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Diagnostic yield of a heart failure referral pathway using N-terminal pro-brain natriuretic peptide

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ABSTRACT

Objective To determine the diagnostic yield of a 'high' N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with suspected heart failure (HF) referred from primary to secondary care.

Methods In this retrospective study, cardiac diagnoses were quantified in consecutive patients with an NT-proBNP>400 ng/L referred from primary care centres to a specialist HF service.

Results Among 654 consecutive patients (age: 78.5±9.72 years; 45.9% men; left ventricular ejection fraction (LVEF): 55.4±12.5% (mean±SD)), the primary diagnoses were: valvular disease (39.4%), HF (29.2%; 13.3% with LVEF<40%) and atrial fibrillation (AF; 17.3%). In terms of primary or secondary diagnoses, 68% of patients had valve disease, 46.9% had AF and 29.2% had HF. A cardiac diagnosis was made in 85.9%. In multivariable analyses, NT-proBNP predicted HF with LVEF<40% (OR: 10.2, 95% CI: 5.63 to 18.3) and HF with any LVEF (OR: 6.13, 95% CI: 3.79 to 9.93). In canonical linear discriminant analyses, NT-proBNP correctly identified 54.5% of patients with HF. The remainder were misclassified as valvular disease, AF or no cardiac diagnosis.

Conclusion Among patients with an NT-proBNP>400 ng/L referred through a primary care HF pathway, most patients had valve disease or AF rather than HF. NT-proBNP cannot discriminate among HF, valve disease and AF. On this basis, NT-proBNP may be best employed in detecting cardiac disease in general rather than HF per se.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The observation of elevations in N-terminal pro-brain natriuretic peptide (NT pro-BNP) in heart failure (HF) led to its adoption in the diagnostic triage to echocardiography.
⇒ NT pro-BNP levels are raised in other cardiac conditions.

WHAT THIS STUDY ADDS

⇒ Among patients with an NT-proBNP>400 ng/L referred through a primary care HF pathway, most patients have valve disease or atrial fibrillation (AF) rather than HF.
⇒ NT-proBNP cannot discriminate among HF, valve disease and AF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ NT-proBNP may be best employed in detecting cardiac disease in general rather than HF per se.

INTRODUCTION

After their discovery in 1981,[1] physicians envisioned that natriuretic peptides (NPs), specifically brain-type natriuretic peptide (BNP) and its pro-peptide N-terminal pro-BNP (NT-proBNP), could be used to detect and monitor heart failure (HF) in the same way as hormone levels are used in endocrinology.[2 3] In 1998, Cowie showed that a circulating BNP has a negative predictive value of 98% for the diagnosis of HF.[4] This, together with other studies showing that BNP and NT-proBNP are reliable 'rule out' tests[5–7] formed the basis of a class I recommendation for the use of BNP and NT-proBNP in the diagnostic pathway for HF.[8 9]

A 'rule out' test is undoubtedly useful in primary care, insofar as a negative test can avoid referral for a specialist opinion and echocardiography. In secondary care HF services, the primary concern is not so much to exclude patients with HF, but to positively identify them. Unfortunately, the positive predictive value (PPV) of BNP or NT-proBNP is, at best, modest.[4–7] In this context, we should consider that elevations in NP levels do not just occur in HF, but also in atrial fibrillation (AF),[10] valvular disease,[11 12] cardiomyopathies,[13] acute coronary syndromes, myocarditis and left ventricular hypertrophy.[14 15] Non-cardiac factors, which also contribute to variations in NP levels, include anaemia, renal disease, sepsis, pulmonary disease, cirrhosis and cancer chemotherapy. In healthy individuals, NP levels vary according to age, sex,[11] body mass index[16] and time of day.

On the basis of personal experience of an HF service, we hypothesised that at the point of referral from primary care physicians, a raised NT-proBNP level may not be specific for HF, but a non-specific biomarker for heart disease in general. This study explores the diagnostic yield of patients referred to a specialist HF centre with suspected HF and a raised NT-proBNP. The ability of NT-proBNP to discriminate between different cardiac conditions is also assessed.

METHODS

This is a retrospective study of consecutive patients referred from primary care physicians to a secondary care HF service at Queen Elizabeth Hospital, University Hospitals NHS Trust, Birmingham, UK. Referrals were made using a standard referral form, in line with the requirements of the UK's National Institute for Health and Care Excellence (NICE).[17] This stipulated that patients with suspected HF and a high NT-proBNP (≥400 ng/L) in primary care should be referred for a specialist opinion and echocardiography. The study included consecutive patients referred to the HF service in the period 1 July 2020 to 1 July 2021.

N-terminal pro-brain natriuretic peptide

Circulating NT-proBNP was measured using the Alere NT-proBNP assay (Abbott Laboratories, Maidenhead, UK) in a single laboratory (Queen Elizabeth Hospital, University Hospitals NHS Trust, Birmingham, UK). This is a two-step immunoassay for the in vitro quantitative determination of NT-proBNP using chemiluminescent microparticle immunoassay technology.

Diagnosis

The primary diagnosis was taken from the receiving cardiologist. Other coexisting diagnoses were considered as secondary diagnoses.

Echocardiography

Transthoracic echocardiography was undertaken by technicians certified by the British Society of Echocardiography, using a common protocol. The left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method. Valvular disease was classified as mild, moderate or severe according to British Society of Echocardiography[18–20] and European Association of Cardiovascular Imaging[21] guidelines.

HF type

The diagnosis of HF was subdivided according to LVEF: HF with reduced ejection fraction (HFrEF, LVEF<40%); HF with mid-range ejection fraction (HFmrEF, (LVEF=40–49%); and HF with preserved ejection fraction (HFpEF, LVEF≥50%). The diagnosis of 'valvular HF' was made if symptoms and signs of HF were associated with echocardiographically severe valvular disease.

Electrocardiogram

The ECG was recorded in the same session as the echocardiogram. Only ECGs that were completely normal were classified as normal. All other ECGs (including those showing any conduction abnormality, supraventricular or ventricular ectopy, AF, bundle branch block, a paced rhythm, ST and T wave abnormalities or features of left ventricular hypertrophy) were classified as abnormal. Patients were regarded as having AF if this had previously been documented on an ECG or if it appeared on the ECG at undertaken at the point of referral. AF was regarded as uncontrolled if the ECG at the point of referral showed a heart rate of >90 bpm.

Statistical analysis

Continuous variables are expressed as mean (±SD). Non-normally distributed variables, such as NT-proBNP, were expressed as median (IQR) and were log-transformed for statistical analyses. Group differences were assessed using the Student's t-test and Fisher's post hoc test. Logistic regression was used to assess relationships between NT-proBNP levels and the ECG in relation to the presence of HF. Diagnostic performance was assessed using receiver operator characteristic curves (ROCs). The ability of NT-proBNP to discriminate between different clinical conditions was assessed using canonical linear discriminant analysis.[22] All statistical analyses were undertaken using Stata V.15 (StataCorp, Texas, USA). The '*candisc*' package was used for canonical linear discriminant analysis. A two-sided p≤0.05 was considered statistically significant.

RESULTS

Over a 12-month period, 679 patients with suspected HF and a 'high' NT-proBNP were referred from primary care to a secondary care, specialist HF service. The analytic population comprised 654 patients (figure 1). As shown in table 1, patients were aged 78.5±9.72 years. They were

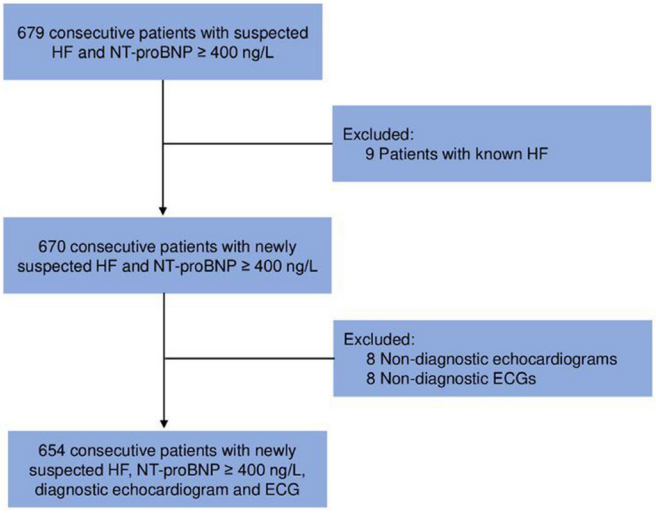

Figure 1 Study flowchart. HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Table 1 Characteristics of the study group

N	654
Age (years)	78.5±9.72
Sex (n; male)	300 (45.9)
LVEF (%)	55.4±12.5
<40	84 (6.12)
≥40	570 (87.2)
NT-proBNP (ng/L)	2411 (668.0–2489.0)
Creatinine (µmol/L)	98.1±46.6
eGFR (mL/min/1.73 m^2)	66.4±26.4
Comorbidities	
Diabetes mellitus	190 (29.1)
COPD	115 (17.6)
Hypertension	440 (67.3)
Myocardial infarction	150 (22.9)
Chronic kidney disease*	255 (39.0)
Permanent pacemaker	31 (4.74)

Continuous variables are expressed as mean±SD except NT-proBNP, which is shown as median (IQR). Categorical variables are expressed as n (%).
*Defined as eGFR<60 mL/min/1.73 m^2.
COPD, chronic obstructive pulmonary disease.eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction;

mostly women (54.1%) and the median NT-proBNP was 2411 ng/L (IQR: 668–2489 ng/L).

Primary diagnoses

A cardiac diagnosis was reached in 562 (85.9%) patients and 1 or more abnormality of the ECG or echocardiogram were observed in 601 (91.9%) patients (table 2). The primary diagnoses made by HF specialists, after ECG an echocardiography, were valvular disease (39.4%), HF (of any type) (29.2%) and AF (17.3%) (online supplemental file 2 and table 2). Among patients with HF, 13.3% had HFrEF.

Heart failure

Patients with no cardiac diagnosis had the lowest NT-proBNP levels, while the highest were observed in patients with HF (table 2 and figure 2). In patients with HF, those with HFrEF had higher NT-proBNP levels than those with HFpEF (p<0.001) and similar levels to those with HFmrEF and patients with valvular HF (figure 3).

In univariate analyses, both log NT-proBNP and an abnormal ECG emerged as predictors of HFrEF and HF of any type. The results of ROC analyses are shown in the online supplemental file 1. In multivariable logistic regression using log NT-proBNP and ECG (normal or abnormal) as independent variables (table 3), NT-proBNP emerged as a predictor of HFrEF (OR: 10.2, 95% CI: 5.63 to 18.3) and HFrEF/HFmREF/HFpEF (OR: 6.13, 95% CI: 3.79 to 9.93), while ECG did not reach statistical significance.

Table 2 Diagnoses and diagnostic features following referral

Diagnosis or diagnostic feature	N (%)	NT-proBNP (ng/L)*
Any cardiac diagnosis†		
Present	562 (85.9)	1353.0 (743.0–3010.0)
Absent	92 (14.1)	664.0 (472.0–927.0)
ECG and echocardiogram		
Normal	53 (8.1)	616.0 (467.6–874.3)
Abnormal	601 (91.9)	1297.0 (697.0–2783.0)
Primary diagnosis‡		
HF	191 (29.2)	2121.0 (1089.0–5051.5)
Valve disease	258 (39.4)	1093.0 (665.0–1910.0)
Atrial fibrillation	113 (17.3)	1368.0 (710.5–2932.8)
None	92 (14.1)	664.0 (472.0–927.0)
Primary or secondary diagnoses		
No HF	483 (67.4)	989.0 (621.3–1863.3)
HF	191 (29.2)	2121.0 (1089.0–5051.5)
HFrEF	87 (13.3)	2489.0 (1459.0–6081.0)
HFmrEF	36 (5.50)	2133.0 (1206.5–4074.5)
HFpEF	40 (6.12)	935.0 (517.0–2725.0)
Valvular HF	28 (4.28)	2547.0 (1072.0–6370.0)
Atrial fibrillation	307 (46.9)	1638.0 (979.5–3424.3)
LVEF<50%	56 (8.56)	2428.5 (1482.5–4932)
LVEF≥50%	249 (38.1)	1455.0 (919.5–3114.3)
Valvular disease	445 (68.0)	
Valve type§		
Aortic	98 (15.0)	1058.0 (675.5–2097.0)
Mitral	155 (23.7)	1308.5 (705.0–3335.0)
Tricuspid	192 (29.4)	1638.5 (892.0–3466.0)
Valve disease severity¶		
Mild	262 (40.1)	1166.0 (673.0–2270.0)
Moderate	154 (23.5)	1711.0 (1056.0–3511.0)
Severe	40 (67.3)	3007.5 (1330.0–6664.0)

*Expressed as median (IQR).
†Refers to a formal diagnosis, excluding ECG and echocardiographic abnormalities which were not deemed significant.
‡Refers to the primary clinical diagnosis made by the receiving HF specialist.
§Refers to the predominant valve affected.
¶Refers to the severity of valvular disease, assessed echocardiographically.
HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Valvular disease

Patients with a primary diagnosis of valvular disease had significantly higher NT-proBNP levels than those with no cardiac diagnosis (figure 2). As shown in figure 4, increasing

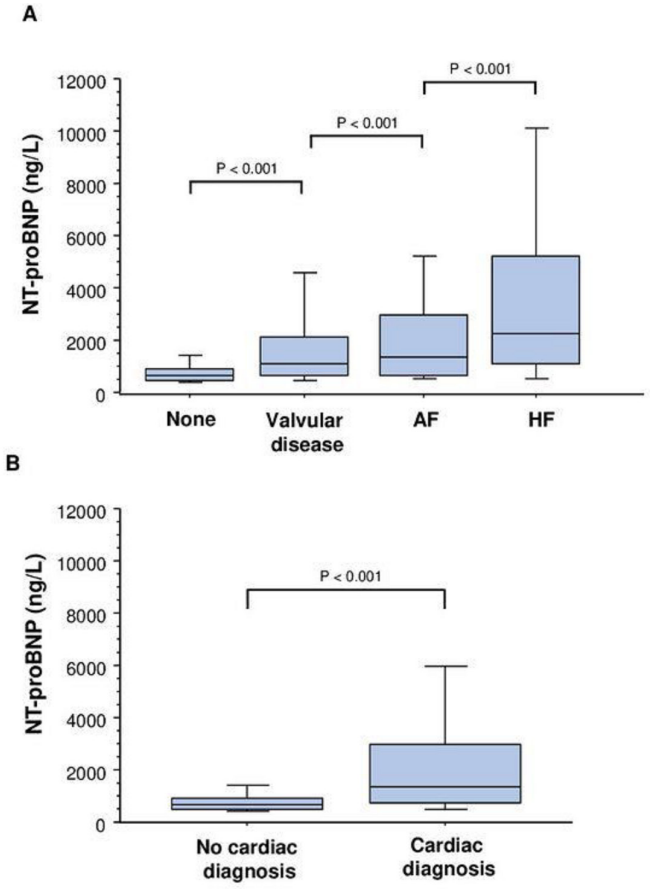

Figure 2 NT-proBNP according to diagnosis. Box and whisker plots of NT-pro-BNP levels according to: (A) diagnosis and (B) presence or absence of any cardiac diagnosis. The five horizontal lines represent the 10th, 25th, 50th, 75th and 90th percentiles, from bottom to top. See table 2 for corresponding data. AF, atrial fibrillation; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide

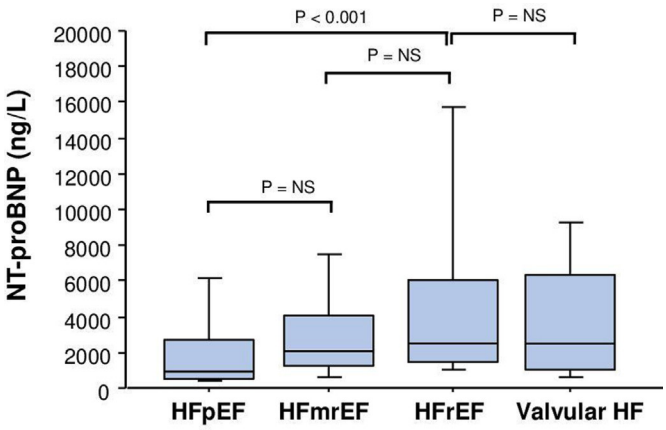

Figure 3 NT-proBNP according to type of heart failure. Box and whisker plots of NT-pro-BNP levels according to the type of heart failure (HF). The five horizontal lines represent the 10th, 25th, 50th, 75th and 90th percentiles, from bottom to top. See table 2 for corresponding data. HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide.

severity of valve disease, assessed echocardiographically, was associated with increasing NT-proBNP levels. However, no significant differences emerged between patients with moderate or severe valvular disease. In univariate analyses, NT-proBNP predicted 'any' valvular disease (OR: 5.07, 95% CI 3.07 to 8.36). The results of ROC analyses are shown in the online supplemental file 1.

Atrial fibrillation

Patients with AF had higher levels than patients in sinus rhythm (table 2). In patients with AF, those with an LVEF<50% had higher levels than those with an LVEF≥50% (p<0.001). In univariate analyses, NT-proBNP predicted 'any' AF (OR:4.44, 95% CI 2.91 to 6.79). The results of ROC analyses are shown in the online supplemental file 1.

Cardiac diagnoses and abnormalities on the ECG or echocardiogram

As shown in table 3, NT-proBNP predicted 'any' cardiac diagnosis (OR: 34.6, 95% CI 12.8 to 93.9) and 'abnormal ECG or echocardiogram (OR: 42.3, 95% CI 11.1 to 161.7), regardless of whether or not a clinical cardiac diagnosis was made. The results of ROC analyses are shown in the online supplemental file 1.

Discriminant analysis

As shown in figure 5, 104 (54.5%) were correctly classified as HF and 87 (45.5%) were incorrectly classified: 19 (9.95%) as AF, 39 (20.4%) as no diagnosis and 29 (15.2%) as valvular disease.

DISCUSSION

This is the largest study to explore the diagnostic yield of NT-proBNP in patients with suspected HF referred from primary care to a specialist HF service. Several findings have emerged. First, among patients with a raised NT-proBNP, less than a third had a primary diagnosis of HF while the majority had valvular disease or AF. Second, only 13.5% of patients had HFrEF. Third, although the highest values of NT-proBNP were observed in patients with HF, there was considerable overlap in levels across the diagnostic groups. Fourth, over 90% of patients with a raised NT-proBNP had an abnormal ECG or echocardiogram and 86% had a cardiac diagnosis. Last, a high NT-proBNP was unable to discriminate among HF, valvular disease and AF.

Diagnostic yield

Numerous studies have explored the diagnostic utility of BNP and NT-pro-BNP in HF using ROC analyses. In the latter, NT-proBNP levels of >125 pg/mL in the non-acute setting were associated with NPVs between 94% and 98%.[4 6 7] In the general population, NT-proBNP of >304.5 ng/L has an NPV of 100% (area under the receiver operating characteristic curve of 0.92).[23] In a pooled analysis of three studies, the UK's NICE found that NT-proBNP≥400 ng/L was associated with an NPV of

Table 3 Univariate and multivariable analyses

Univariate analyses	OR	95% CI		P value
HFrEF				
Log NT-proBNP	10.5	5.59	18.9	<0.001
ECG (abnormal)	2.12	1.14	3.93	0.018
HF (any LVEF)*				
Log NT-proBNP	6.43	4.00	10.3	<0.001
ECG (abnormal)	1.80	1.15	2.83	0.010
Any valvular disease				
Log NT-proBNP	5.07	3.07	8.36	<0.001
Any atrial fibrillation				
Log NT-proBNP	4.44	2.91	6.79	<0.001
Abnormal ECG or echocardiogram				
Log NT-proBNP	42.3	11.1	161.7	<0.001
Any cardiac diagnosis				
Log NT-proBNP	34.6	12.8	93.9	<0.001
Multivariable analyses				
HFrEF				
Log NT-proBNP	10.2	5.63	18.3	<0.001
ECG (abnormal)	1.48	0.75	2.89	0.256
HF (any LVEF)*				
Log NT-proBNP	6.13	3.79	9.93	<0.001
ECG (abnormal)	1.29	0.80	2.09	0.303

Results of univariate and multivariable logistic regression analyses for the various diagnoses, expressed as OR and 95% CI. The term 'any' refers to the occurrence of the various conditions, regardless of whether they were considered a primary or a secondary diagnosis.
*Includes HFrEF, HFmrEF or HFpEF and excludes valvular HF.
HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction.NT-proBNP, N-terminal pro-brain natriuretic peptide;

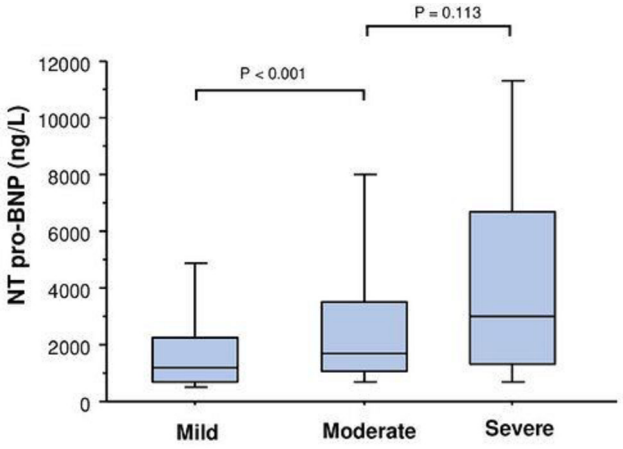

Figure 4 NT-proBNP according to severity of valvular disease. Box and whisker plots of NT-pro-BNP levels according to the severity of valvular disease, assessed using echocardiography. The five horizontal lines represent the 10th, 25th, 50th, 75th and 90th percentiles, from bottom to top. See table 2 for corresponding data. NT-proBNP, N-terminal pro-brain natriuretic peptide.

90%.[17] Clearly, NT-proBNP is excellent at excluding HF, which is essential for primary care in identifying patients who do not require specialist referral.

For secondary care services, the main concern is to identify, or 'rule in' patients with HF, which depends on the PPV. In this regard, PPVs for NT-proBNP are not as high as the NPVs. For example, NICE found that an NT-proBNP had a PPV of 58% at a cut-off of 400 ng/L. In the present study, which is restricted to patients with an NT-proBNP≥400 ng/L, 29.2% of patients had HF of any type and only 13.3% had HFrEF. In practice, this low diagnostic yield means that the majority of patients referred to specialist HF services do not have HF, but other cardiac conditions or none at all.

NT-proBNP as a test for heart disease in general

The early observation that circulating NP levels correlate inversely with cardiac output[24] supported the use of NT-pro-BNP for the detection of HFrEF. However, the primary stimulus for secretion of BNP is myocardial stretch[25] rather than reductions in cardiac output. Accordingly, many cardiac conditions,[10–15] including valve disease and AF, also lead to elevations in NP levels, as we have indeed found. The fact that conditions other than HF also lead to elevations in NT-proBNP has been recognised by guideline groups. However, the diagnostic cut-offs for NT-proBNP remain unchanged at 125 ng/L[8 9] or 400 ng/L.[17]

If an elevated NT-proBNP occurs in manifold cardiac and non-cardiac conditions, we may ask why it is used specifically in the diagnostic pathway for HF. In this respect, we found that 86% of patients referred with an NT-proBNP≥400 ng/L had a cardiac diagnosis and 92% had some ECG or echocardiographic abnormality. Most patients had an identifiable cardiac 'issue', but not necessarily HF.

LIMITATIONS

We acknowledge all the limitations of a retrospective study. However, a prospective design may have led to selection bias and may not have reflected 'real-world' clinical practice. As patients with an NT-proBNP<400 ng/L were excluded, the ROC analyses presented herein were not designed to address the diagnostic value of NT-proBNP in primary care but rather, the diagnostic utility once referred to secondary care, after excluding patients with an NT-proBNP<400 ng/L.

CONCLUSIONS

In this study of an HF referral pathway based on NT-proBNP, the minority of patients had HF. Over 90% had some ECG or echocardiographic abnormality and most had either valvular disease or AF. Given this

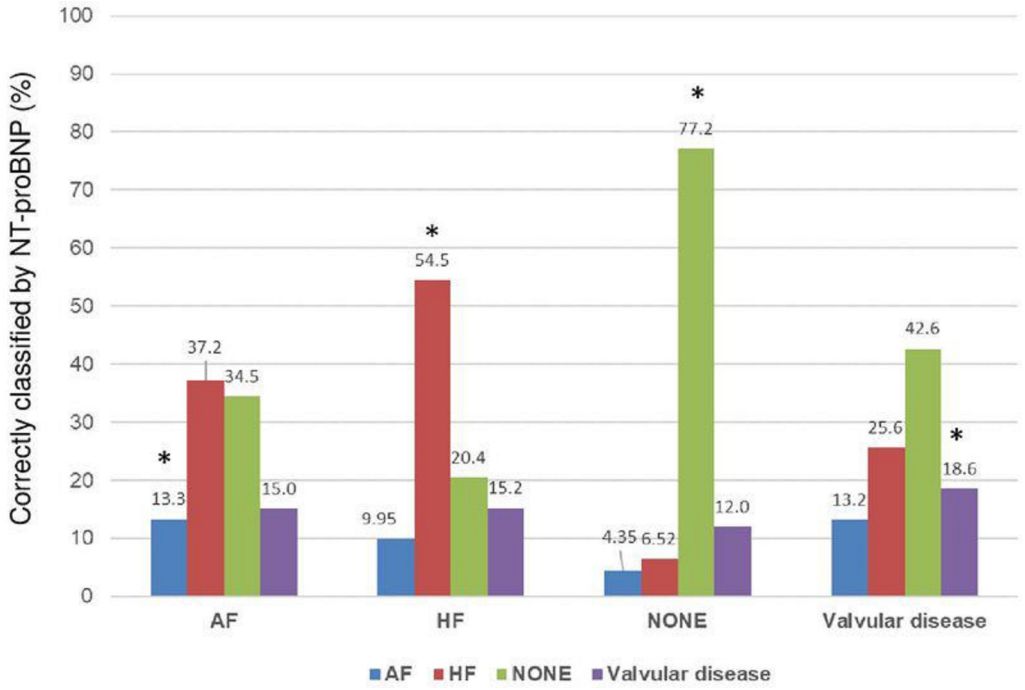

Figure 5 Discriminant analysis. Results of canonical linear analyses showing the proportion of patients which are correctly and incorrectly classified by NT-proBNP levels. For example, of the 191 patients adjudicated as having HF, 104 (54.5%) are classified correctly as having HF and 87 (45.5%) are classified incorrectly (19 (9.95%) as AF, 39 (20.4%) as no diagnosis and 29 (15.2%) as valvular disease). The correct classifications in each diagnostic group are marked with an asterisk (*). Details of this analysis are shown in the online supplemental file 1. AF, atrial fibrillation; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide.

diagnostic yield, NT-proBNP may be best employed in detecting heart disease in general, rather than, specifically, HF.

Contributors AZe, TN and RV collected data and contributed to data analysis and writing of the manuscript. PD, SW, PAP and FL made diagnoses and revised the manuscript. TQ, BS and AZa provided data analysis and drafted and revised the final manuscript. FL is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Clinical audit department, University Hospitals Birmingham, Queen Elizabeth, approved the study and specified that ethics committee approval was not required as this was a retrospective study undertaken for the purposes of service evaluation. Clinical audit department waived the need for patient consent on the basis that this was an audit undertaken for the purposes of service evaluation.

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