey) in the perimyocytes were consistent with amyloidosis in the interstitium of the myocardium (Masson's trichrome, bar = 50 μm).

CMR and other non-invasive modalities. Then, if the combined diagnosis fails, EMB can be used as a second diagnostic modality.

Study limitations

This study had several limitations. First, all of the patients with HF of unknown aetiology were not assigned to receive both EMB and CMR; EMB was performed to reveal the underlying aetiology of HF, according to the Scientific Statement,[23] whereas CMR was performed in all patients without contraindications for CMR. Secondly, we included patients admitted to the Department with HF, and there were remarkably few patients in our Department who had coronary artery disease. However, even if such patients had been included, CMR would have probably been more useful to diagnose prior myocardial infarction due to spontaneous recanalization or coronary vasospasm than EMB. Thirdly, in the clinical setting, there are always cases with an ambiguous diagnosis despite a detailed investigation. We excluded these cases primarily on the premise that we would achieve a more precise diagnostic yield by avoiding these cases. Regarding EMB procedures, we took 3–5 biopsy specimens for each patient in our study, in accordance with the appropriate guidelines.[23] Additionally, all samples were taken from the right ventricle according to the protocol of our facility. In most patients, we took five samples to decrease sampling error, although the sampling number was decreased to three specimens in patients with both a pre-existing LBBB with a high risk for developing complete atrioventricular block[8] and obvious idiopathic DCM. The collection of samples from both ventricles may have increased the significance of the findings, but we collected the minimum requirement to decrease the procedural risk of EMB. Finally, this was also a retrospective study from a single centre. Our findings must be carefully interpreted and should be replicated in a prospective, large, multicentre investigation. Despite these limitations, our study has important strengths, such as the inclusion of a sufficient number of patients administered both EMB and CMR, a more precise final diagnosis using all available data, and broad clinical applications.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

Funding

The Ministry of Health, Labor, and Welfare-Japan (grants-in-aid H23-Nanchi-Ippan-22 to M.K.), the Ministry of Education, Culture, Sports, Science and Technology-Japan (grants-in-aid 21390251 to M.K.), the Japan Heart Foundation (grants to M.K.), the Japan Cardiovascular Research Foundation (grants to M.K.).

Conflict of interest: none declared.

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Hypertension Research (2013) 36, 450–456

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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.
Hypertension Research (2013) **36**, 450–456; doi:10.1038/hr.2012.200; published online 20 December 2012

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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Received 12 September 2012; revised 7 October 2012; accepted 29 October 2012; published online 20 December 2012

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

METHODS

Ethics statement

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

Subjects and clinical parameters

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

Cardiac catheterization

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

Echocardiography

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

The mathematical model for the rehospitalization process

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

Assumption 1. A mean elapsed time τ_i from discharge to the rehospitalization of patient i depends on some of the given clinical factors $X^i = \{x_1^i, \ldots, x_p^i\}$ 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:

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

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.

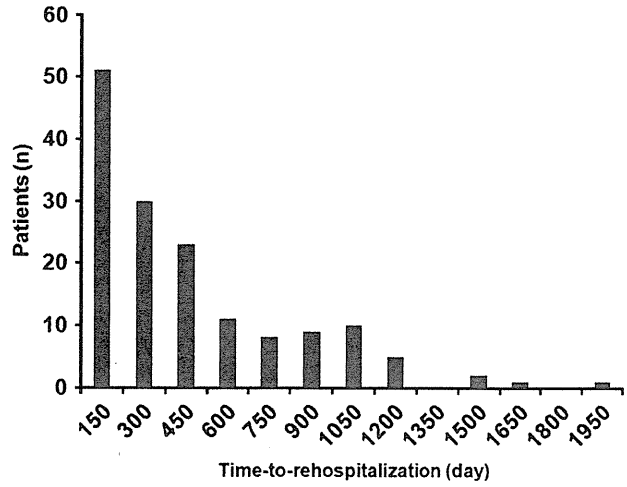


Figure 1 Time-to-rehospitalization histogram for all patients.

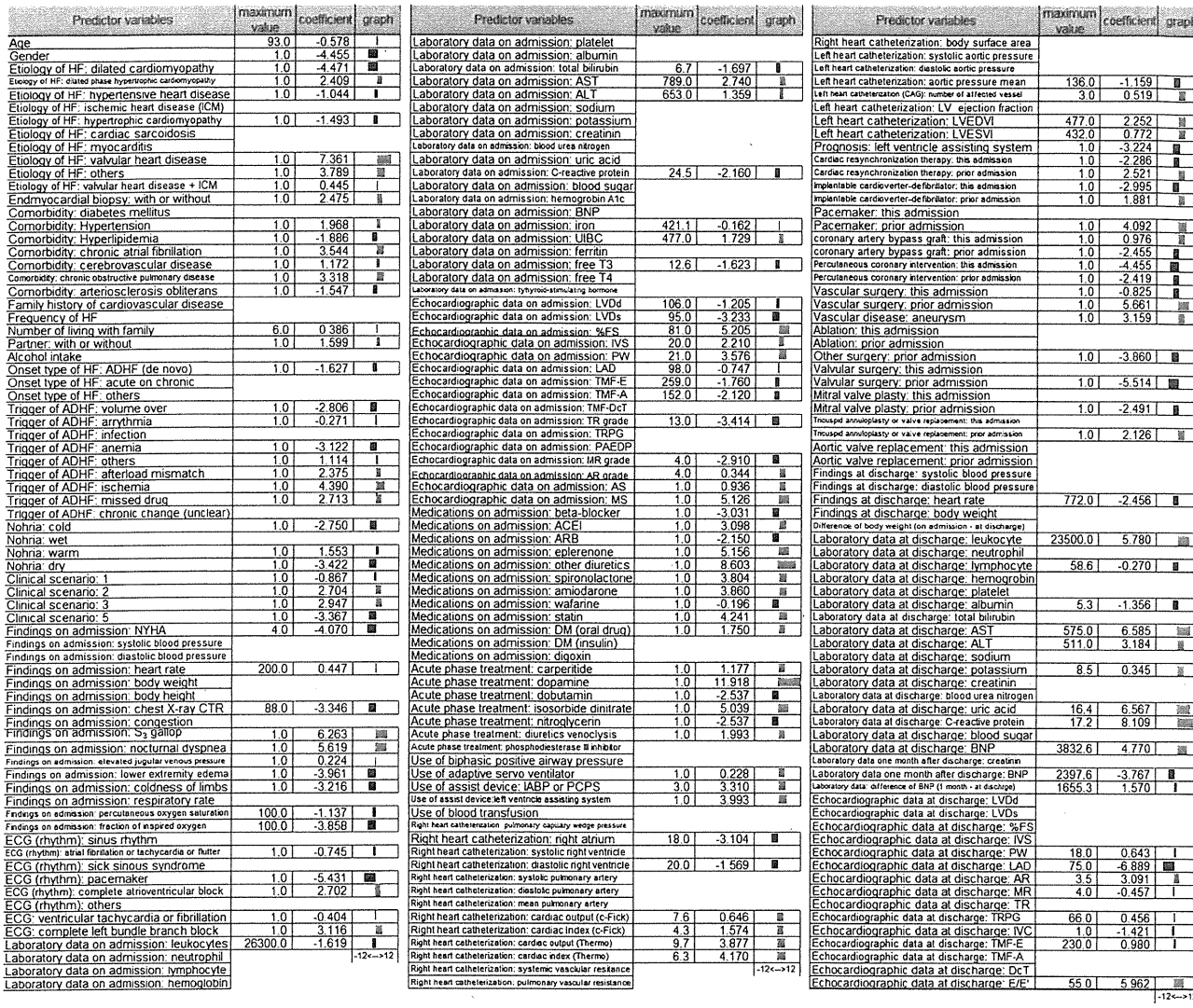
Fitting the model to clinical data

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			

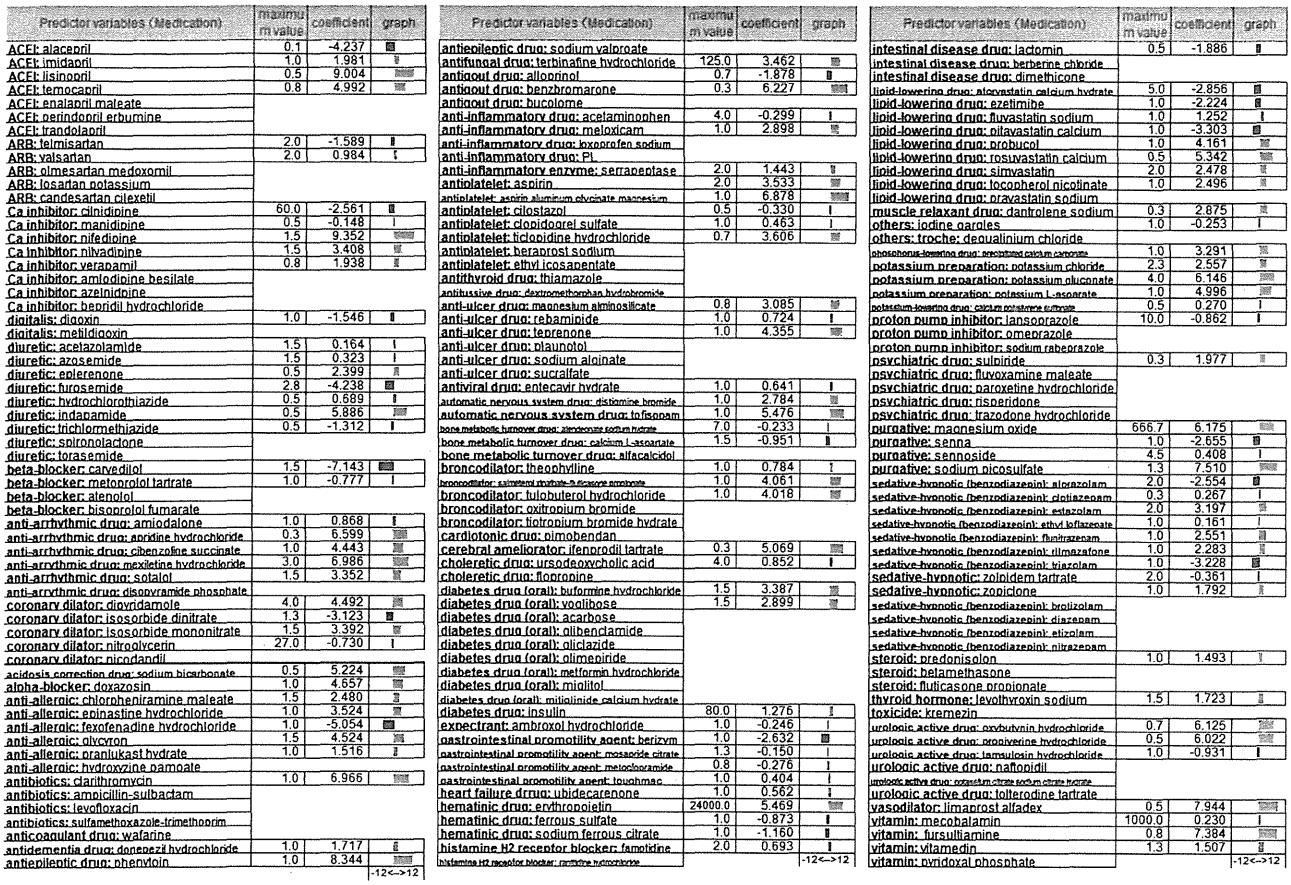
Predictor variables	maximum value	coefficient	graph
Laboratory data on admission: platelet			
Laboratory data on admission: albumin			
Laboratory data on admission: total bilirubin	6.7	-1.697	
Laboratory data on admission: AST	789.0	2.740	
Laboratory data on admission: ALT	653.0	1.359	
Laboratory data 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: hemoglobin A1c			
Laboratory data on admission: BNP			
Laboratory data on admission: iron	421.1	-0.162	
Laboratory data on admission: UIBC	477.0	1.729	
Laboratory data on admission: ferritin			
Laboratory data on admission: free T3	12.6	-1.623	
Laboratory data on admission: free T4			
Laboratory data on admission: hyhyroid-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 capulary 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	
Tricuspd annuloplasty or valve replacement: this admission			
Tricuspd 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.



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

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

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

-12<->12

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

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

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

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

LIMITATIONS

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

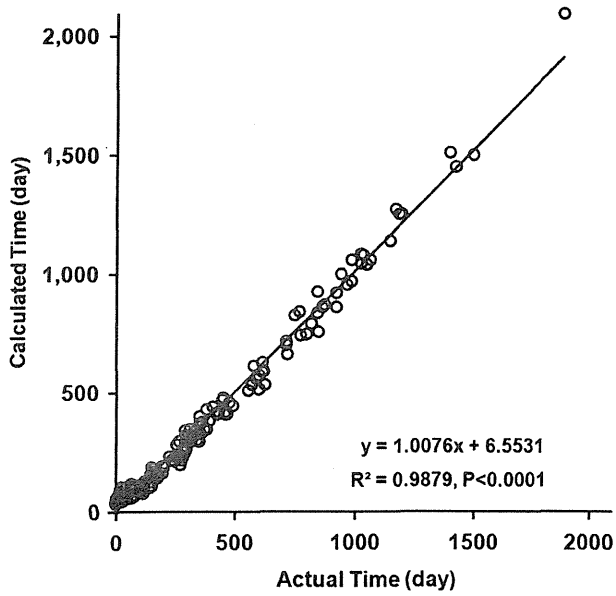


Figure 4 Correlation between the clinical data and the values calculated using the mathematical formula. The clinical data are in excellent agreement with the calculated times.

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

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

CONCLUSIONS

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

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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

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