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ORIGINAL ARTICLE
Heart failure

Risk stratification of Stage B heart failure with BNP levels of 35–100 pg/mL: development of the PHASE Index from the CHART-2 Study

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Aims B-type natriuretic peptide (BNP) levels of 35–100 pg/mL, common in preclinical heart failure (HF), are associated with heterogeneous prognosis and are influenced by age and renal function. We aimed to characterize risk heterogeneity in preclinical HF patients with BNP levels of 35–100 pg/mL and to develop a practical risk stratification model.

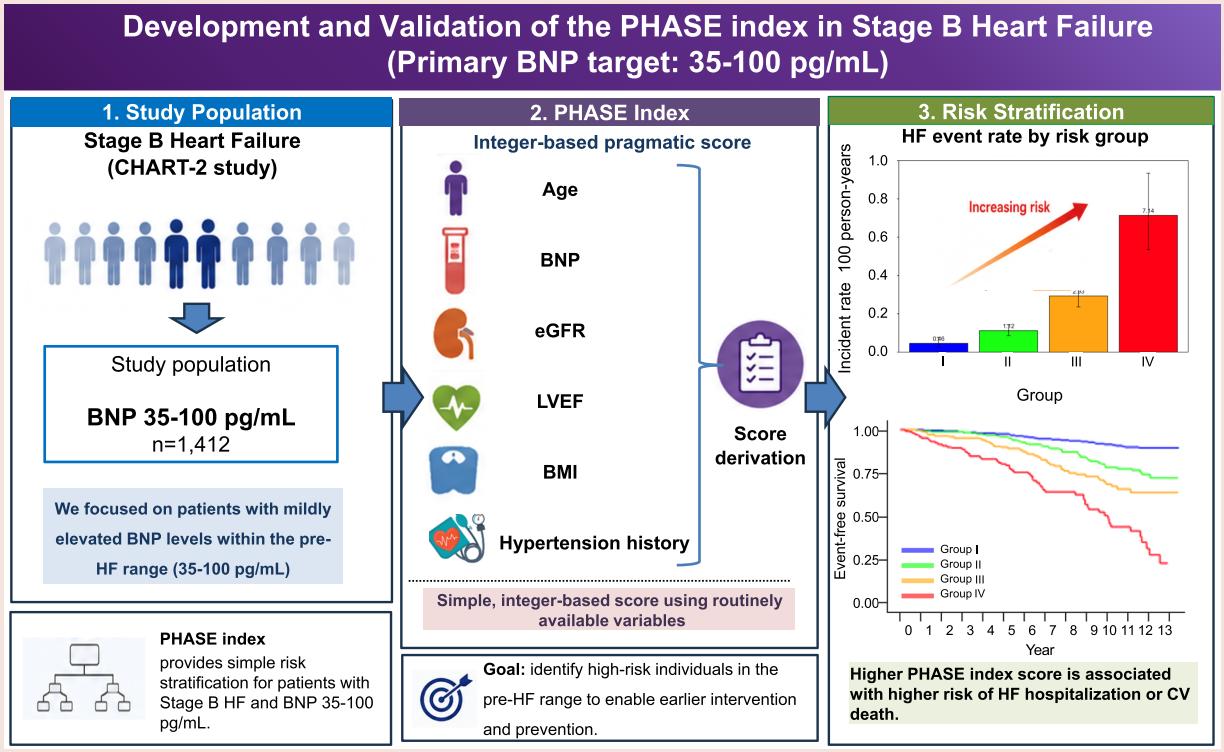
Methods and results Data from the Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2) Study, a prospective multicentre cohort with long-term follow-up, were analysed. Among patients with Stage B HF (n = 4074; age 67.6 ± 12.0 years), the predictability of BNP for 10-year HF-related events was evaluated across strata of age and estimated glomerular filtration rate (eGFR). In patients with BNP levels of 35–100 pg/mL, a composite risk score—the Pre-Heart Failure Assessment and Screening Evaluation (PHASE) Index—was developed using classification and regression tree analysis and multivariable Cox proportional hazards modelling. BNP discrimination varied significantly by age and eGFR (P < 0.05), indicating that a single BNP threshold is insufficient for risk stratification in preclinical HF. The PHASE Index, incorporating age, BNP, eGFR, left ventricular ejection fraction, body mass index, and hypertension, stratified patients with BNP levels of 35–100 pg/mL into four categories and demonstrated superior discrimination compared with BNP alone (c-index 0.723 vs. 0.587, P < 0.05).

Conclusion Patients with preclinical HF and BNP levels of 35–100 pg/mL exhibit substantial risk heterogeneity. The PHASE Index improves identification of high-risk individuals and provides a pragmatic tool for risk stratification beyond the conventional BNP threshold.

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Graphical abstract



Keywords Heart failure • B-type natriuretic peptide • Epidemiology • Pre-heart failure

Introduction

Heart failure (HF) is a progressive disorder where prognosis is often determined before the onset of overt symptoms. Consequently, early identification of individuals at high risk for developing HF represents an important goal of contemporary management.[1–3] Although current preventive strategies emphasize early interventions to delay progression,[1,4] accurately identifying patients with preclinical HF remains challenging.

Current guidelines define Stage B HF as the presence of structural heart disease (SHD) or evidence of increased cardiac stress, including elevated B-type natriuretic peptide (BNP) levels without symptoms.[1,2] Recent evidence has demonstrated that even in the absence of overt SHD, elevated cardiac biomarkers are significantly associated with an increased risk for incident HF.[5] Specifically, BNP levels <35 pg/mL are generally used to exclude overt HF in ambulatory settings,[3,6] whereas higher thresholds (e.g. >100 pg/mL) are applied in acute settings for diagnostic purposes.[7,8] The present study does not propose alternative diagnostic cut-offs. Instead, it focuses on risk stratification among patients with Stage B heart failure and this range: BNP levels of 35–100 pg/mL, a clinically heterogeneous population without overt HF for whom no established risk stratification strategy currently exists. The present study aimed to improve risk stratification for the progression from Stage B to symptomatic (Stage C) HF in this population, rather than to redefine diagnostic thresholds. Furthermore, interpretation of BNP is often confounded by clinical modifiers,[9–12] necessitating a re-evaluation of these factors to optimize its predictability for HF events.

Using data from the Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2) study, we first examined clinical factors that modify the prognostic performance of BNP within a well-defined Stage B HF population. Based on these findings, we focused on the clinically uncertain subgroup with BNP levels of 35–100 pg/mL to develop a multivariable, easily applicable risk stratification model to better identify individuals at increased risk for future HF events.

Methods

Study patients

The Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2) Study is a prospective, observational, multicentre cohort study designed to investigate the full spectrum of HF in the Tohoku district of Japan.[13] Between 2006 and 2010, a total of 10 209 consecutive patients with established HF or at risk for HF were enrolled and followed up for more than 10 years, as previously described.[14–16]

In accordance with contemporary guideline definitions, Stage B HF (pre–heart failure) was defined as the presence of SHD and/or elevated BNP levels (≥35 pg/mL), in the absence of signs or symptoms of HF.[1,2] Within the CHART-2 cohort, detailed criteria for SHD have been described previously.[13] Briefly, SHD was defined by the presence of at least one of the following: left ventricular (LV) enlargement [LV end-diastolic diameter (LVEDD) ≥ 55 mm], systolic

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dysfunction [LV ejection fraction (LVEF) ≤ 50%], LV hypertrophy [thickened interventricular septum (>12 mm) and/or thickened LV posterior wall (>12 mm) measured by echocardiography], significant valvular disease, congenital abnormalities, or history of cardiac surgery. All participants classified as Stage B HF were evaluated in stable outpatient settings without evidence of acute decompensated HF at the time of BNP measurement.

Consistent with this definition, patients were classified as having Stage B HF if they met either criterion. Individuals with Stage A, Stage C, or Stage D HF, as well as those without baseline BNP data, were excluded from the present analysis. Accordingly, a total of 232 patients without SHD but with BNP levels ≥35 pg/mL were included and were newly categorized as Stage B HF. After application of these criteria, the final analytic cohort consisted of 4074 patients with Stage B HF (see Supplementary material online, *Figure S1*).

The present study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (No. 2023-1-625-1), and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Outcomes

The primary composite endpoint was defined as the first occurrence of HF or cardiovascular death. HF hospitalization was defined as hospitalization for worsening HF requiring intravenous treatment or inpatient management, and was adjudicated separately from cardiovascular death. The analysis was performed as a time-to-first-event composite endpoint. HF-related events were assessed over a 10-year follow-up period. Clinical outcomes were adjudicated independently by at least two experienced cardiologists from the CHART-2 investigation team who were not involved in the patients' clinical care. Adjudication was based on review of medical records, interviews with treating physicians, and death certificates, as previously described.[15,16] HF hospitalization was defined as the first occurrence of hospitalization for worsening HF requiring administration of at least two diuretics or intravenous inotropes or vasodilators, accompanied by at least two clinical symptoms consistent with HF.[16] All-cause mortality was not included in the primary endpoint because the primary objective of this study was to evaluate progression from Stage B (pre-heart failure) to symptomatic Stage C HF, rather than overall mortality.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate based on their distribution. Categorical variables are presented as counts and percentages. Event-free survival was estimated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. For age-stratified analyses, participants were divided into quartiles. Univariable and multivariable survival analyses were conducted using Cox proportional hazards models incorporating clinically relevant covariates. To evaluate the discriminative ability of baseline BNP for predicting 10-year HF-related events across clinical strata (***Figure 1***), receiver operating characteristic (ROC) curve analyses were performed after dichotomizing the outcome as the presence or absence of events within 10 years. Participants who were censored before 10 years were excluded from this ROC analysis. The area under the ROC curve (AUC) was calculated for each stratum, and optimal BNP cut-off values were determined by maximizing the Youden index. AUCs were compared between strata using DeLong's test with two-sided *P*-values corresponding to the pairwise comparisons.

We selected the clinical factors modifying the association between BNP and future HF-related events based on prior evidence. Specifically, candidate variables (age, BNP, BMI, estimated glomerular filtration rate (eGFR), LVEF, and history of hypertension) were identified based on clinical relevance and existing literature.[9–11,17–20] To identify optimal cut-off values for continuous variables and to explore potential interactions among predictors, classification, and regression tree (CART) analysis was applied as a non-parametric recursive partitioning method that divides the cohort into subgroups with similar risk profiles.[21,22] Based on CART-derived thresholds and hazard ratios from multivariable Cox models, a composite risk score—the Pre-Heart Failure Assessment and Screening Evaluation (PHASE) Index—was constructed specifically for patients with BNP levels of 35–100 pg/mL. To identify cut-off values for the CART analysis, the continuous predictors were then categorized according to the CART-derived thresholds, whereas hypertension was treated as a binary variable. Adjusted hazard ratios (HRs) for the resulting categories were estimated using a multivariable Cox proportional hazards model. For each non-reference category, integer points were assigned by rounding the adjusted HR to the nearest whole number, whereas all reference categories were assigned 0 points. The PHASE Index was calculated as the sum of these points. A second CART analysis was subsequently applied to the total PHASE Index score to identify cut-off values for classification into four risk categories. Internal validity of the PHASE Index was evaluated using 10-fold cross-validation and bootstrap resampling with 10 000 iterations. Predictive accuracy and reproducibility were determined using Harrell's C-index.

To assess potential nonlinear relationships between covariates and outcomes, an additive Cox proportional hazards model was additionally applied using the survival package (version 3.5-7) and mgcv package (version 1.9-1) in R. All statistical tests were two-sided, and a *P*-value <0.05 was considered statistically significant. Analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics of Stage B HF

To characterize the clinical heterogeneity of Stage B HF in this context, we examined baseline features of the overall Stage B cohort ($n = 4074$) (*Table 1*). Patients were stratified into three groups according to the presence of SHD and baseline BNP levels: (i) those with both SHD and BNP levels ≥ 35 pg/mL ($n = 2397$), (ii) those with SHD but BNP levels < 35 pg/mL ($n = 1445$), and (iii) those without SHD but BNP levels ≥ 35 pg/mL ($n = 232$).

As shown in *Table 1*, patients with SHD and BNP levels ≥ 35 pg/mL exhibited larger LVEDD and lower LVEF than patients in the other two groups. In contrast, patients without SHD but with BNP levels ≥ 35 pg/mL tended to be less frequently treated with cardiovascular medications despite elevated BNP levels.

Determinants of BNP performance in Stage B HF

To understand why a single BNP threshold is insufficient for risk stratification in Stage B HF, we first examined clinical factors modifying the association between BNP and future HF-related events in the entire Stage B cohort. Among the candidate variables identified from prior evidence,[9–11,17–20] univariable analyses supported the associations of these variables with the study outcome (see Supplementary material online, *Tables S1 and S2*), and we focused on age, eGFR, and BMI as key determinants of BNP variability and its predictability.

As shown in *Figure 1*, the discriminative ability of BNP for predicting 10-year HF-related events differed markedly across the clinical subgroups. The area under the curve (AUC) was significantly larger in younger patients (<60 years) compared with those in the oldest age quartile (≥76 years; $P < 0.05$, *Figure 1A*), indicating that BNP level becomes less reliable as a predictive marker with advancing age. Similarly, predictive performance of BNP level was lower in patients with impaired renal

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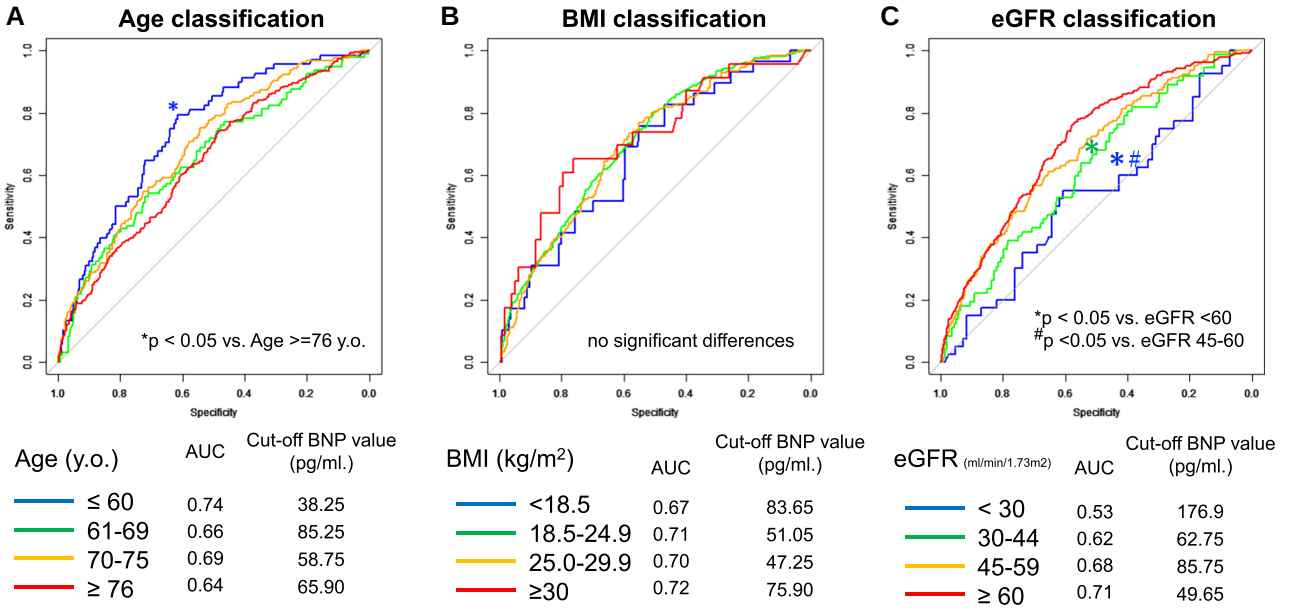


Figure 1 Modulation of BNP predictability for heart failure hospitalization across clinical strata. BNP predictability for heart failure hospitalization stratified by major clinical modifiers. (*A*) Age strata. Patients were categorized into four age quartiles: ≤60 years (blue), 61–69 years (green), 70–75 years (orange), and ≥76 years (red). *P < 0.05 vs. ≥ 76 years. (*B*) Body mass index (BMI) strata. Patients were classified according to World Health Organization BMI categories: <18.5 kg/m^2 (blue), 18.5–24.9 kg/m^2 (green), 25.0–29.9 kg/m^2 (orange), and ≥30 kg/m^2 (red). (*C*) Renal function strata. Patients were stratified by estimated glomerular filtration rate (eGFR) based on chronic kidney disease stages: <30 mL/min/1.73 m^2 (blue), 30–44 mL/min/1.73 m^2 (green), 45–59 mL/min/1.73 m^2 (orange), and ≥60 mL/min/1.73 m^2 (red). *P < 0.05 vs. eGFR ≥60 mL/min/1.73 m^2; #P < 0.05 vs. eGFR 45–59 mL/min/1.73 m^2.

function, i.e. those with eGFR <30 mL/min/1.73 m^2, who exhibited significantly smaller AUCs than those with preserved renal function (P < 0.05, *Figure 1C*). In contrast, the AUCs did not vary significantly across BMI categories (*Figure 1B*). Concordant with these findings, the optimal BNP cut-off for predicting HF events shifted considerably by age, with the lowest threshold (38.25 pg/mL) observed in the youngest quartile.

Targeted risk stratification for patients with BNP levels of 35–100 pg/mL in preclinical HF

Given the substantial heterogeneity in BNP performance, we subsequently focused specifically on patients with BNP levels between 35 and 100 pg/mL. Among the initial 4074 patients with Stage B HF, 1412 patients had BNP levels within the prespecified range of 35–100 pg/mL and were included in the primary risk stratification analysis (*Table 2*). This population represents preclinical HF, yet it remains challenging to identify high-risk individuals reliably using current methods. Compared with patients with BNP ≥ 100 pg/mL, this group exhibited higher LVEF. Guided by prior literature[9–11,17,19,20] and the univariable analyses, we selected age, BNP, BMI, eGFR, LVEF, and history of hypertension as candidate predictors. Blood pressure and heart rate were excluded from the model because of their marked short-term variability. Using CART analysis, we determined optimal thresholds for each continuous variable (see Supplementary material online, *Figure S2*), followed by multivariable Cox modelling to estimate hazard ratios for HF-related events (*Table 3*). Each variable was weighted according to its hazard ratio to construct a composite risk score. Points were assigned to each variable based on the magnitude of its hazard ratio (*Table 3*, right column). The total risk score was then calculated for each individual by summing these points. For BNP, the initial CART analysis identified three risk strata within the 35–100 pg/mL range, which were incorporated into the multivariable model and assigned integer points accordingly (*Table 3*).

Subsequently, we performed a second CART analysis using this total risk score to derive the PHASE Index. This analysis categorized patients into four distinct PHASE Index risk groups: Group I (score ≤4.5, n = 309), Group II (4.5–7.4, n = 590), Group III (7.5–10.4, n = 388), and Group IV (≥10.5, n = 125) (*Figure 2A*). Because each component variable of the PHASE Index is evaluated using discrete risk categories with assigned points, the final score is expressed as a simple integer, facilitating clinical application.

As shown in *Figure 2B*, HF-related event rates increased stepwise across the PHASE Index categories, with significant differences observed across the strata. The PHASE Index showed superior discriminative performance compared with BNP alone (P < 0.05, *Table 4*), indicating that the integration of BNP with key clinical variables improves identification of high-risk individuals for HF events within the BNP range of 35–100 pg/mL. The index demonstrated a Harrell's C-index of 0.72 (95% CI: 0.69–0.76). Internal validation supported model stability; the mean C-index estimated by 10-fold cross-validation was 0.71 (SD: 0.044), and bootstrap validation with 10 000 iterations yielded a similar mean C-index of 0.72 (SD: 0.0045). These validation results indicate consistent model performance across resampling procedures.

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Table 1 Baseline characteristics of patients with stage B heart failure

	Overall	(–) SHD (BNP ≥ 35 pg/mL)	(+) SHD (BNP < 35 pg/mL)	(+) SHD (BNP ≥ 35 pg/mL)	*P*-value
Patient number	4074	232	1445	2397	
Age (y.o.)	67.6 ± 12	72.4 ± 7.9	62.8 ± 12.8	70 ± 10.9	<0.001
Gender (Female, *n* [%])	1167 [28.6]	85 [36.6]	305 [21.1]	777 [32.4]	<0.001
BMI (kg/m^2)	24.2 ± 3.5	23.2 ± 3.1	24.8 ± 3.5	23.9 ± 3.4	<0.001
History					
Hypertension, *N* (%)	3700 (90.8)	215 (92.7)	1282 (88.7)	2203 (91.9)	0.002
DM, *N*, (%)	1330 (32.6)	85 (36.6)	482 (33.4)	763 (31.8)	0.255
Dyslipidaemia, *N* (%)	3394 (83.3)	200 (86.2)	1233 (85.3)	1961 (81.8)	0.009
AF, *N* (%)	548 (13.5)	22 (9.5)	29 (2.0)	497 (20.7)	<0.001
Stroke, *N* (%)	782 (19.2)	54 (23.3)	210 (14.5)	518 (21.6)	<0.001
Cancer, *N* (%)	559 (13.7)	40 (17.2)	156 (10.8)	363 (15.1)	<0.001
CKD, *N* (%)	1323 (32.6%)	73 (31.7%)	330 (22.9%)	920 (38.5%)	<0.001
Vital signs					
Systolic BP (mmHg)	130.1 ± 17.9	129.3 ± 19.2	130.4 ± 16.7	129.9 ± 18.4	0.557
Heart rate (bpm)	69.6 ± 13.3	67.1 ± 11.8	69.6 ± 12.5	69.9 ± 13.9	0.011
Echocardiography					
LVEDD (mm)	48.9 ± 7.1	46.0 ± 4.7	48.9 ± 6.8	49.3 ± 7.4	<0.001
LVEF (%)	64.3 ± 11.8	69.1 ± 7.5	65.3 ± 10.8	63.2 ± 12.6	<0.001
LV mass index	124.5 ± 38	101 ± 21.3	116.9 ± 33.6	131.3 ± 39.9	<0.001
LAD (mm)	40.1 ± 7.7	38.3 ± 6.3	37.4 ± 6.1	41.8 ± 8.2	<0.001
Laboratory data					
Hb (g/dL)	13.6 ± 1.7	13.0 ± 1.6	14.1 ± 1.5	13.3 ± 1.8	<0.001
LDL-C(mg/dL)	106.6 ± 29.2	99.8 ± 27.3	109.4 ± 29.8	105.6 ± 28.8	<0.001
eGFR (mL/min/1.73m^2)	67 ± 19.4	66.8 ± 18	72.1 ± 18.3	64 ± 19.6	<0.001
BNP (pg/mL)	101.2 ± 188.9	92.7 ± 68.2	18.2 ± 8.9	152.1 ± 231.1	<0.001
Medication					
ACEi, *N* (%)	1151 (28.3)	49 (21.1)	389 (26.9)	713 (29.7)	0.008
ARB, *N* (%)	1498 (36.8)	83 (35.8)	539 (37.3)	876 (36.5)	0.850
Beta blockers, *N* (%)	1384 (34.0)	84 (36.2)	364 (25.2)	936 (39.0)	<0.001
MRA, *N* (%)	193 (4.7)	8 (3.4)	40 (2.8)	145 (6.0)	<0.001
Ca-antagonists, *N* (%)	2023 (49.7)	158 (68.1)	714 (49.4)	1151 (48)	<0.001
Loop diuretics, *N* (%)	503 (12.3)	21 (9.1)	98 (6.8)	384 (16.0)	<0.001

Results are presented as the average or patient number, *N* (%).
P-values were calculated using one-way ANOVA for continuous variables and the chi-squared test for categorical variables across the three groups.
Abbreviations: SFHD, structural/functional heart disease; BMI, body mass index; DM, diabetes mellitus; AF, Atrial fibrillation; CKD, chronic kidney disease (eGFR <60 mL/min/1.73m^2); BP, blood pressure; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; Hb, haemoglobin; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Discussion

The present study addresses a major unmet need in preclinical (Stage B) HF, i.e. the identification of individuals at the highest risk for future HF events among patients with BNP levels of 35–100 pg/mL, which is a range classified as preclinical HF but marked by profound risk heterogeneity. The results demonstrate that the predictive value of BNP for HF events is strongly modulated by age and renal function, underscoring the limitation of a single universal BNP threshold for risk stratification in this population, while simultaneously emphasizing the validity of 35 pg/mL as a robust rule-out threshold. To address this challenge, a CART-based multivariable risk stratification model—the Pre-Heart Failure Assessment and Screening Evaluation (PHASE) Index—was developed specifically for patients with BNP levels of 35–100 pg/mL. The PHASE Index integrated BNP with key clinical variables to classify patients into four distinct risk categories with stepwise increment in the incidence of future HF events, offering significantly superior risk discrimination compared with BNP alone. This study demonstrated a very high prevalence of hypertension (~90%) in the cohort (*Table 1*), whereas the use of cardioprotective therapies such as renin–angiotensin–aldosterone system inhibitors and beta-blockers remained low. These findings highlight a substantial treatment gap and may indicate an opportunity for earlier preventive intervention to reduce the risk of progression to overt HF in Stage B patients.

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Table 2 Baseline characteristics of patients with pre–heart failure (BNP 35–100 pg/mL)

	Pre-heart failure (BNP ranged 35–100 pg/mL)	Stage B (BNP above 100 pg/mL)	*P*-value
Patient number	1412	1217	
Age (y.o.)	69.6 ± 10.6	70.9 ± 10.8	0.001
Gender (female %)	434 (30.7%)	428 (35.2%)	0.018
BMI (kg/m^2)	24 ± 3.3	23.7 ± 3.4	0.010
History			
Hypertension, *N* (%)	1287 (91.1%)	1131 (92.9%)	0.098
DM, *N*, (%)	474 (33.6%)	374 (30.7%)	0.122
Dyslipidaemia, *N* (%)	1201 (85.1%)	960 (78.9%)	<0.001
AF, *N* (%)	152 (10.8%)	367 (30.2%)	<0.001
Stroke, N (%)	277 (19.6%)	295 (24.2%)	0.004
Cancer, *N* (%)	202 (14.3%)	201 (16.5%)	0.128
Vital signs			
Systolic BP (mmHg)	130.3 ± 17.9	129.4 ± 19.1	0.238
Heart rate (bpm)	68.8 ± 13	70.6 ± 14.5	<0.001
Echocardiography			
LVEDD (mm)	48.9 ± 7.1	49.1 ± 7.5	0.437
LVEF (%)	64.4 ± 11.9	62.9 ± 12.7	0.003
LV mass index	123.4 ± 36.2	134.2 ± 42.3	<0.001
LAD (mm)	39.9 ± 7.7	43.3 ± 8.2	<0.001
Laboratory data			
Hb (g/dL)	13.4 ± 1.6	13.1 ± 1.9	<0.001
Alb(g/dL)	4.1 ± 0.4	4.0 ± 0.5	<0.001
LDL-C (mg/dL)	105.4 ± 28.5	104.7 ± 28.9	0.597
eGFR (mL/min/1.73 m^2)	66.6 ± 18.5	61.4 ± 20.1	<0.001
BNP (pg/mL)	60.6 ± 18.1	247.0 ± 296.1	NA
Medication			
ACEi, *N* (%)	404 (28.6%)	358 (29.4%)	0.666
ARB, *N* (%)	517 (36.6%)	442 (36.3%)	0.903
Beta blockers, *N* (%)	471 (33.4%)	549 (45.1%)	<0.001
MRA, *N* (%)	66 (4.7%)	87 (7.1%)	0.007
Ca-antagonists, *N* (%)	722 (51.1%)	587 (48.2%)	0.148
Loop diuretics, *N* (%)	169 (12%)	236 (19.4%)	<0.001

Abbreviations are listed in *Table 1*.
Values are mean ± SD or n (%). *P*-values were calculated using Student's *t*-test for continuous variables and the chi-squared test for categorical variables.

Table 3 Multivariable cox proportional hazards model for HF-related events

Variables	HR	95% CI (Lower)	95% CI (Upper)	*P*-value	Assigned points
BNP ranged 41.45–84.25 pg/mL	1.97	1.20	3.22	0.007	2
BNP > 84.25 pg/mL	2.69	1.55	4.67	<0.001	3
Age ranged 70.5–78.5 y.o.	2.02	1.46	2.81	<0.001	2
Age > 78.5 y.o.	3.73	2.62	5.32	<0.001	4
BMI < 22.14	1.29	0.97	1.73	0.078	1
eGFR < 44.75 mL/min/1.73m^2	2.66	1.88	3.74	<0.001	3
LVEF ranged 38–68%	1.84	1.37	2.47	<0.001	2
LVEF < 38%	3.52	1.98	6.25	<0.001	4
History of hypertension	1.60	0.84	3.05	0.150	2

HR, hazard ratio; CI, confidence interval. Other abbreviations are listed in *Table 1*.

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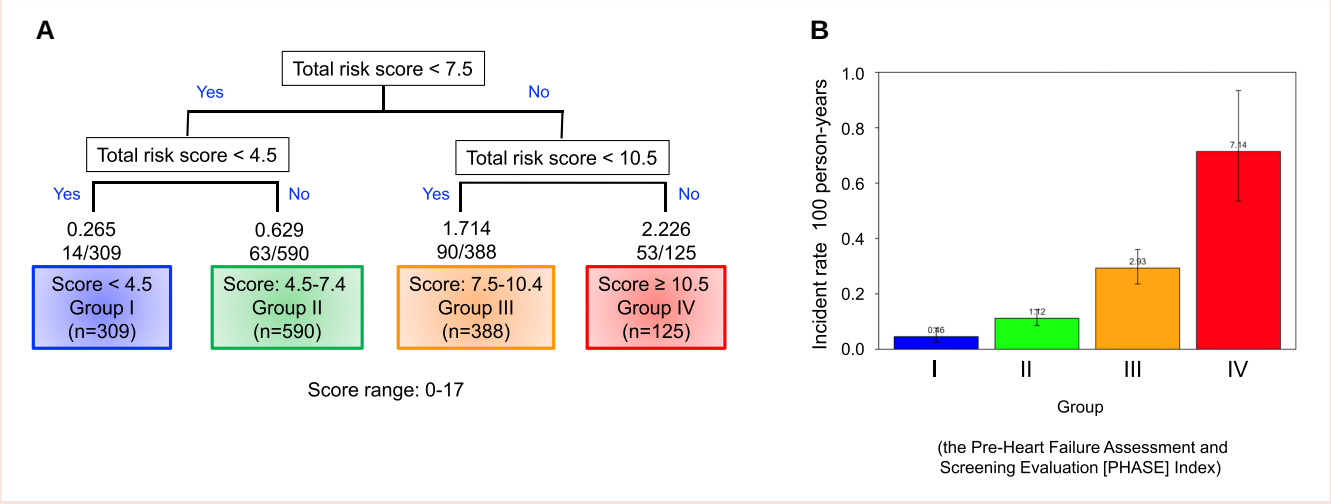


Figure 2. Development of the Pre-Heart Failure Assessment and Screening Evaluation (PHASE) Index in patients with BNP 35–100 pg/mL. Risk stratification among patients with BNP levels of 35–100 pg/mL using classification and regression tree (CART) analysis. CART-derived risk classification. *(A)* The decision tree–based, data-driven derivation of optimal cut-off values used to define the PHASE index risk categories prior to final classification into four study groups. (*B*) Pre-Heart Failure Assessment and Screening Evaluation (PHASE) Index risk categories. Based on CART analysis, patients were classified into four risk categories using the PHASE Index: Group I (blue), score ≤4.5; Group II (green), score 4.5–7.4; Group III (orange), score 7.5–10.4; Group IV (red), score ≥10.5. Because each component variable is evaluated using clearly defined categorical criteria with assigned points, the PHASE Index is expressed as a simple integer score, facilitating clinical applicability.

Table 4 Comparison of predictive performance between BNP alone and the pre–heart failure assessment and screening evaluation (PHASE) Index for HF-related events

	HR	95% CI (lower)	95% CI (upper)	*P*-value	c-index
BNP alone	1.02	1.01	1.02	<0.001	0.587
PHASE Index	1.37	1.31	1.44	<0.001	0.723

PHASE Index: the Pre-Heart Failure Assessment and Screening Evaluation Index

An unmet need in risk stratification for BNP levels of 35–100 pg/mL

Although circulating BNP levels are influenced by age, body habitus, and renal function,[9,10,18] our findings demonstrate that this variability itself is not the central issue. Rather, the critical limitation is that within the commonly used range of 35–100 pg/mL—often labelled 'preclinical' HF—evaluation based on BNP alone is insufficient for effective risk stratification.

While younger and older patients showed lower (38.25 pg/mL) and higher (65.9 pg/mL) optimal cut-offs, such recalibrations of cut-off values do not meaningfully improve clinical decision-making. Accordingly, the guideline threshold of 35 pg/mL should be viewed primarily as a rule-out point for Stage B HF identification, but not as a risk discriminator. In this range (BNP 35–100 pg/mL), clinicians currently lack a reliable method to distinguish low- from high-risk patients—an important unmet need that motivated this study.

Multivariable risk stratification using the PHASE Index and clinical implications

To address this unmet need, we developed the PHASE Index, which is a CART-derived, multivariable risk stratification tool that integrates BNP with key clinical modulators—pressure (hypertension), height/weight (BMI), age, Serum creatinine–based renal function (eGFR), and ejection fraction (LVEF)—rather than relying on a single biomarker threshold. This data-driven approach identified clinically interpretable combinations of variables that stratified risk effectively among patients with BNP levels of 35–100 pg/mL and demonstrated significantly superior predictability compared with BNP alone. Although the analysis focused on patients within the 35–100 pg/mL BNP range, rather than relying on a single binary threshold, BNP levels were stratified into three distinct categories using CART-derived cut-offs to assign weighted risk points. This approach preserves granular risk gradients while contextualizing modest BNP elevations through integration with key clinical modifiers.

From a clinical perspective, the PHASE Index provides a pragmatic framework for the management of Stage B (preclinical) HF. Patients classified into higher PHASE risk categories represent a subgroup with a substantially elevated likelihood of future HF events, for whom closer surveillance with serial BNP measurements and echocardiography may be justified. In such individuals, intensified management of modifiable risk factors—including hypertension, metabolic disorders, and atrial fibrillation—and consideration of early preventive therapeutic strategies are warranted, even in the absence of overt symptoms. Conversely, patients in lower PHASE risk categories may be managed conservatively, thereby minimizing unnecessary testing and overtreatment.

Collectively, these findings indicate that the PHASE Index evolves clinical decision-making beyond a uniform BNP cut-off

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and towards individualized risk assessment within the BNP range of 35–100 pg/mL, facilitating more targeted and efficient prevention strategies aimed at delaying or preventing progression to symptomatic HF.

Limitations

Several limitations of the present study should be acknowledged. First, although the CHART-2 study is a large-scale, prospective, multicentre registry with adjudicated outcomes and 10-year follow-up, our analyses were derived from a single dataset. The absence of an external cohort with comparable longitudinal data precluded independent external validation. Internal validation using bootstrapping and cross-validation demonstrated consistent model performance, but confirmation in independent populations is required. Future studies in diverse ethnic populations with standardized phenotyping and long-term follow-up are needed to evaluate the generalizability of this risk-stratification approach. Second, the study population was limited to Asian patients. In this registry, the prevalence of severe obesity (BMI ≥30 kg/m^2) was low at 5.0% (n = 205), which might have influenced the observed relationship between BMI and BNP levels. Because body size distributions significantly differ across regions,[20,23,24] the generalizability of our risk-stratification approach needs to be confirmed in non-Asian cohorts encompassing broader BMI ranges. In addition, beyond differences in BMI, ethnicity reflects underlying genetic, biological, and pathophysiological variability that may influence circulating biomarker levels and their prognostic thresholds.[25] Therefore, the fixed BNP-based cut-offs used in the PHASE index, derived from a Japanese population, may require recalibration and external validation before application to ethnically diverse populations. Third, regarding natriuretic peptides, BNP was used rather than NT-proBNP because BNP was the uniformly measured biomarker across all participating institutions during the CHART-2 study period, ensuring longitudinal consistency and minimizing inter-assay variability within this long-term observational cohort. The PHASE index was specifically derived and internally evaluated using BNP values within this harmonized dataset. Although BNP and NT-proBNP are strongly correlated and have been reported to have comparable predictability,[26] they are not directly interchangeable within the PHASE index framework. Furthermore, while conversion formulas between BNP and NT-proBNP have been proposed,[26] their application to PHASE index calculation may introduce additional variability and uncertainty in risk stratification due to biological and analytical non-linearity across concentration ranges. Therefore, the present findings may not be directly generalizable to settings in which NT-proBNP is the primary biomarker, and external validation in independent NT-proBNP–based cohorts is required before broader clinical application. Fourth, because the CHART-2 study was designed before 2005, advanced echocardiographic parameters (e.g. myocardial strain) were not collected, and some echocardiographic criteria used to define structural heart disease differ from those recommended in current guidelines. These differences should be considered when interpreting the present findings. Finally, the PHASE Index demonstrated modest discriminative ability (C-index = 0.723). Accordingly, its predictive performance should be interpreted with appropriate caution. Nevertheless, its principal value lies in providing a simple and practical approach to risk stratification using routinely available clinical variables. Furthermore, because Stage B HF comprises patients with diverse underlying cardiac disorders, the present study was designed to develop a risk stratification tool applicable to this overall population rather than to individual disease aetiologies. Further studies are warranted to evaluate the performance of the PHASE index in specific disease subgroups.

Conclusion

Although BNP is useful as a screening marker for Stage B HF, its ability to stratify future risk is limited within the range of 35–100 pg/mL. A multivariable, clinically interpretable framework, as represented by the PHASE Index, enables more refined risk stratification within this range and may support identification of individuals at increased risk for subsequent HF events, based on adjudicated 10-year follow-up data from the prospective CHART-2 cohort.

Data availability

Data are available from the corresponding author upon reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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