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Head-to-head comparison of diagnostic scores for acute heart failure in the Emergency Department: results from the PARADISE cohort

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Abstract

Background

BREST and PREDICA scores have recently emerged for the diagnosis of acute heart failure (AHF) in the emergency department (ED). This study aimed to perform a head-to-head comparison in a large contemporary cohort.

Method

BREST and PREDICA scores were calculated from respectively 11 and 8 routine clinical variables recorded in the ED in 1386 patients from PArADIsE cohort. The diagnostic performance of the scores for adjudicated AHF diagnosis was assessed by the area under the ROC curve (AUC). Acute HF diagnosis were adjudicated according to the European Society of Cardiology criteria and BNP levels.

Results

A BREST score ≤3 or PREDICA score ≤1 was associated with low probabilities of AHF (5.7% and 2.6% respectively). Conversely, a BREST score ≥9 or PREDICA score ≥5 was associated with a high risk of AHF diagnosis (77.3% and 66.9% respectively) although more than half of the population were within the "grey zone" (4-8 and 2-4 for the BREST and PREDICA scores, respectively). Diagnostic performances of both scores were good (AUC 79.1%, [66.1-82.1] for the BREST score and 82.4%, [79.8-85.0] for the PREDICA score). PREDICA score had significantly higher diagnostic performance than BREST score (increase in AUC 3.3 [0.8-5.8], p=0.009).

Conclusion

Our study emphasizes the good diagnostic performance of both BREST and PREDICA scores, albeit with a significantly higher diagnostic performance of the PREDICA score. Yet, more than half of the population are classified within the "grey zone" by these scores; additional diagnostic tools are needed to ascertain AHF diagnosis in the ED in a majority of patients.

Clinical Trial Registration: NCT02800122

Key words: Heart failure; Dyspnea; Diagnostic; Cardiac edema; Cardiovascular diseases.

INTRODUCTION

Acute Heart Failure (AHF) is a significant health concern often revealed by acute dyspnea. It is one of the leading causes of hospitalization in Western countries and is associated with mortality rates within months from diagnosis comparable or worse to most cancers and acute myocardial infarction [1,2]. In patients with acute dyspnea, accurately identifying AHF among other dyspnea causes remains a challenge in the Emergency Department (ED) [3–5]. An appropriate diagnosis in the ED is associated with better outcomes in patients with AHF [5,6], which prompted the most recent ESC guidelines to emphasize the importance of early AHF treatment [7–9].

Many AHF scores have been developed such as the NEWS [10] and GASP4R [11] scores although these scores are mostly prognostic. In addition, most of the latter were not designed in ED or prehospital settings. These scores moreover usually rely on biological or radiological findings which can – by nature - delay AHF diagnosis and subsequent treatment initiation. Surprisingly, the first clinical score designed in the ED for diagnosing AHF was published in 2016 by Basset et al. and was referred to as the "BREST Score" [12]. This score is built on 11 distinct clinical and anamnestic items. Following this seminal publication, another ED-oriented diagnostic score was published by Roncalli et al (the "PREDICA" score), using only clinical criteria [13]

In the present study, we aimed to perform a head-to-head comparison of these two diagnostic scores for AHF in the ED in a large external cohort - the "PARADISE" cohort (NCT02800122) [14,15].

METHODS:

Study population

The PAthwAy of Dyspneic patients in Emergency (PArADIsE) cohort was established from the Nancy University Hospital electronic database. This database was used in order to search for patient records fulfilling the required characteristics of the study population. Inclusion criteria consisted of all patients with acute dyspnea aged 18 years or older admitted in the academic ED of the Nancy University Hospital (France) over a 27-month period from August 1st, 2013 to October 31st, 2015. PARADISE is a retrospective, single-center, observational cohort, registered on clinicaltrials.gov under number NCT02800122. Medical history, clinical parameters, laboratory results, treatment received in the ED and in-hospital outcome were retrieved from the patients' medical records. The PARADISE cohort was approved by the French *Commission Nationale Informatique et Libertés* (CNIL) under number R2016-08.

A total of 1,589 patient files matching the criteria as defined above were extracted. One hundred eighteen medical records did not have a complete diagnosis, while 10 patients had one or more missing items from the BREST score and another 202 had missing items from the PREDICA score. Overall, 1386 patients were included in the present analysis (Figure 1).

Outcome

The "gold standard" was adjudicated AHF diagnosis. Medical history, anamnestic data, and clinical parameters in the ED were collected from the medical files (Figure 1). Two medical physicians (GG and TH) reviewed all electronic charts (including the discharge letter) and entered the data in an eCRF. Homogenous coding was ensured by a trained senior

physician (TC) as outlined below. Specifically, acute HF diagnosis, regardless of etiology and systolic function, were coded according to the European Society of Cardiology criteria (clinical, electrocardiographic, echocardiographic and according to BNP levels) [7].

To ensure coding homogeneity, 20 charts were randomly selected during the early phase of the coding process as well as during the coding process and were reviewed by the senior physician blinded to the initial coding performed by the medical reviewers. A mismatch between the two chart reviews was observed in less than 5% of items. Our center (Clinical Investigation Center of Nancy, France) data management team performed coherence tests and a senior physician addressed all queries after chart reevaluation.

Calculation of the BREST score and PREDICA score (Central Figure)

For the BREST score, all of the ensuing variables were considered: age > 65 years, sudden dyspnea, night outbreak, orthopnea, prior CHF episode, chronic pulmonary disease, myocardial infarction, pulmonary crackles, ST segment abnormalities, atrial fibrillation / flutter, along with their logistic regression coefficients as defined in the original article [12].

We then proceeded in the same manner with the PREDICA score. The considered variables along with their logistic regression coefficients were: >80 years old, >3 cardiac medical treatments, paroxysmal dyspnea, jugular vein distention (JVD) or hepato-jugular reflux (HJR), lower limb edema, crackling rales, prior bronchodilator treatment, normal ECG [13].

Study analysis

All analyses were performed using the R software. The two-sided significance level was set at $p < 0.05$. Continuous variables are described as mean ± standard deviation or median (1st and 3rd quartiles), and categorical variables as number and percentage.

The two groups of patients (AHF and non-AHF) were compared using the Wilcoxon test for continuous variables and Fisher's exact test or Chi-2 test for categorical variables.

The diagnostic achievement of the BREST and PREDICA scores was assessed by the AUC (area under the ROC curve). The resulting AUCs were compared with the non-parametric DeLong test.

RESULTS:

Patient characteristics

A total of 1,386 patients were studied, 1106 (79.8%) in the “no-AHF group” and 280 (20.2%) in the “AHF group”. Patients with AHF were older (82.0±10.2 vs. 66.7±21.1, p<0.0001) and had more co-morbidities (hypertension 72.1% vs. 47.2%, p<0.0001; peripheral vascular disease 17.1% vs. 7.1%, p<0.0001, atrial fibrillation 21.8% vs. 6.1%, p<0.0001 and chronic pulmonary disease 31.1% vs. 27.2%, p<0.0001). They also had higher systolic blood pressure (138.8 ± 28.9 vs. 130.6 ± 24.5, p<0.0001) and respiratory rate (27.5 ± 8.2 vs. 25.7 ± 8.0, p=0.002) but similar Sp02 (94.7 ± 3.7 vs. 94.4 ± 4.5, p=0.91). BNP was markedly higher in the AHF group (788.5 ± 924.5 vs. 257.3 ± 361.5, p<0.0001). Oxygen therapy and non-invasive ventilation was most often used in the AHF group (67.1% vs. 45.6%, p<0.0001 and 12.9% vs. 3.2%, p<0.0001 respectively).

Diagnostic performance of the BREST and PREDICA scores for AHF (Table 2).

Most criteria of both the BREST and PREDICA scores were found to be individually significantly associated with AHF diagnosis (Table 2); only 2/11 individual variables of the BREST score (sudden dyspnea and night outbreak) and 2/8 individual variables of the

PREDICA (Paroxysmal dyspnea and bronchodilator treatment) were not significantly different across groups.

A BREST score lower or equal to 3 or a PREDICA score lower or equal to 1 was associated with low probabilities of AHF (5.7% and 2.6% respectively). Conversely, a BREST score equal or higher than 9 or a PREDICA score equal or higher than 5 was associated with a high risk of AHF diagnosis (77.3% and 66.9% respectively) (Table 2). However, the proportion of patients within the grey zone (4-8 for the BREST score and 2-4 for the PREDICA score) represented approximately 2/3 of the population (69.3% and 62.1% respectively).

Using ROC curves, the overall diagnostic performance of both scores were good, ranging from 79.1% (66.1 to 82.1) for the BREST score to 82.4% (79.8 to 85.0) for the PREDICA score (Central Figure). The diagnostic performance of exact coefficients was marginally higher than when using rounded coefficients. The PREDICA score had significantly higher diagnostic performance than the BREST score (increase in AUC 3.3 (0.8 to 5.8), p=0.009) (Figure 2).

Association of BREST and PREDICA scores with BNP levels.

Significant associations of the BREST and PREDICA score categories were found with BNP levels (Figure 3). Patients with low BREST scores had markedly lower BNP levels (mean BNP 306±457 with BREST score 0-3 vs. 807±1181 with BREST score 9-15, p<0.0001). Similarly, patients with low PREDICA scores had low BNP levels in comparison to patients with high PREDICA scores (223±423 vs. 759±978, p<0.0001).

DISCUSSION

Our study emphasizes the good diagnostic performance of both the BREST and PREDICA scores, a finding which should likely prompt a more systematic use of these scores in the ED. In addition, we show a significantly higher diagnostic performance of the PREDICA score, which should further support the use of this specific score in the ED, possibly embedded within digital health records.

Scores and early adequate diagnosis of AHF

The ESC guidelines emphasize the importance of assessing the congestion level as quickly as possible in order to provide adequate treatment to patients [7]. This recommendation is supported by the work of Matsue et al. [8] which highlighted the association between early furosemide treatment, particularly in the most at-risk patients, and improved outcome. The results presented herein support a more systematic use of clinical scores to achieve this early adequate treatment of AHF. In addition, our results emphasize the better performance of the PREDICA score, possibly because it includes more physical examination features (JVD/HJR, Lower limb edema) and prior medical history through the assessment of ongoing treatments (>3 cardiac medical treatments, bronchodilators).

In the two seminal publications of Basset et al. [12] (for the BREST score) and Roncalli et al. (for the PREDICA score) [13], nearly 60% of the patients were in the a diagnostic "grey zone". In our cohort, this grey zone represented 69.3% (n=194) of the population using the BREST score and 62.1% (n=174) for the PREDICA score. This result suggests that clinical scores are useful in ruling in or ruling out rather "extreme" patients, but should additionally be complemented by more refined strategies in this relatively frequent zone of uncertainty [16]. Notwithstanding, the high clinical likelihood acquired using the clinical BREST and/or

PREDICA score allows both a rapid diagnosis and treatment initiation in a sizeable number of patients.

Biomarkers and imaging to complement clinical findings

Several studies have shown the utility of biomarkers in the diagnostic approach of dyspneic patients [17,18] prompting the recommendation of natriuretic peptide quantification in ESC guidelines [7] in the diagnostic scheme of AHF. However, natriuretic peptide quantification usually requires a few hours (unless point-of-care BNP is used) [19]. Importantly, a number of variables can affect natriuretic peptide measurements such as age and weight, for example [20]. Other circulating biomarkers, such as CD 146, may help AHF diagnosis in the future. CD146 is a biomarker expressed primarily in endothelial cell junctions. and is involved in cellular control and tissue architecture as well as in angiogenesis[21,22]. The diagnostic performance of CD146 for the diagnosis of AHF has been reported to be 0.86 (95%, [0.82-0.90]), matching the diagnostic performance of NR-proBNP (0.90 (95%, [0.86-0.92]). In addition, the addition of CD146 on top of NT-proBNP can significantly improve diagnostic performance for patients in the "grey" diagnostic uncertainty zone of NT-proBNP ($p = 0.02$). Other simple biomarkers could further help AHF diagnosis, such as estimates of plasma volume. Our group reported the good diagnostic value of estimated plasma volume status in 1369 patients from the PARADISE cohort [14]. In multivariable analysis, higher estimated plasma volume status (3rd tertile, >5.12 dL/g) was associated with a higher probability of AHF (OR = 1.64 [1.16-2.33], $p = 0.005$). The best integrative approach to AHF combining clinical and biological findings is yet to be determined.

The low sensitivity of chest X-rays for the diagnosis of pulmonary edema has been repeatedly described[23,24], with chest X-rays unfortunately considered as “normal” in 20% of AHF patients [25] . New approaches such as congestion index score (CSI) [26] may help AHF diagnosis in the future. Lung ultrasound has recently shown its value in emergency medicine,

particularly for AHF [27]. In several recent studies, the diagnostic contribution of lung ultrasound has been deemed superior to the diagnostic contribution of chest X-ray[28]. Our group also recently showed the good diagnostic performance on top of the BREST score in patients with diagnosis uncertainty[29].

A number of tools can complement clinical evaluation for diagnosing AHF. However, the present results strongly suggest that the systematic approach to AHF using clinical scores, given the good achieved diagnostic performance of these tools, should be perceived as the first step to AHF diagnosis.

Limitations

Our analysis is based on a large but retrospective single-center study. While this design ensures homogeneity, additional studies are warranted to assess the diagnostic performance of the BREST and PREDICA diagnostic scores.

Our work was strictly focused on clinical scores and further analyses are needed to assess the complementarity of biological, imaging and clinical approaches to AHF in the ED.

Conclusion

Early diagnosis and subsequent accurate etiological treatment is key for the proper management of patients with dyspnea. We provide strong evidence regarding the good diagnostic performance of the PREDICA score (which was superior to that of the BREST score) in a large cohort of dyspneic patients admitted to the ED. Nonetheless, in patients with intermediate scores, which represent more than half of patients with acute dyspnea, a “multi-tool strategy” possibly combining biomarkers, X-ray and lung ultrasound, is needed.

Declarations

Funding: None

Conflict of interest/competing interests: TC has received honoraria from Novartis for his participation on scientific boards. NG has received honoraria from Boehringer AstraZeneka, Vifor and Novartis for his participation on scientific boards. PR reports personal fees (consulting) for Idorsia and G3P, and honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Servier, Stealth Peptides, Ablative Solutions, Corvidia, Relypsa and Vifor Fresenius Medical Care Renal Pharma, outside the submitted work; P.R. is the cofounder of CardioRenal. All the other authors of this research do declare no conflict of interest.

Availability of data and material: Data are available upon reasonable request to the principal investigators of the studies.

Code availability: Not applicable

Ethics approval: Under French law, no formal IRB approval is required for data extraction from patients' medical records in mono-center studies. The PARADISE cohort was approved by the French Commission Nationale Informatique et Libertés (CNIL) under number R2016-08.

Consent to participate: This monocenter retrospective study on patients' files is in compliance with the Commission Nationale Informatique et Libertés (CNIL). Informed written consent was not required by regulation

Consent for publication: This monocenter retrospective study on patients' files is in compliance with the Commission Nationale Informatique et Libertés (CNIL). Informed written consent was not required by regulation

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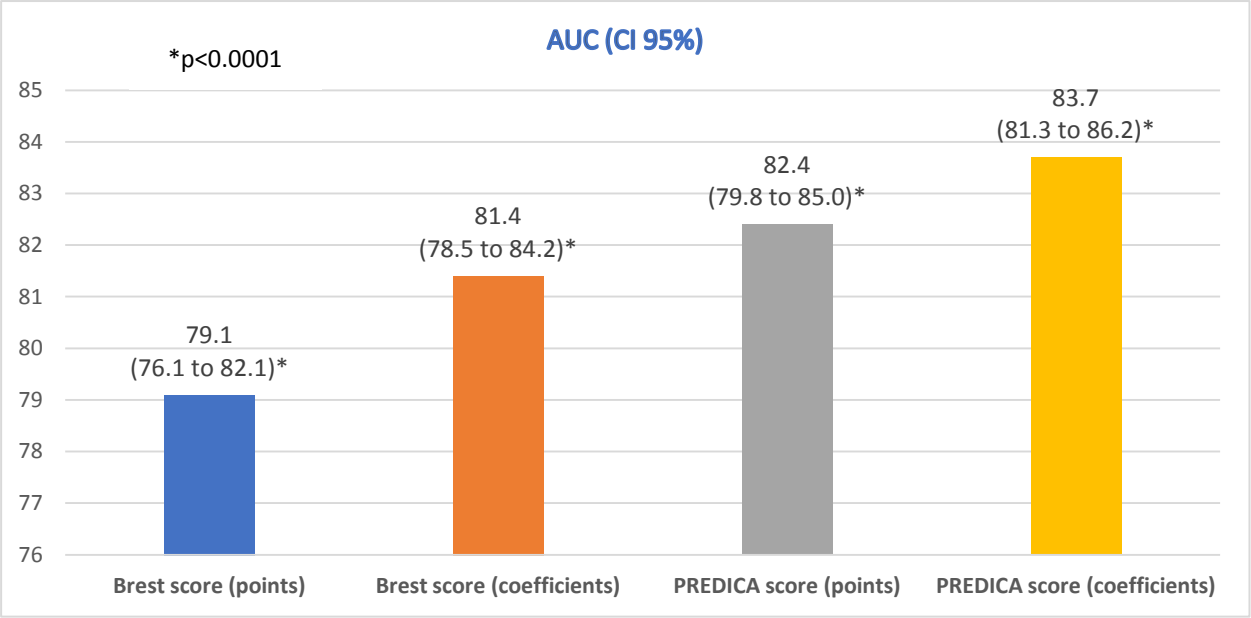
Diagnostic scores for AHF in the Emergency Department

BREST Score			PREDICA Score		
	Score based on			Score Based on	
Variables	Logistic regression coefficients	Points	Variables	Logistic regression coefficients	Points
	+1.51	+2		- log(0.51) - log(0.35) ≈ 1.72	+ 2
Age > 65 years	1.05	1	>80 years old	log(1.99) ≈ 0.69	1
Sudden dyspnea	1.75	2	>3 cardiac medical treatments	log(2.24) ≈ 0.81	1
Night outbreak	0.81	1	Paroxysmal dyspnea	log(3.62) ≈ 1.29	1
Orthopnea	1.27	1	JVD/HJR	log(2.53) ≈ 0.93	1
Prior CHF episode	1.50	2	Lower limb edema	log(3.74) ≈ 1.32	1
Chronic pulmonary disease	-1.51	-2	Crackling rales	log(4.13) ≈ 1.42	1
Myocardial infarction	1.08	1	Bronchodilator treatment	log(0.51) ≈ -0.67	-1
Pulmonary crackles	1.88	2	Normal ECG	log(0.35) ≈ -1.05	-1
ST segment abnormalities	1.08	1			
Atrial fibrillation / flutter	0.99	1			
Minimal score	0	0	Minimal score	0	0
Maximal score	14.17	15	Maximal score	≈ 8.17	8

JVD: jugular vein distention; HJR: hepato-jugular reflux

Diagnostic accuracy of scores for AHF in the Emergency Department



Central figure: Diagnostic performances of the BREST and PREDICA scores and comparison of AUCs.
AUC: area under the ROC curve

Figure 1. Study flowchart

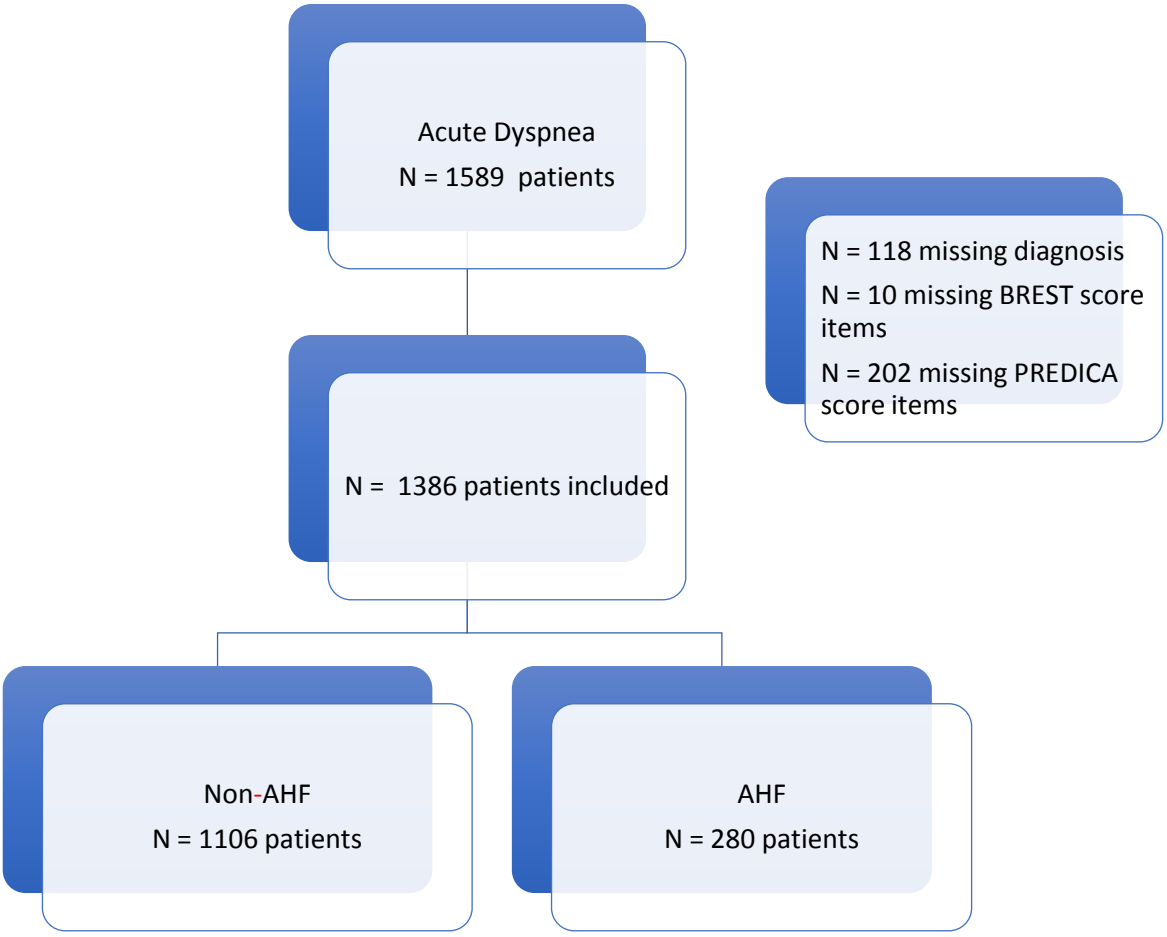


Figure 2: ROC curves for the BREST and PREDICA scores

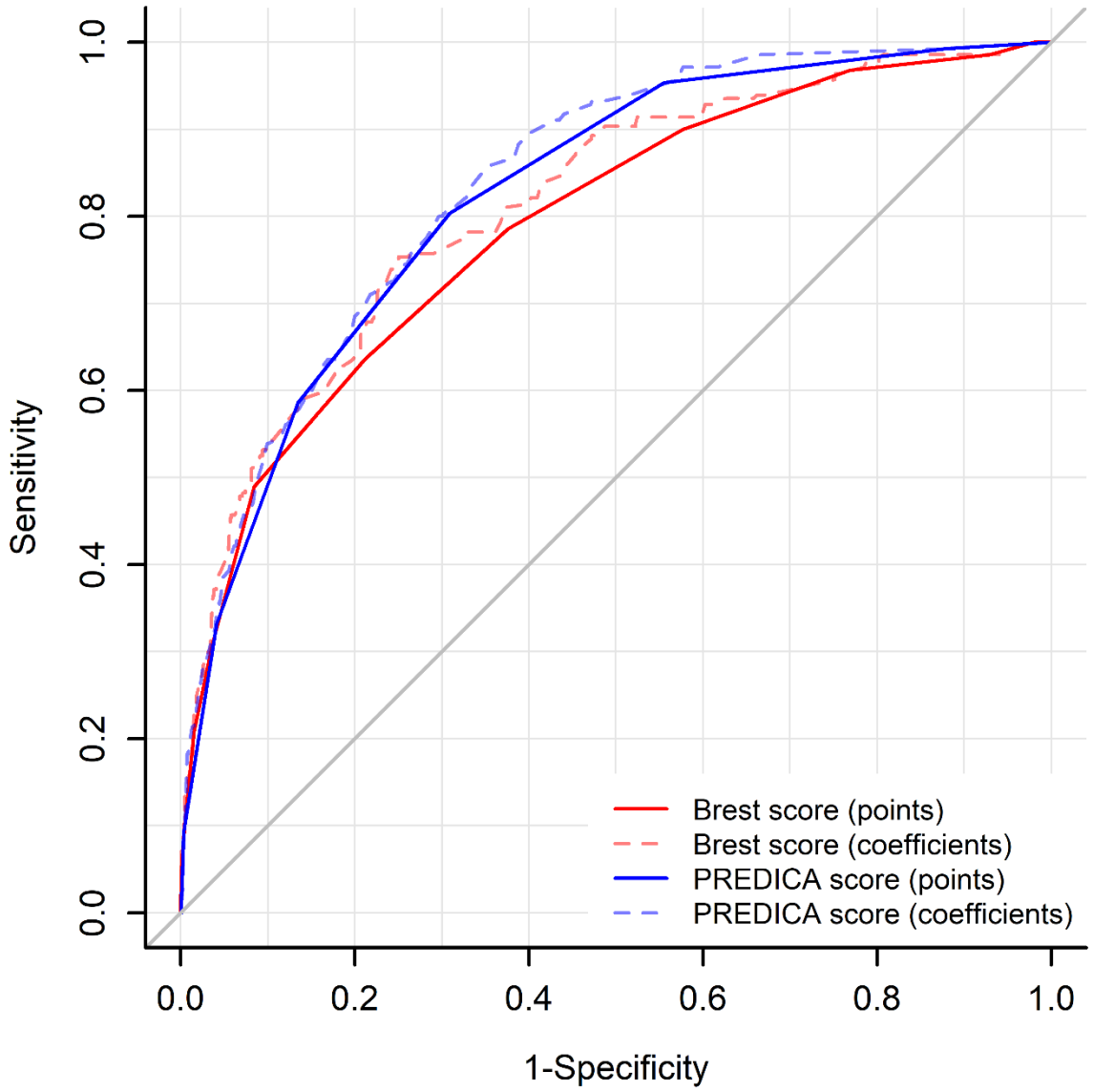
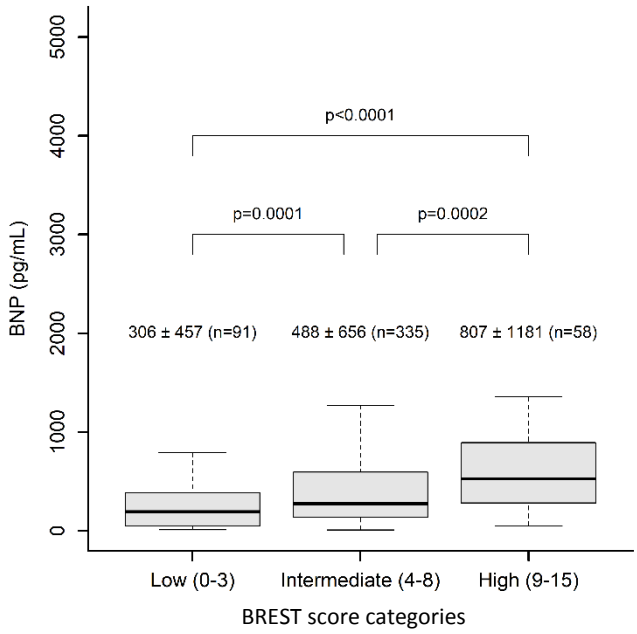
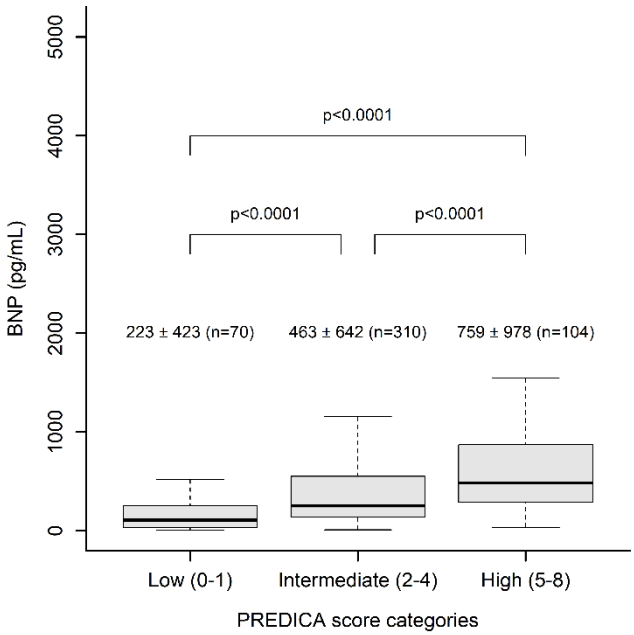


Figure 3: BNP according to BREST score categories and PREDICA score categories





Spearman's rho correlation coefficient between BREST score (integer between 0 and 15) and BNP: rho=0.348 (p<0.0001)

Spearman's rho correlation coefficient between PREDICA score (integer between 0 and 8) and BNP: rho=0.400 (p<0.0001).

The non-parametric Wilcoxon test was used to compare BNP values between low and high probability scores, low and intermediate probability scores, and intermediate and high probability scores.

The non-parametric Wilcoxon test was used to compare BNP values between low and high probability scores, low and intermediate probability scores, and intermediate and high probability scores.

Table 1 : Population characteristics according to AHF and non-AHF diagnosis

	N	Non AHF N=1106 (79.8 %)		AHF N=280 (20.2%)		p-value
		Mean ± SD / n (%)	Median (Q1 - Q3)	Mean ± SD / n (%)	Median (Q1 - Q3)	
Physiological characteristics						
Age (years)	1386	66.7 ± 21.1	71 (54 - 84)	82.0 ± 10.2	84.5 (76 - 89)	<0.0001
Men	1386	577 (52.2 %)		131 (46.8 %)		0.11
Heart rate (bpm)	1378	96.0 ± 20.2	95 (82 - 109)	93.0 ± 21.3	92 (77 - 107)	0.015
Systolic blood pressure (mmHg)	1384	130.6 ± 24.5	128.5 (114 - 145)	138.8 ± 28.9	137 (117 - 158)	<0.0001
Diastolic blood pressure (mmHg)	1384	74.2 ± 17.1	74 (62 - 85)	73.0 ± 18.0	73 (60 - 86)	0.40
Respiratory rate (b/min)	940	25.7 ± 8.0	24 (20 - 30)	27.5 ± 8.2	27 (21 - 32)	0.002
SpO2 (%)	1384	94.7 ± 3.7	95 (93 - 97)	94.4 ± 4.5	95 (92 - 97)	0.91
Oxygen therapy	1382					<0.0001
Air		561 (50.9 %)		56 (20.0 %)		
O_2		506 (45.9 %)		188 (67.1 %)		
NIV		35 (3.2 %)		36 (12.9 %)		
Air under oxygen (mL/min)	694	4.5 ± 3.2	3 (2 - 6)	4.9 ± 3.4	3 (2 - 6)	0.17
Risk factors						
Previous CHF episodes	1386	36 (3.3 %)		66 (23.6 %)		<0.0001
Arterial hypertension	1386	522 (47.2 %)		202 (72.1 %)		<0.0001
History of AMI	1386	79 (7.1 %)		48 (17.1 %)		<0.0001
Chronic heart failure	1386	119 (10.8 %)		133 (47.5 %)		<0.0001
Chronic pulmonary disease	1386	301 (27.2 %)		104 (37.1 %)		0.002
Clinical examination						
Pulmonary crackles	1386	275 (24.9 %)		175 (62.5 %)		<0.0001
Pitting leg edema	1386	171 (15.5 %)		162 (57.9 %)		<0.0001
Spontaneous jugular veins distension	1386	16 (1.4 %)		23 (8.2 %)		<0.0001
Anamnesis						
Night outbreak	1386	120 (10.8 %)		36 (12.9 %)		0.34
Sudden dyspnea	1386	327 (29.6 %)		90 (32.1 %)		0.42
Orthopnea	1386	310 (28.0 %)		153 (54.6 %)		<0.0001
Tachycardia	1378	858 (78.1 %)		192 (68.8 %)		0.002
Atrial fibrillation/flutter	1386	67 (6.1 %)		61 (21.8 %)		<0.0001
ST segment abnormalities	1386	116 (10.5 %)		69 (24.6 %)		<0.0001
Biological parameters						
BNP (pg/mL)	484	257.3 ± 361.5	161 (75 - 316)	788.5 ± 924.5	508.5 (286 - 947)	<0.0001
BNP (3 categories)	484					<0.0001
<100 pg/mL		87 (32.2 %)		7 (3.3 %)		
100-400 pg/mL		138 (51.1 %)		76 (35.5 %)		
>400 pg/mL		45 (16.7 %)		131 (61.2 %)		

Non-AHF: non acute heart failure; AHF: acute heart failure; N: number of non-missing values; NIV: non invasive ventilation; SD: standard deviation; Q1: first quartile; Q3: third quartile.

Table 2: BREST and PREDICA scores (and their components) according to AHF and non-AHF diagnosis

	Non-AHF N=1106 (79.8 %)		AHF N=280 (20.2%)		p-value
	Mean ± SD / n (%)	Median (Q1 - Q3)	Mean ± SD / n (%)	Median (Q1 - Q3)	
BREST score components					
Age > 65 years	657 (59.4 %)		260 (92.9 %)		<0.0001
Sudden dyspnea	327 (29.6 %)		90 (32.1 %)		0.42
Night outbreak	120 (10.8 %)		36 (12.9 %)		0.34
Orthopnea	310 (28.0 %)		153 (54.6 %)		<0.0001
Prior CHF episode	36 (3.3 %)		66 (23.6 %)		<0.0001
Chronic pulmonary disease	301 (27.2 %)		104 (37.1 %)		0.002
Myocardial infarction	79 (7.1 %)		48 (17.1 %)		<0.0001
Pulmonary crackles	275 (24.9 %)		175 (62.5 %)		<0.0001
Pitting leg edema	171 (15.5 %)		162 (57.9 %)		<0.0001
ST segment abnormalities	116 (10.5 %)		69 (24.6 %)		<0.0001
Atrial fibrillation / flutter	67 (6.1 %)		61 (21.8 %)		<0.0001
BREST score (sum of regression coefficients)	3.6 ± 1.8	3.4 (2.6 - 4.7)	6.2 ± 2.2	6.3 (4.8 - 7.9)	<0.0001
BREST score (sum of points)	4.0 ± 1.9	4 (3 - 5)	6.4 ± 2.3	6 (5 - 8)	<0.0001
BREST score (3 categories)					<0.0001
Low probability (score 0-3)	468 (42.3 %)		28 (10.0 %)		
Intemediate probability (score 4-8)	621 (56.1 %)		194 (69.3 %)		
High probability (score 9-15)	17 (1.5 %)		58 (20.7 %)		
PREDICA score components					
>80 years old	365 (33.0 %)		188 (67.1 %)		<0.0001
>3 cardiac medical treatments	253 (22.9 %)		141 (50.4 %)		<0.0001
Paroxysmal dyspnoea	120 (10.8 %)		36 (12.9 %)		0.34
JVD/HJR	16 (1.4 %)		23 (8.2 %)		<0.0001
Lower limb oedema	171 (15.5 %)		162 (57.9 %)		<0.0001
Crackling rales	275 (24.9 %)		175 (62.5 %)		<0.0001
Bronchodilator treatment	402 (36.3 %)		94 (33.6 %)		0.40
Normal ECG	881 (79.7 %)		134 (47.9 %)		<0.0001
PREDICA score (sum of regression coefficients)	1.8 ± 1.4	1.4 (0.7 - 2.7)	3.8 ± 1.5	3.8 (2.6 - 4.9)	<0.0001
PREDICA score (sum of points)	1.9 ± 1.3	2 (1 - 3)	3.8 ± 1.4	4 (3 - 5)	<0.0001
PREDICA score (3 categories)					<0.0001
Low probability (score 0-1)	492 (44.5 %)		13 (4.6 %)		
Intemediate probability (score 2-4)	568 (51.4 %)		174 (62.1 %)		
High probability (score 5-8)	46 (4.2 %)		93 (33.2 %)		

AHF: acute heart failure; Non-AHF: non acute heart failure ; N: number of non-missing values; JVD: jugular vein distention; HJR: hepato-jugular reflux ; SD: standard deviation; Q1: first quartile; Q3: third quartile;