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The Clinical Utility of Noninvasive Forrester Classification in Acute Heart Failure from PREDICT study

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Brief title: Noninvasive Forrester classification in acute heart failure

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Abstract

The Forrester classification plays a crucial role in comprehending the underlying pathophysiology of heart failure (HF), and is employed to categorize the severity and predict the outcomes of patients with acute HF. Our objective was to assess the predictive value of the Forrester classification, based on noninvasive hemodynamic measurements obtained through Doppler echocardiography at admission, in forecasting the short-term prognosis post-hospitalization of patients with acute HF. Patients were recruited for the PREDICT study, a multi-center, prospective study conducted in Japan. Participants were stratified into four profiles using cardiac index (CI) and E/e′ ratio obtained from Doppler echocardiography upon admission (Profile Ⅰ: CI>2.2, E/e'≦15, Profile Ⅱ: CI>2.2, E/e'>15, Profile Ⅲ: CI≦2.2, E/e'≦15, Profile Ⅳ: CI≦2.2, E/e'>15). The primary composite outcome of the study was all-cause mortality or worsening heart failure during the 14 days of hospitalization. Cox proportional hazards model analysis was employed to identify prognostic factors during the observation period. A total of 270 subjects, with a mean age of 74 ± 14 years and a male proportion of 60%, were enrolled in the study. During the 14 day period of hospitalization, 58 participants (22%) had a composite outcome. Patients with low CI (i.e. Profiles III and IV) demonstrated an elevated risk of composite outcome after adjusting for confounding variables, as evidenced by the adjusted hazard ratios of 5.85 (95% confidence interval [CI], 1.17 to 29.09; $p<0.01$, vs. Profile Ⅲ) and 6.50 (95% CI, 1.53 to 27.68; $p<0.01$, vs. Profile Ⅳ) in comparison to Profile Ⅰ, respectively. In conclusions, the Forrester classification, derived from noninvasive Doppler echocardiography at admission, may predict early deterioration in patients hospitalized with acute HF.

Key Words: echocardiography; heart failure; Forrester classification.

Introduction

In heart failure (HF) patients, an in-depth understanding of an individual's hemodynamics is crucial in selecting effective treatment options. Forrester et al. [1] categorized patients with acute myocardial infarction into four hemodynamic profiles, utilizing invasive right heart catheterization. This approach has been widely adopted in clinical practice for many HF patients. [2] Nonetheless, prior reports indicate that this invasive hemodynamic assessment method is not recommended as a routine examination for HF patients. [3] Recently, the use of noninvasive hemodynamic evaluation via Doppler echocardiography to estimate pulmonary capillary wedge pressure (PCWP) [4] and cardiac index (CI) [5] has gained widespread acceptance, allowing for the creation of noninvasive Forrester classifications. This hemodynamic assessment can be performed expeditiously and recurrently at the patient's bedside, with a single-center, retrospective report attesting to its potential utility in particular clinical scenarios. [6] [7] The present study aimed to examine if the Forrester classification, based on hemodynamic parameters obtained noninvasively through Doppler echocardiography, can predict the hospitalization outcome in patients with acute HF in a multicenter prospective study.

Methods

This study constituted a post hoc analysis of the PREDICT trial. The PREDICT trial's design has been documented elsewhere. [8] In brief, the study was a nationwide, prospective, multicenter registry that took place at 16 institutions in Japan and was endorsed by the Japanese Society of Echocardiography. All of these institutions were training facilities that had been certified by the Japanese Circulation Society. The study protocol was approved by the ethical committees of each participating institution, with written informed consent obtained from all subjects. Patients diagnosed with acute decompensated HF (ADHF) and

requiring admission to participating hospitals from January 2019 to September 2020 were enrolled in the study. The attending physician, a cardiologist certified by the Japanese Circulation Society, diagnosed acute decompensated heart failure (ADHF) based on the Framingham criteria.[9] Patients were excluded if they had acute coronary syndrome, were undergoing hemodialysis, or had received positive inotropic agents before the index echocardiography and immediately after the initial examination including the index echocardiography. After admission, patients underwent a comprehensive physical evaluation and transthoracic echocardiography to determine cardiac function. Following evaluation, the attending physician based treatment on clinical data obtained from the physical examination and echocardiography. Outcomes were recorded subsequent to hospitalization.

The attending physician documented in the medical record the evaluation of jugular venous distension (JVD) and leg edema as indicative of congestive profile, as well as cool extremities and impaired consciousness as indicative of hypoperfusion profile. [2] In the present study, the quantity of these positive findings was recorded as a physical assessment score, ranging from 0 to 4.

Transthoracic echocardiography was administered at an outpatient clinic or, if unfeasible, promptly after hospital admission. With the primary aim of evaluating the efficacy of echocardiography in urgent settings, a limited set of parameters including left ventricular (LV) stroke volume, cardiac output, visually-assessed LV ejection fraction (LVEF), diameters of the inferior vena cava and its degree of respiration-related variation, early- and late-diastolic transmitral Doppler flow velocities, early-diastolic septal mitral annular velocity, and peak flow velocity of tricuspid regurgitation (TRV) were obtained during the initial examination in order to shorten image acquisition time. As previously described[8], the quality of LV output measurements was ensured through adherence to performance

recommendations, and LV stroke volume and cardiac output were estimated from LV outflow pulsed-wave Doppler images and LV outflow tract diameter (LVOTd). LVOTd was measured in mid-systole with a zoomed parasternal long-axis LV outflow view and cross-sectional area of LV outflow (CSA) was calculated as $(LVOTd/2)^2 \times \pi$. Stroke distance was measured as time velocity integral of ejection flow from pulsed wave Doppler image of LV outflow with apical long-axis view. Accordingly, stroke volume was calculated as stroke distance times CSA. Heart rate during the initial echocardiographic examinations was recorded as that at the time of LV outflow Doppler recordings and cardiac output (CO) was calculated as stroke volume times heart rate. Finally, CI was calculated by correcting CO for body surface area. These conventional 2-dimensional and Doppler parameters were recorded according to guidelines. [10] [11] In patients with atrial fibrillation, measurements were taken from a heartbeat of approximately average cycle length.

Patients were categorized as either "warm" or "cold" based on their cardiac index (CI), with values greater than 2.2 L/min/m^2 designating the former and values equal to or less than 2.2 L/min/m^2 the latter. [12] Additionally, patients were classified as either "wet" or "dry" according to the ratio of their early diastolic transmitral Doppler flow velocities and early-diastolic septal mitral annular velocity (E/e'), with values greater than 15 denoting the former and values equal to or less than 15 the latter. [10] Based on the CI and E/e' values obtained through echocardiography, patients were grouped into the following noninvasive Forrester classification: Profile I; warm and dry (CI > 2.2 L/min/m^2 and E/e' $\leqq$ 15), Profile II; warm and wet (CI > 2.2 L/min/m^2 and E/e'>15), Profile III; cold and dry (CI $\leqq$ 2.2 L/min/m^2 and E/e'>15), and or Profile IV; cold and wet (CI $\leqq$ 2.2 L/min/m^2 and E/e'> 15).

The primary objective of this study was the composite outcome of early worsening heart failure (WHF) and all-cause mortality within 14 days of admission. Early WHF was defined

as patients who required initiation of inotropic or temporary circulatory support due to hemodynamic deterioration. The administration of inotropic agents was explicitly targeted toward patients who exhibited resistance to normalizing parameters, including hypotension, peripheral circulatory disturbance, and circulating blood volume after initial treatment. This approach was guided by the individual clinical judgment of each healthcare provider.

For continuous variables, the normality of the distribution was assessed using the Shapiro-Wilk test. Variables with normal distributions were expressed as mean values ± standard deviation, while those with non-normal distributions were reported as medians with lower and upper quartiles (Q1-Q3). Categorical data was presented as both the percentage and number of patients. Where equality of variance was established between groups using the Levene's test, a one-way general linear model analysis of variance was employed, followed by a Tukey-Kramer post-hoc test analysis, to assess differences between each profile. For data with unequal variance between profiles, a Kruskal-Wallis test was performed, followed by a Conover post-hoc test. Due to the measurement of plasma N-terminal pro brain natriuretic peptide (NT-pro BNP) levels rather than plasma brain natriuretic peptide (BNP) levels in 76 patients, conversion of the latter was necessary for multivariable analysis purposes. This was achieved through application of the formula: $\log BNP = 0.8 \times \log NT\text{-pro} BNP - 0.018$. [13] To determine the odds ratio (OR) and 95% confidence interval values for prediction of the composite outcome, logistic regression was utilized, both before and after adjustment for various factors such as age, gender, New York Heart Association (NYHA) functional classification, log BNP levels, and non-invasive Forrester profiles. The composite outcome was evaluated through Kaplan-Meier survival analysis, with comparisons made through the log-rank test. Furthermore, hazard ratio (HR) and 95% confidence interval values were determined for prediction of the composite outcome through Cox proportional-hazards analysis, with adjustments made for the previously mentioned factors. Statistical significance

was determined through two-tailed P values less than 0.05. Sequential Cox models were employed to assess the incremental prognostic benefit of incorporating blood test results (log BNP levels) and noninvasive Forrester classification, as compared to a baseline model that relied solely on physical assessment. This benefit was defined as a statistically significant increase in the global chi-square value. The statistical analyses were conducted utilizing MedCalc 15.8 (MedCalc Software 17; Mariakerke, Belgium) and SPSS 21.0 (SPSS, Chicago, IL, USA).

Results

  Of the 303 individuals enrolled in the PREDICT study, 33 were omitted prior to categorization due to the absence of echocardiographic data (E/e') necessary for categorization. Subsequently, data was only documented for the 270 individuals who completed the study (Figure 1). All echocardiographic studies were obtained immediately before or after admission, with a median time of 2.0 hours post-admission.

  The baseline characteristics of the subjects are enumerated in Table 1. The mean age of the cohort was 74 ± 14 years, with 60% of the individuals being male. The most prevalent cardiac affliction was ischemic heart disease (26%), followed by non-ischemic dilated cardiomyopathy (17%) and left-sided valvular heart disease (16%). The mean LVEF prior to discharge was $41 \pm 18\%$, with approximately 51% of the patients classified as having heart failure with reduced LVEF (HFrEF; LVEF <40%).

  The patients were classified into different profiles as follows, Profile Ⅰ (warm/dry) 15%, Profile Ⅱ (warm/wet) 42%, Profile Ⅲ (cold/dry) 11%, and Profile Ⅳ (cold/wet) 32%, using

the noninvasive Forrester classification. Patient characteristics for each profile are shown in Table 1. The patients categorized under Profile Ⅳ exhibited diminished systolic blood pressure, inferior renal functionality, elevated BNP levels, and diminished LVEF compared to those under Profile Ⅰ. During the 14 day observation period, 60 patients reached the primary endpoint, out of which 4 patients died and the remaining 56 patients experienced an early WHF. The incidence of composite outcome was highest for Profile Ⅳ, followed by Profile Ⅲ and Profile Ⅱ among the various profiles (Figure 2).

Table 2 shows the results of univariate and multivariate logistic regression analyses to determine composite outcome. The final model demonstrated good discrimination, as evidenced by the area under the receiver-operator characteristic curve value of 0.89. Figure 3 displays the event-free survival rates based on profiles, as determined by the Kaplan-Meier method. Following adjustment through multivariate analysis, Profiles Ⅲ and Ⅳ exhibited a significantly higher event rate than Profiles Ⅰ as evidenced by the adjusted hazard ratios of 5.85 (p<0.01, vs. Profile Ⅲ) and 6.50 (p<0.01, vs. Profile Ⅳ), respectively (Figure 4). Regarding the prognostication of the primary endpoint, the incorporation of BNP values and noninvasive Forester profiles into the physical findings substantially enhanced the predictive capacity (Model 1, physical assessment score, χ^2=24.2; Model 2, additional BNP values, χ^2=57.7, P=<0.01 and Model 3, additional profile, χ^2=83.2, P=<0.01).

Discussion

In the present investigation, we observed that in patients admitted to the hospital with acute HF, the low CI subgroup classified as Profile Ⅲ and Ⅳ, based on noninvasive Forester classification using echocardiographic indices at the time of admission, had a significantly higher risk for the composite outcome after adjusting for multiple variables. Moreover, augmenting the physical examination with the assessment of BNP levels and noninvasive

Forrester classification upon hospital admission significantly enhanced the predictive power of the early deterioration during the initial hospitalization phase.

In our investigation, we have discerned that hypoperfusion based on echocardiography exerts a distinct influence on the acute prognosis of patients suffering from HF. On the other hand, a report by Nohria et al. [2], which focused on noninvasive physical findings, showed an augmented propensity for chronic mortality and emergent heart transplantation in heart failure patients exhibiting a congestive profile. The observed contradiction with previous studies could stem from the challenges associated with estimating PCWP exclusively through E/e'. This is because a subset of patients who show E/e'<15 may also have elevated LV filling pressures. It has been reported that implementing a comprehensive diagnostic approach, which incorporates multiple parameters following the guidelines proposed by the American Society of Echocardiography, enhances the accuracy of diagnoses for these patients and has the potential to reclassify a minority of patients. [14,15]   While a threshold E/e' value of 15 is practical and straightforward, the need for a further investigation remains in accurately estimating PCWP and assigning a definitive "wet" or "dry" profile in this patient cohort. Other noninvasive measures that reflect LV filling pressure comprise JVD [16] and TRV[17]. However, certain limitations have been documented for these parameters as well. Since JVD serves as an approximation of right atrial pressure (RAP) and does not directly measure LV filling pressure, inconsistencies between RAP and PCWP have led to inaccurate estimates of LV filling pressure assessment, affecting 30% of heart failure patients. [18] Similarly, in the case of TR, up to 50% of patients with pulmonary hypertension exhibit an unmeasurable TR waveform. [19] Due to these reasons, we have employed E/e' as the index in this study, which is widely recommended in various guidelines. Our results do not contradict previous reports, within each profile, as defined by the noninvasive Forrester classification, subgroups other

than those categorized as profiles 1 and 4, in which prognostic outcomes are unequivocal, may be regarded as candidates for invasive testing to enable more detailed evaluation.

Early prediction of clinical outcomes in patients with HF is crucial to guide subsequent treatment. It has been reported that various indices, such as physical examination [2] and BNP value [20], hold prognostic value for predicting the prognosis of patients with HF. Additionally, noninvasive echocardiographic parameters, including left ventricular contractility [21] and left ventricular diastolic function [22], have demonstrated prognostic significance in HF. These parameters are recognized for their strong correlation with values obtained from invasive testing. [23] [4] This study proposes that a combination of these non-invasive parameters could be a predictive tool for acute prognosis in patients with acute HF.

This is the first multicenter, prospective study to evaluate acute outcomes in patients with acute HF using noninvasive Forrester classification. Echocardiography offers a major advantage over right heart catheterization because it is noninvasive. Patients presenting with low CI and high E/e' values exhibit a higher event rate during hospitalization and require meticulous treatment selection. A combination of physical examinations, biomarker analyses, and noninvasive Forrester classification using echocardiography as an initial assessment could be effectively employed to risk-stratify patients with acute heart failure.

Our study has certain limitations. First, concern remains that the assessment of congestion by E/e' is suboptimal. It is important to emphasize that congestion is a well-known risk factor for adverse outcomes, and this study does not overturn that knowledge but focuses solely on the acute phase of heart failure hospitalization. Second, there exists ambiguity concerning the definition of WHF. Four out of the fifty-eight patients who encountered the WHF were administered inotropic drugs less than two hours following initial therapy. Determining

whether these cases indicate HF exacerbation or management strategy errors is not feasible. Additionally, due to the multicenter design of the study, the indication for inotropic agents may vary across centers. The lack of clarity in the definitions of these outcomes may have impacted the investigation results. Third, the echocardiographic findings before treatment in this investigation were not concealed from the clinician, potentially impacting patient management. Although the administration of inotropic agents was explicitly intended for patients who exhibited resistance to normalizing parameters such as hypotension, peripheral circulatory disturbances, and circulating blood volume following initial treatment, it cannot be denied that echographic findings of low output might drive inotrope initiation, and thus primary endpoint, remains a concern. A sensitivity analysis excluding cases in which inotropic were used within 6 hours after echocardiography (averaging 11 hours after the hospital visit) yielded results that support the present study (Supplemental Figure). Fourth, the short observation period underestimates event rates. The investigation centered on the acute prognosis of individuals suffering from acute heart failure, in part to curtail attrition resulting from hospital discharge, and the duration of the observation interval was limited to 14 days. Therefore, the results cannot be extrapolated to the chronic HF population. Fifth, the study used LV stroke volume and cardiac output were estimated from LV outflow pulsed-wave Doppler images and LV outflow tract diameter, which may not be accurate in cardiomyopathy with LV outflow obstruction or in patients with aortic valve disease. Sixth, the study's design imposed constraints on the case count as the protocol mandated precise echocardiographic data immediately upon admission for patients with ADHF. Finally, we did not evaluate using an external validation cohort.

 In conclusion, the Forrester classification, derived from noninvasive Doppler echocardiography at admission, may predict early deterioration in patients hospitalized with acute HF.

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Figure legends

Figure 1: Patient selection. CI, cardiac index

Figure 2: a) Definition of each profile b) Composite outcome incidence within 14 days according to profile. CI, cardiac index

Figure 3: Kaplan-Meier major adverse cardiovascular event-free survival according to profile.

Figure 4: Unadjusted and adjusted 14 days composite outcome incidence according to profile within 14 days.

Table 1

1

Table 1: Clinical characteristics

Variable	All (n=270)	Profile Ⅰ (dry-warm) (n=40)	Profile Ⅱ (wet-warm) (n=114)	Profile Ⅲ (dry-cold) (n=31)	Profile Ⅳ (wet-cold) (n=85)	p value for trend
Age.y	74±14	74±14	79±10	68±17	70±14	<0.01
Male sex, n (%)	162 (60)	21 (53)	57 (50)	23 (74)	61 (72)	<0.01
Body mass index	24±5	24±5	23±4	25±5	24±5	0.32
Systolic BP, mmHg	138±36	150±39	144±32	127±33*	127±38*	<0.01
Diastolic BP, mmHg	80±22	87±24	81±23	77±16	78±23	0.17
Heart rate, beats/min	93±27	99±26	93±27	97±32	88±23	0.15
NYHA functional class	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	0.95
Cardiac disease, n(%)						<0.01
Ischemic heart disease	69 (26)	9 (23)	31 (27)	6 (19)	23 (27)	
Non-ischemic dilated cardiomyopathy	46 (17)	8 (20)	8 (7)	5 (16)	25 (29)	
Left-sided valvular heart disease	44 (16)	5 (13)	27 (24)	2 (7)	10 (12)	
Hypertensive heart disease	30 (11)	4 (10)	15 (13)	1 (3)	10 (12)	
Hypertrophic cardiomyopathy	10 (4)	0 (0)	5 (4)	2 (7)	3 (4)	
Others	71 (26)	14 (35)	28 (25)	15 (48)	14 (17)	
Medications, n(%)						
Loop diuretics	151 (56)	21 (53)	65 (57)	14 (45)	51 (60)	0.52
ACE inhibitors or ARBs	126 (47)	21 (53)	52 (46)	10 (32)	43 (51)	0.30
Beta blockers	147 (54)	25 (63)	60 (53)	12 (39(	50 (59)	0.18
Calcium channel blockers	84 (31)	13 (33)	50 (44)	8 (26)	13 (15)	<0.01
MRAs	77 (29)	8 (20)	28 (25)	7 (23)	34 (40)	0.04
Physical assessment, n(%)						
cold extremities	69 (26)	14 (35)	24 (21)	10 (32)	21 (25)	0.28
impaired mentation	20 (7)	4 (10)	6 (5)	4 (13)	6 (7)	0.47
extremities edema	165 (61)	17 (43)	81 (71)	17 (55)	50 (59)	0.01
jugular vein distention	117 (43)	12 (30)	50 (44)	31 (48)	40 (47)	0.29
physical assessment score	1 (0-2)	1 (0-2)	1 (1-2)	1 (0-2)	1 (0.8-2)	0.59
Laboratory data						
Hemoglobin, g/dL	12±3	12±3	11±2	13±3	13±2	<0.01
eGFR, mL/min/1.73m^2	47±21	55±21	46±22	49±21	44±18*	0.03
Sodium, mEq/L	139±4	139±3	139±4	138±6	138±4	0.23
Potassium, mEa/L	4.2±0.6	4.2±0.6	4.1±0.6	4.3±0.7	4.2±0.6	0.14

Log BNP	6.5±0.8	6.2±0.9	6.5±0.7	6.4±0.8	6.8±0.7*	<0.01
Echocardiographic data at admission						
E/e'	21±11	12±3	25±12*	11±3	24±7*	*
LVOT-VTI	14±6	16±6	17±6	11±4	11±4	*
Cardiac index, L/min/m^2	2.5±1.0	3.1±0.8	3.1±0.9	1.7±0.4*	1.6±0.4*	*
LV ejection fraction, %	41±18	44±16	47±17	38±18	31±15*	<0.01
TR peak velocity, m/s	3.0±0.6	2.9±0.6	3.0±0.5	2.7±0.6	3.0±0.5	0.11

Values are mean ± SD or median (interquartile range) or n (%). *p<0.05, each profiles versus profile I.

CI= cardiac index, BP= blood pressure, NYHA=New York Heart Association, ACE=angiotensin-converting enzyme, ARB=aldosterone receptor blocker, MRA=mineralocorticoid receptor antagonist, eGFR = estimated glomerular filtration rate, BNP = plasma B-type natriuretic peptide level, E = early diastolic transmitral flow velocity, e' = early diastolic mitral annular velocity, LVOT-VTI=left ventricle outflow tract-velocity time integral, LV=left ventricle, TR= tricuspid regurgitation. * definitional variables

Table 2

Table 2 Determinations of composite outcome

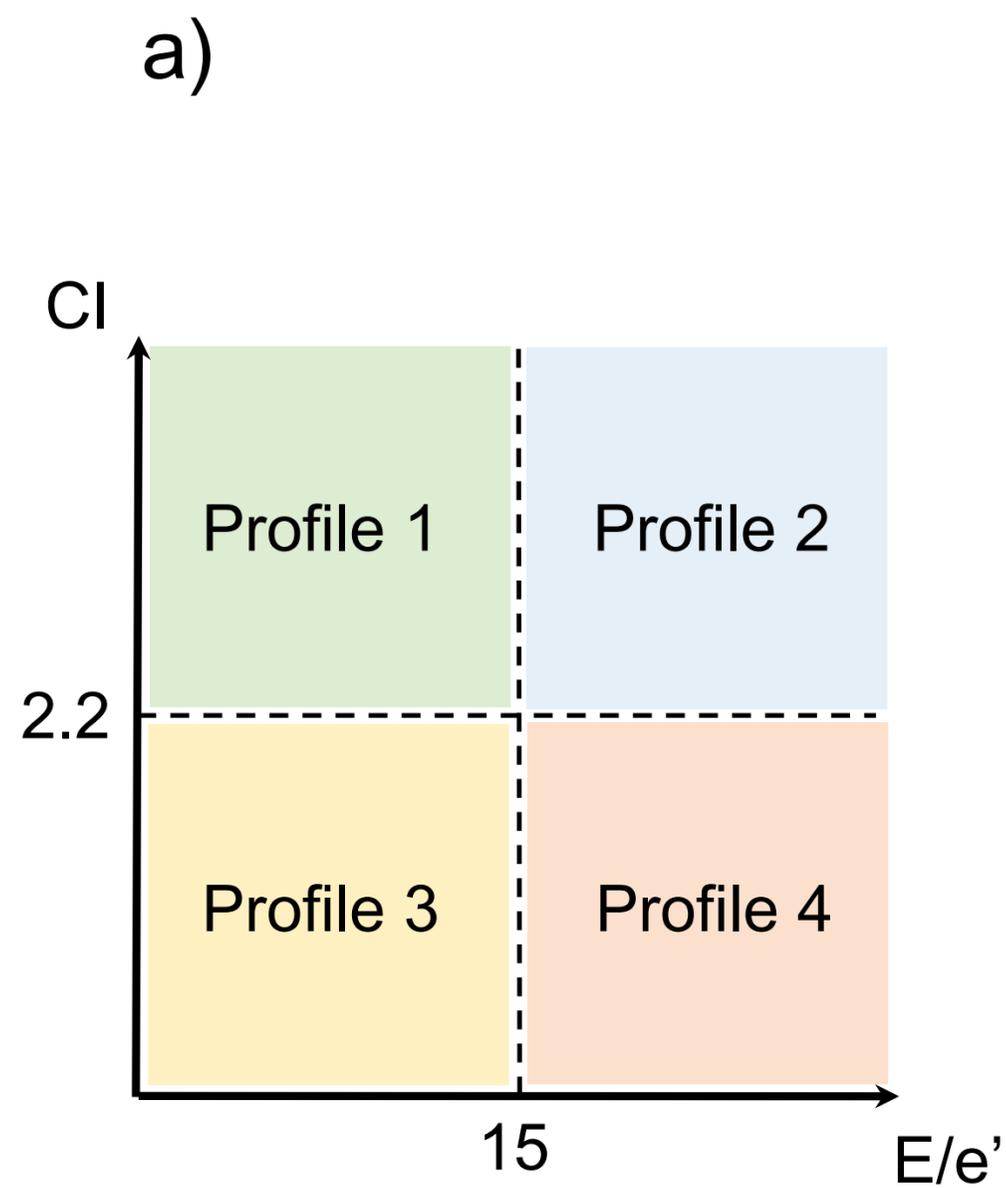| Variables	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age. 1year	0.96 (0.94-0.98)	<0.01	0.97 (0.95-1.00)	0.03
Sex, male	4.38 (2.11-9.09)	<0.01	5.01 (1.98-12.69)	<0.01
Log BNP, 0.1	1.14 (1.09-1.20)	<0.01	1.14 (1.08-1.21)	<0.01
NYHA, 1 grade	2.84 (1.77-4.54)	<0.01	3.52 (1.96-6.31)	<0.01
Profile, 1 grade	2.27 (1.67-3.07)	<0.01	1.93 (1.35-2.77)	<0.01
CI<2.2	5.27 (2.78-9.99)	<0.01		
E/e'≧15	1.78 (0.87-3.66)	0.12		

BNP = plasma B-type natriuretic peptide level, NYHA=New York Heart Association functional class, CI= cardiac index, E = early diastolic transmitral flow velocity, e' = early diastolic mitral annular velocity.
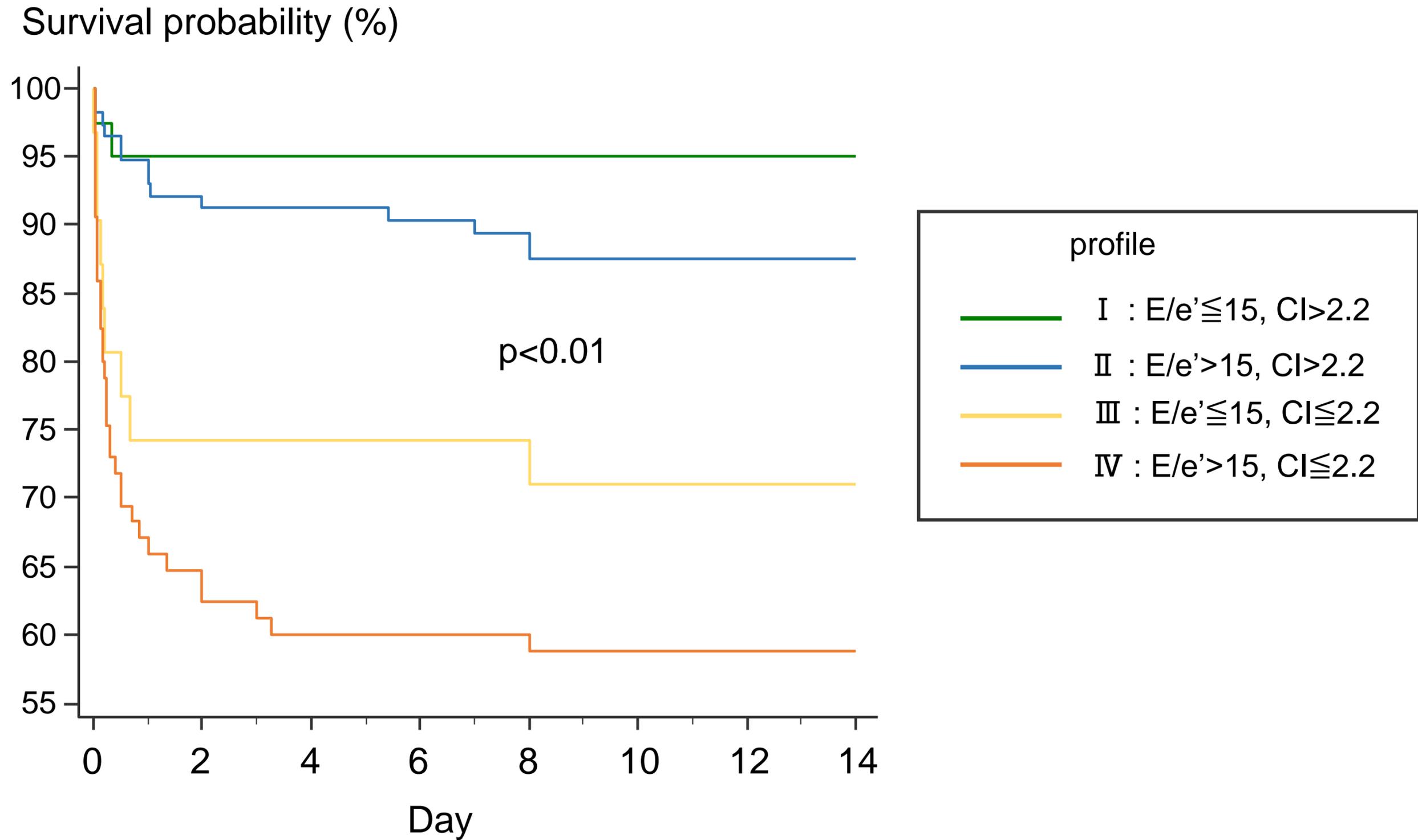
Figure 1

Figure 1

Top

Registered in the PREDICT study
(n=303)

Lack of data necessary
for classification (n=33)

Classified by E/e' ratio and CI values
on echocardiography at admission
(n=270)

Profile I :
E/e'≦15, CI>2.2
(n=40)

Profile II :
E/e'>15, CI>2.2
(n=114)

Profile III :
E/e'≦15, CI≦2.2
(n=31)

Profile IV :
E/e'>15, CI≦2.2
(n=85)

Bottom

Figure 2

Figure 2

Figure 3

Figure 3

Top

Bottom

Figure 4

Figure 4
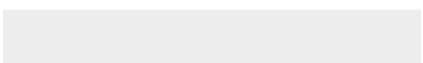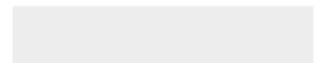
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