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## **Comparison of the Diagnostic Accuracy of Plasma N-Terminal Pro-Brain Natriuretic Peptide in Patients <80 to those >80 Years of Age with Heart Failure**

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**Running Title:** NTproBNP in patients >80

**Declarations of interest:** none

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**Abstract:**

Plasma N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) is known to increase with age however the performance of this biomarker is unclear in patients >80. This study sought to define the diagnostic accuracy of plasma NTproBNP in patients > 80 in a large unselected population of heart failure (HF) patients admitted to a Tertiary Hospital in the United Kingdom. 1995 consecutive patients over a 12 month period were screened for HF through our NTproBNP led heart failure service. 413 patients had their first presentation of HF and 36.1% of these patients were > 80. There was a reduction in accuracy of NTproBNP with age according to the Area under the curve (AUC), with an AUC for all HF patients of 0.734 and a 7.5% reduction in receiver operating characteristic curve (ROC) area for patients > 80 years compared to those under 60-79 years of age. The lowest NTproBNP recorded for patients with HF > 80 years of age was 466pg/mL. In HF patients > 80, 40.6% patients were diagnosed with HF<sub>r</sub>EF, 31.1% with HF<sub>p</sub>EF and 28.2% with HF<sub>mr</sub>EF. Overall NTproBNP is less accurate at identifying HF in patients > 80 years of age and the lowest NTproBNP recorded for a HF patient was 466pg/mL suggesting that the NTproBNP threshold for ruling out HF in patients >80 years of age should be modified.

**Keywords:** N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP), Heart Failure (HF), Area under the curve (AUC)

## Introduction

The average age of a patient newly diagnosed with heart failure (HF) in the United Kingdom (UK) is 76 years<sup>1</sup> which is set to rise as our population becomes older. The use of biomarkers such as N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) is long established in the diagnosis of HF;<sup>2-4</sup> in the emergency department (ED) the use of clinical judgements and biomarkers combined have shown improved diagnostic accuracy and cost savings<sup>5-7</sup>. Recent European Society of Cardiology (ESC) and National Institute of Clinical Excellence (NICE) HF guidelines<sup>8,9</sup> recommend an optimal 'rule out' cut point for suspected HF of 300pg/ml in the acute setting irrespective of age. However, NTproBNP levels are known to increase with age in the absence of cardiovascular disease processes<sup>10</sup> and BNP levels have been shown not to be useful acutely for older patients<sup>11</sup>, making the use of these biomarkers uncertain and placing undue strain on limited resources such as echocardiography and specialist HF services. This study sought to define the diagnostic accuracy of NT-proBNP in patients presenting acutely with suspected decompensated HF > 80 years of age.

## Methods

All consecutive patients who had acute presentations of suspected decompensated HF (dyspnoea and/or peripheral oedema) and NT-proBNP tested in our institution over one year were included, between 10/09/2014 and 09/09/2015. Patients were diagnosed with HF after an expert physician review according to the 2016 ESC guidelines.<sup>8</sup> HF<sub>r</sub>EF was defined as HF with LVEF <40%, HF<sub>m</sub>rEF and HF<sub>p</sub>EF as HF with raised NTproBNP, diastolic

dysfunction/structural heart disease and LVEF 41-49%, >50% respectively. In case of uncertainty, diagnoses were adjudicated through the heart failure multidisciplinary team. Data were collected as part of our Institution's approved Clinical Audit and Governance work.

Patients were categorised by: age (in decades and in groups: <40, 40-59, 60-79 and >80 years old), HF classification according to current European guidelines and gender.

NTproBNP analysis was performed with the commercially available immunoassay using the Elecsys 1010, 2010, or E170 proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany). Details of the assays, cross-reactivity and coefficients of variation, have previously been reported.<sup>12,13</sup>

The electronic frailty index was not measured, but conditions known to contribute to frailty, such as asthma, atrial fibrillation, Chronic Kidney Disease, diabetes mellitus, HF, Hypertension and Ischaemic Heart Disease were recorded. AF was detected according to the patient's history and admitting 12 lead electrocardiogram.

Data was given as mean  $\pm$  standard deviation (SD) when normally distributed, as median and interquartile range (Q1-Q3) for plasma NTproBNP and other data not normally distributed or skewed, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated using 1 way analysis of variance, Mann-Whitney U, T-test and chi-square tests, where appropriate. The accuracy of using NTproBNP to detect HF was assessed using area under the curves,

calculated using Prism. Diagnostic utilities were calculated using specificity, sensitivity and negative and positive predictive values. The optimal 'rule out' cut point was defined as a negative predictive value (NPV) of 0.98 and optimal 'rule in' cut point was defined as 90% sensitivity. The 'grey zone' was defined as NTproBNP values between optimal 'rule in' and 'rule out' cut points, Figure 1. Statistical significance was defined as a p value of  $<0.05$ .

## Results

Of the 1995 patients screened using NTproBNP during an acute presentation of suspected decompensated HF, 37.7% (n= 752) were  $> 80$  years of age. In total 413 had their first presentation of HF (mean age  $72.7 \pm 14.3$  years; 58.1% male) and 36.1% of these patients were  $> 80$  years of age (149 new patients with HF  $> 80$  years of age). The demographics and comorbidities of patients are given in Table 1. The distribution of patients per decade is shown in Figure 2, highlighting that there were more patients in the 80-89 years of age category than any other.

There was a reduction in accuracy of NTproBNP with age according to the AUC, with an AUC for all HF patients of 0.734. The AUC results were as follows: 60-79 v  $>80$  ( $p=0.01$ ); 40-59 v  $>80$  ( $p=0.04$ );  $<40$  years to  $>80$  years of age ( $p=0.02$ ), Figure 3. There was a 7.5% reduction in receiver operating characteristic curve (ROC) area for patients  $> 80$  years compared to those under 60-79 years of age.

For all patients, the optimal NTproBNP 'rule out' and 'rule in' cut points were calculated as 465pg/mL and 786pg/mL, respectively, Table 2. The

lowest NTproBNP recorded for patients with HF > 80 years of age was 466pg/mL. At 300pg/mL threshold in this age group, the NPV was calculated to be 1, sensitivity 1 and accuracy of the test 0.42. In contrast the NPV was 0.93, 0.95, 0.95 sensitivity 0.97, 0.96, 0.91 and accuracy 0.54, 0.61, 0.67 for patients 60-79, 40-59 and under 40 years of age respectively. The NTproBNP threshold in patients > 80 years of age for ruling out heart failure to 400, 500 and 600pg/ml, changed the NPV to 0.97, 0.94, 0.90 and the sensitivity to 0.98, 0.97 and 0.96.

In HF patients > 80, 40.6% patients were diagnosed with HFrEF compared to 57.7% in the 60-79 year old age group (p 0.002), 31.1% with HfpEF compared to 20.8% (p 0.039) and 28.2% with HfmrEF compared to 21.4% (p 0.167), respectively, Figure 3. The median LVEF (and IQR) for the HFpEF, HFmrEF and HFrEF population were 56% (2.5), 44% (5) and 26% (5) respectively.

73% of the HF patients > 80 years were white, compared to 12% AfroCaribbean and 3% Asian. The remaining patients reported themselves as mixed race. The optimal 'rule out' and 'rule in' cut points, percentage in the grey zone and AUC for NTproBNP for patients > 80 years of age for white patients were 512pg/mL, 1008pg/mL, 59.6%, AUC 0.65; for Afrocaribbean 467pg/mL, 592 pg/mL, 11.1%, AUC 0.52 and 1700pg/mL, 1700 pg/mL, 0%, AUC 0.63 for Asian patients.

## Discussion



In our large real life population NTproBNP was a poor discriminant for diagnosing HF in patients >80 presenting with suspected HF. The mean age of patients presenting with their first presentation of HF in our institution was 72.7 years, with 36.1% of these patients > 80 years of age. No patients > 80 years of age with HF had admission NTproBNP <300 pg/ml with the lowest NTproBNP recorded in this age group of 466pg/ml. Statistically more patients >80 presented with HFpEF and less with HFrEF.

There has been uncertainty as to how useful natriuretic peptides are in patients > 80<sup>14-17</sup> although recent publications have reported that BNP was not useful in this population.<sup>11</sup> Furthermore, despite the 'grey zone' being used to exclude and identify HF patients,<sup>18-21</sup> we found that similar numbers of HF patients fell into this grey zone, suggesting there is little benefit in using the optimal 'rule-in' cut point, or the grey zones, as it would routinely miss approximately 8% of HF patients.

Moreover, we calculated a lower AUC for clinical assessment and NTproBNP in diagnosing HF, 0.635 in patients > 80 years of age compared to published literature of 0.86 in patients > 75 years of age<sup>18</sup> and 0.68 in patients > 80 years of age.<sup>11</sup> This variation may result from differences in practices requesting NTproBNP and the fact that our data represents real life clinical decision making, and is not part of a trial.

Nearly 1/3 of patients > 80 years of age were diagnosed with HFpEF, which is not surprising given the increased comorbidities associated with this age group, Figure 2. Medical management is the modification of risk factors

and alleviation of symptoms and it is crucial that this is achieved by heart failure experts working closely with geriatricians.

The implications of this study are that patients with HF symptoms > 80 years of age would benefit from a raised NTproBNP 'rule out' cut point as part of a triage process to determine priority for echocardiogram. In order not to miss any patients with HF in patients > 80 years of age, we would recommend using 466pg/ml rather than 484pg/ml (optimal 'rule in' cut point defined as sensitivity 0.9). Defining these lower levels is of utmost importance in clinical practice when there are mounting pressures on our healthcare systems with limited resources. The minimum cost implications of this include the echocardiogram (£66/echocardiogram)<sup>22</sup> and increased length of stay when patients are being investigated. The assumption from NICE is that patients stay an additional two days if they are falsely assessed as being likely or unlikely to have HF.<sup>9</sup>

Limitations of this study are that this work was collected retrospectively and that we did not include a failty index. The data regarding ethnicity is limited by the small number of Asian and AfroCarribbean patients.

In conclusion, over one third of the patients with HF admitted acutely to hospital within one year were > 80 years of age. The lowest NTproBNP recorded for patients with HF > 80 years of age was 466pg/mL suggesting that the NTproBNP threshold for ruling out HF in patients > 80 years of age should be modified.

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## Figure Legends

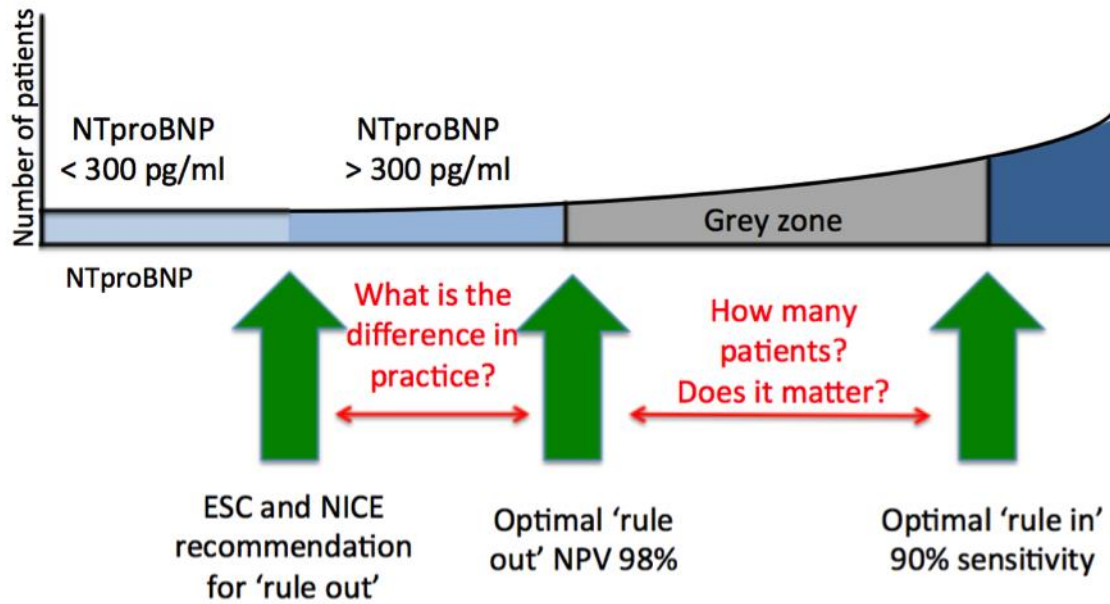


Figure 1: Explanation of 'rule out' and 'rule in' cut points for NTproBNP in diagnosing HF



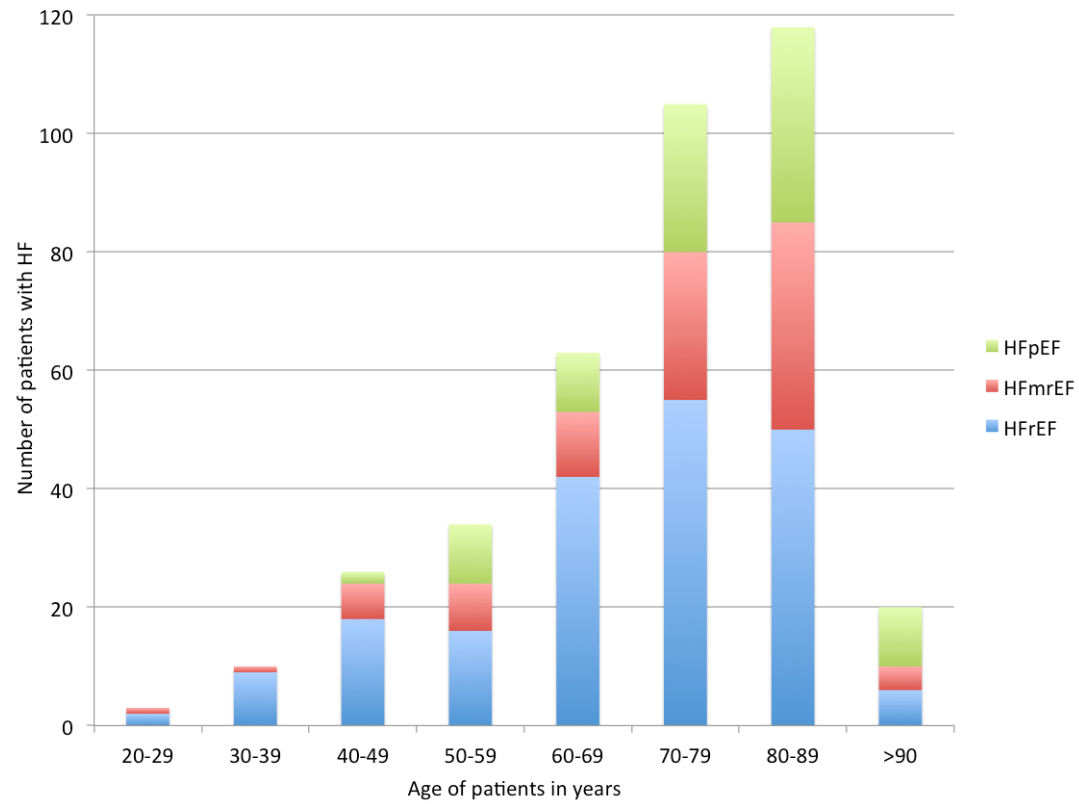


Figure 2: Distribution of “new” diagnosis of HF patients classified by age and type of Heart Failure

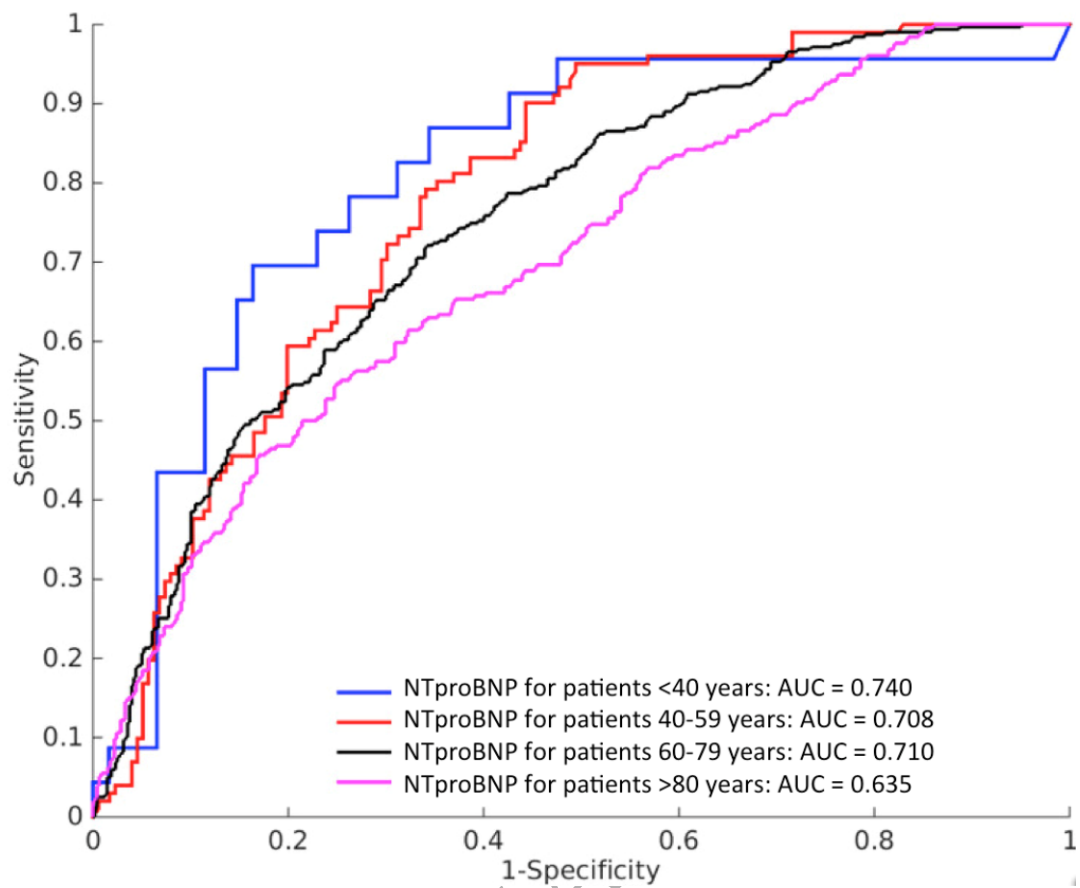


Figure 3: Receiver Operating Curves for different age categories

Table 1: Demographics of patients with Heart Failure

Variable	Age in years		P value
	<80 years (N=264)	>80 years (N=149)	
Age (IQR)	65 (13)	86 (4)	
Male	164 (62 %)	72 (48 %)	0.007
White	171 (65 %)	109 (73 %)	NS
AfroCaribbean	46 (17 %)	18 (12 %)	NS
Asian	17 (7 %)	4 (3 %)	NS
Left ventricular ejection fraction (IQR)	39 (15)	44 (13)	0.0007
NTproBNP (SD)	8529 (12645)	9636 (13536)	NS
Estimated Glomerular filtration rate (IQR)	74 (46)	34 (26)	0.0001
Atrial Fibrillation	95 (36 %)	82 (55 %)	0.0002
Ischaemic Heart Disease	84 (32 %)	61 (41 %)	NS
Diabetes Mellitus	102 (39 %)	54 (36 %)	NS
Hypertension	154 (58 %)	96 (64 %)	NS
Asthma	73 (28 %)	45 (30 %)	NS
Dyslipidaemia	92 (35 %)	52 (35 %)	NS

Dyslipidaemic defined as patients on statin therapy as total cholesterol elevated

Table 2: Plasma NTproBNP 'rule out', 'rule in' cut points (pg/ml) for different age categories in patients with first presentation of HF

Variable	NTproBNP Rule out (pg/ml)	NTproBNP Rule in (pg/ml)	% HF patients in grey zone	% Patients in grey zone
All patients (N=1995)	465	786	7.7	1.6
<40 years (N=89)	176	565	7.1	1.1
40-59 (N=295)	80	663	2.8	0.7
60-79 (N=859)	270	835	8.9	1.9
>80 years (N=752)	484	828	8.7	1.7