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The influence of confounders in the analysis of mid-regional pro-atrial natriuretic peptide in patients with chronic heart failure

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ABSTRACT

Background: Natriuretic peptides play an important role in the diagnosis and risk stratification of patients with acute and chronic heart failure. Multiple studies have shown that these peptides are liable to the influence of individual factors. For N-terminal-pro-B-type natriuretic peptide (NT-proBNP) some of these confounding factors have been evaluated over the years such as age, gender, New York Heart Association (NYHA) class and body mass index (BMI). The aim of this study was to establish confounding factors of mid-regional pro-atrial natriuretic peptide (MR-proANP) assessment.

Methods and results: We studied 684 patients (94% male, age 61.2 ± 11.2, left ventricular ejection fraction [LVEF] < 35%–45%, NYHA class (I/II/III/IV: 8.4/45.8/39.5/6.3%), ischaemic aetiology 71%, body mass index [BMI] 26.5 ± 4.3 kg/m^2, mean MR-proANP 296.0 ± 281.0 pmol/L, mean NT-proBNP 2792.0 ± 5328.6 pg/mL, mean creatinine level 110.2 ± 38.0 μmol/L and mean haemoglobin 13.9 ± 1.5 g/dL) with clinically stable chronic heart failure. MR-proANP levels increased with increasing NYHA class ($p < 0.0001$) and an increasing BMI category was associated with decreasing values of MR-proANP ($p < 0.0001$). We found MR-proANP to be independently associated with BMI, creatinine, ischaemic aetiology, LVEF and NYHA class. Meanwhile, NT-proBNP was independently associated with BMI, creatinine, haemoglobin, LVEF and NYHA class.

Conclusion: MR-proANP is subject to the almost identical influencing factors like NT-proBNP. The effects of anaemia warrant further study.

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1. Introduction

Heart failure (HF) is a common syndrome in industrialised countries around the world. Currently, an estimated 5.8 million people in the United States [1] and roughly 1–2% of the adult population in developed countries [2] are living with HF. Recent projections in the United States show an estimated increase in the prevalence of HF by 23%, which means that by 2030 > 8 million people in the United States will live with HF [3]. HF is a condition with poor long-term prognosis and therefore it is important to diagnose and treat the syndrome as early as possible. To date, a definitive diagnosis of HF based on symptoms and physical exam findings is often not sensitive enough to reach an accurate diagnosis [4]. Known as the gold standard, echocardiography is time-consuming, comparatively expensive, not available everywhere and may not always reflect an acute condition [4]. Over the last decades, natriuretic peptides, which are being secreted from the atria and the ventricles as a consequence of increased tension due to volume expansion [5], have been established as having an important role in the diagnostic and prognostic assessment of patients with HF. The two most recognised natriuretic peptides are atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) with their readily assessable and more stable precursors pro-ANP and pro-BNP. The first assays for mature BNP became available in 1993 [6], the first for its N-terminal precursor N-terminal-proBNP (NT-proBNP) in late 2002 [6]. Over the years,

Abbreviations: MR-proANP, mid-regional pro-atrial natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

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various studies have shown the diagnostic and prognostic value of measuring BNP and NT-proBNP [7,8]. Today, the measurement of the natriuretic peptides BNP and NT-proBNP carries a class IIA recommendation in the HF guidelines of the European Society of Cardiology (ESC) and a class I recommendation in the joint HF guidelines of the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) [2,9]. Since the development of an immunoassay able to detect the mid-regional sequence of NT-pro-ANP [10], commercially available since early 2004 [10], the novel marker MR-proANP has received increasing attention as a cardiac marker, and a large number of studies have investigated its clinical utilities. Different studies verified MR-proANP to be non-inferior to BNP and NT-proBNP with regards to diagnostic and prognostic questions in HF patients' assessment [11,12,13]. In particular, the non-inferiority of MR-proANP in the diagnosis of acute HF among patients presenting with acute dyspnoea to the emergency department has been established [14].

Previous studies confirmed BNP and NT-proBNP to be prone to influences of confounding factors such as age, gender, race, or body mass index (BMI) [7]. With advancing age, serum levels of BNP and NT-proBNP rise and with increasing BMI the levels of both NPs decrease. Knowledge of such factors may be important, as they may have significant effects on test results and on the management of a given patient. A thorough evaluation of confounding factors of MR-proANP has not been performed to date. Using data from a large cohort of patients, we aimed to establish clinically significant confounders of MR-proANP serum values in patients with chronic HF and to compare our findings with confounding factors of NT-proBNP assessment.

2. Methods

2.1. Study population

Patients for this analysis were recruited as part of a previous biomarker project by von Haehling et al. [13]. This approach yielded a patient population of 684 patients with stable chronic HF, recruited at 5 European centres in Athens (Greece, n = 33), London (UK, n = 84), Verona (Italy, n = 196), Wroclaw (Poland, n = 242) and Zabrze (Poland, n = 129) (Fig. 1). All participants were recruited for a study designed to investigate prognostic biomarkers [13] and had signed written informed consent in this regard. The study protocol was approved by the local ethics committees. To be included, participants had to have a history of chronic HF of at least 3 month duration with a left ventricular ejection fraction (LVEF) ≤45%. Medication was not to be changed 4 weeks prior to enrolment.

2.2. Biochemical and statistical analysis

MR-proANP and NT-proBNP were assessed from serum or plasma samples frozen at −80 °C until analysis. MR-proANP values were analysed using an automated sandwich chemiluminescence immunoassay on the KRYPTOR System (Thermo Fisher/B.R.A.H.M.S. GmbH, Henningsdorf, Germany) with a within-run imprecision coefficient of variation of 1.2% and a total imprecision of 5.4% and a lower limit of quantification of 4.5 pmol/L as described previously [14]. The median value of MR-proANP in healthy blood donors was 45 pmol/L with a range of 9.6–313 pmol/L [10]. An electrochemiluminescence immunoassay (ELICIA, Roche Diagnostics, Basel, Switzerland) was used for the determination of NT-proBNP values. The values for serum creatinine and haemoglobin were obtained by standard laboratory techniques.

To define anaemia we used the World Health Organisation criteria with haemoglobin <12 g/dl in women and haemoglobin <13 g/dl in men [15].

2.3. Statistical analysis

All data are shown as mean ± standard deviation (SD) and as median with upper and lower quartiles. All data were checked for normal distribution prior to analysis using the Kolmogorov–Smirnov-test. Non-normally distributed data (MR-proANP, NT-proBNP, and creatinine) were log-transformed before analysis to achieve a normal distribution. We used Student's t-test and analysis of variance (ANOVA) to compare differences and simple regression and multivariate stepwise regression using backward selection to identify factors, which are independently associated with MR-proANP and NT-proBNP. A value of $p < 0.05$ was considered to be significant. All analyses were performed using StatView version 5.0 software for Windows (Abacus Concepts, Berkeley, California).

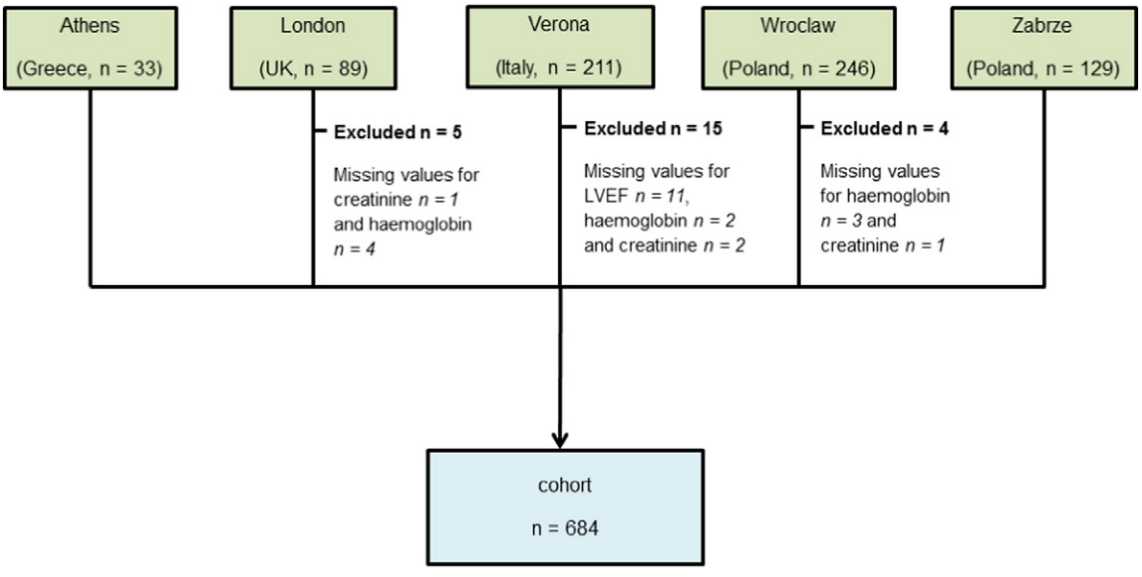

Fig. 1. Flowchart of the study population.

3. Results

3.1. Main cohort

Patients in the cohort (n = 684) were predominantly male (94%) with a mean age of 61.2 ± 11.2 years and a mean BMI of 26.5 ± 4.3 kg/m^2. Anaemia was detected in 161 (24%) patients: 13 women and 148 men. Serum levels of MR-proANP ranged from 24.5–2280.0 pmol/L with a mean of 296.0 ± 281.0 pmol/L and a median of 210.0 pmol/L (25th percentile 122.0 pmol/L, 75th percentile 383.0 pmol/L). The corresponding values for NT-proBNP ranged from 20.0–88,300.0 pg/mL with a mean of 2792.0 ± 5328.6 pg/mL and a median of 1109.5 pg/mL (25th percentile 451.1 pg/mL, 75th percentile 3085.0 pg/mL).

Patients taking aspirin ($p < 0.0001$), diuretics ($p = 0.0003$), spironolactone ($p < 0.0001$), statins ($p = 0.002$), digoxin ($p < 0.0001$) or warfarin ($p = 0.004$) had higher MR-proANP levels than patients not on any of these medications. Serum levels of NT-proBNP were higher in patients taking aspirin ($p = 0.0001$), diuretics ($p = 0.03$), spironolactone ($p = 0.0005$), statins ($p < 0.0001$), digoxin ($p = 0.0008$), or angiotensin converting enzyme inhibitors/angiotensin-receptor-blockers (ACE or ARB) ($p = 0.004$) than in patients without these medications. Patients' characteristics and medication are shown (Tables 1 and 2).

Using simple regression we found that MR-proANP correlated with age ($r = 0.16$, $p < 0.0001$), BMI ($r = -0.23$, $p < 0.0001$), serum creatinine ($r = 0.40$, $p < 0.0001$), and LVEF ($r = 0.31$, $p < 0.0001$). Furthermore, we were able to show that ischaemic aetiology ($r = 0.104$, $p = 0.006$), haemoglobin ($r = -0.191$, $p < 0.0001$) and NYHA class ($r = 0.444$, $p < 0.0001$) were also associated with MR-proANP but not gender ($r = 0.005$, $p = 0.90$) (Fig. 2). Multivariate stepwise regression using backward selection showed MR-proANP to be independently associated with BMI ($sc = -0.17$, $p < 0.0001$), serum creatinine ($sc = 0.29$, $p < 0.0001$), aetiology ($sc = 0.08$, $p = 0.02$), LVEF ($sc = 0.21$, $p < 0.0001$), and NYHA class ($sc = 0.29$, $p < 0.0001$), but not with age ($sc = 0.05$, $p = 0.13$), haemoglobin ($sc = -0.01$, $p = 0.67$), and gender ($sc = 0.01$, $p = 0.75$). Details can be found in (Table 3).

Simple linear regression showed serum NT-proBNP to correlate with BMI ($r = -0.24$, $p < 0.0001$), serum creatinine ($r = 0.30$, $p < 0.0001$), haemoglobin ($r = -0.24$, $p < 0.0001$), LVEF ($r = 0.32$, $p < 0.0001$), and NYHA class ($r = 0.40$, $p < 0.0001$). Our study did not show an independent association of logNT-proBNP and age ($r = 0.05$, $p = 0.16$), ischaemic aetiology ($r = 0.05$, $p = 0.16$) or gender ($r = -0.01$, $p = 0.80$) (Fig. 3). Using multivariate stepwise regression with backwards selection we found NT-proBNP to be independently associated with BMI ($sc = -0.17$, $p < 0.0001$), serum creatinine ($sc = 0.19$, $p < 0.0001$), haemoglobin ($sc = -0.10$, $p = 0.0003$), LVEF ($sc = 0.21$, $p < 0.0001$), and NYHA class ($sc = 0.26$, $p < 0.0001$), but not with age ($sc = -0.03$, $p = 0.38$), gender ($sc = 0.02$, $p = 0.54$) and aetiology ($sc = 0.006$, $p = 0.11$). Details can be found in (Table 3). No material change was noted in the results when women were excluded from the analysis.

We not only found an inverse relationship between haemoglobin values and biomarkers, closer analysis of anaemia revealed a significant correlation between haemoglobin and gender ($p < 0.0001$). Women with anaemia had significantly higher MR-proANP ($p = 0.0097$) and NT-proBNP ($p = 0.0025$) values than women without anaemia. We found the same to be true for men (all $p < 0.0001$, Table 4).

Table 1
Patient's characteristics — part 1.

	n = 684
Age (years)	61.2 ± 11.2
Male gender (%)	94
Weight (kg)	78.8 ± 14.4
BMI (kg/m^2)	26.5 ± 4.3
Cause of heart failure (% ischaemic)	71
NYHA functional class (I/II/III/IV)	58/313/270/43
Left ventricular ejection fraction (%)	30.0 ± 8.0
Left ventricular ejection fraction (%) (Category 1: <35%/2: 35–44%)	65/35
ACE inhibitor or ARB (%)	92
Beta-blockers (%)	73
Aspirin (%)	57
Any diuretic other than spironolactone (%)	75
Spironolactone (%)	36
Warfarin (%)	25

Table 2
Patient's characteristics — part 2.

	n = 684
Patients with anaemia (%)	24
Haemoglobin [g/dL]	13.9 ± 1.5
Sodium [mmol/L]	139.2 ± 4.4
Potassium [mmol/L]	4.4 ± 0.5
Creatinine [μmol/L]	110.2 ± 38.0
White blood cells [×1000/μL]	7.1 ± 2.1
Platelets [×1000/μL]	206.7 ± 62.1
Uric acid [μmol/L]	427.4 ± 145.6
MR-proANP [pmol/L]	296.0 ± 281.0
NT-proBNP [pg/mL]	2792.0 ± 5328.6

4. Discussion

Our study systematically evaluated confounding factors of MR-proANP assessment. Our data show that the main influencing factors of MR-proANP serum levels are NYHA class, serum creatinine, LVEF, and BMI with descending importance. Aetiology of HF also remained a weak, but independently associated confounder of MR-proANP. Apart from disease aetiology, these results are similar to our findings for NT-proBNP, whose most important influencing factors are NYHA class, LVEF, serum creatinine, and BMI with descending significance. In addition, haemoglobin remained independently predictive of NT-proBNP levels. Even though a trend towards significance existed, age was not independently predictive of either MR-proANP or NT-proBNP in this cohort of patients. Gender does not influence either of the two markers. A thorough understanding of such confounding factors is important for the interpretation of MR-proANP results in clinical practise. Indeed, MR-proANP has recently received wider attention, since recent studies have shown its non-inferiority compared to BNP for making a correct diagnosis of acute HF in the emergency setting (Maisel, JACC 2010, BACH) [14]. Some studies have also highlighted better prognostic value compared to BNP and NT-proBNP [11,16,17,18,19].

A recent study of 1352 patients, who came to the emergency room with acute dyspnoea, found MR-proANP levels to increase with age, were higher in men with the final diagnose of HF than women and decreased with increasing BMI. Additionally, they showed that the diagnostic accuracy of MR-proANP was influenced by race and age but not gender or BMI [20]. Indeed, MR-proANP levels increase with NYHA class, reduced kidney function, are higher in patients with a low LVEF and decrease with BMI and rising values of haemoglobin.

For BNP and NT-proBNP, similar results had been published before. In fact, the above described inverse relationship between BMI and MR-proANP as well as NT-proBNP were reported already in previous studies [20,21,22,23,24,25]. Different hypotheses have been proposed to explain this finding. Sarzani et al. postulated that an increased expression of natriuretic peptide clearance receptors (NPR-C) in adipose tissue might be responsible for lower levels of BNP in obese patients due to an increased clearance of natriuretic peptides from the circulation [26]. However, since MR-proANP and NT-proANP are structurally different from BNP, it is unlikely that they are cleared through natriuretic peptide clearance receptors only. In addition, clearance mechanisms of the two natriuretic peptides are presumed to

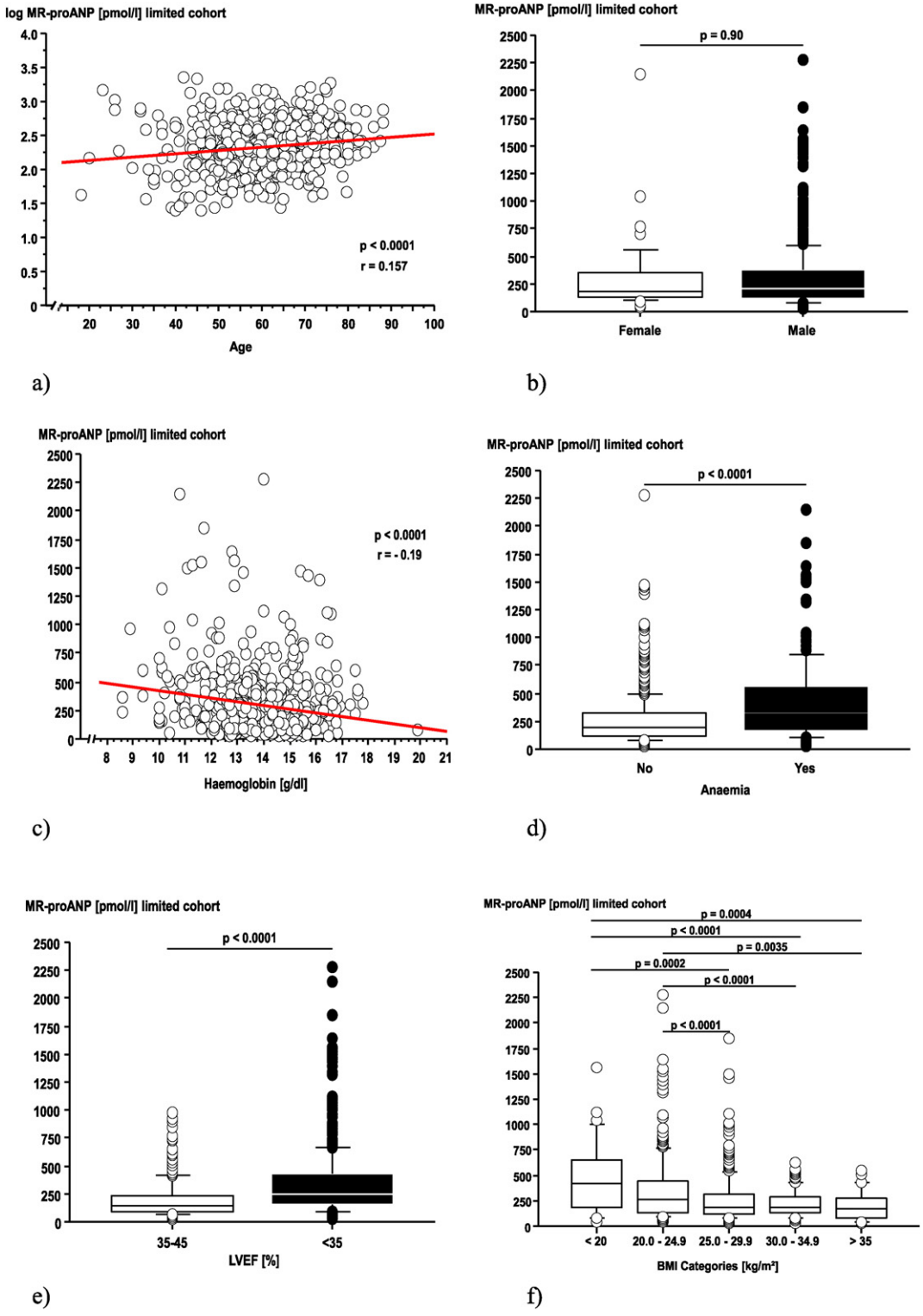

Fig. 2. Relationship between logMR-proANP and age (a), MR-proANP and gender (b), MR-proANP and haemoglobin (c), MR-proANP and anaemia (d), MR-proANP and LVEF (e) and MR-proANP and BMI by categories (f).

be not identical [21]. Whilst various other studies suggested that a decreased secretion or blunted up-regulation of natriuretic peptides are the reason for their lowered levels in obese patients, a reduced clearance appears to play only a secondary role [20,21,24,25,27,28].

Previous studies had observed a significant influence of advancing age on natriuretic peptide levels in healthy subjects as well as in patients with chronic HF [12,13,22,29,30]. In line with these previous findings, we also found MR-proANP to rise with age. Nevertheless, this effect was attenuated after multivariable adjustment for BMI, gender, kidney function, aetiology, and LVEF, with only a trend towards significance remaining. Similar effects were observed for NT-proBNP. Indeed, not all previous studies have established an effect of ageing on natriuretic peptide levels. Schou et al. [31] analysed the data of 345 patients with chronic HF. They found age to be significantly associated

Table 3
Univariable and multivariable regression for MR-proANP and NT-proBNP.

Mode	Univariable regression		Multivariable regression	
Dependent	logMR-proANP	logNT-proBNP	logMR-proANP	logNT-proBNP
Age (years)	**r = 0.157, p < 0.0001**	r = 0.054, p = 0.16	sc = 0.05, p = 0.13	sc = − 0.031, p = 0.38
Sex	r = 0.005, p = 0.90	r = −0.010, p = 0.80	sc = 0.010, p = 0.75	sc = 0.021, p = 0.54
BMI (kg/m^2)	**r = −0.232, p < 0.0001**	**r = −0.240, p < 0.0001**	**sc = −0.173, p < 0.0001**	**sc = −0.171, p < 0.0001**
Aetiology (ischaemic)	**r = 0.104, p = 0.0062**	r = 0.054, p = 0.16	**sc = 0.076, p = 0.0185**	sc = 0.055, p = 0.11
NYHA Class (I/II/III/IV)	**r = 0.444, p < 0.0001**	**r = 0.403, p < 0.0001**	**sc = 0.291, p < 0.0001**	**sc = 0.261, p < 0.0001**
LV-Function (1-best LVEF)	**r = 0.311, p < 0.0001**	**r = 0.322, p < 0.0001**	**sc = 0.210, p < 0.0001**	**sc = 0.218, p < 0.0001**
logCreatinine (μmol/L)	**r = 0.398, p < 0.0001**	**r = 0.297, p < 0.0001**	**sc = 0.285, p < 0.0001**	**sc = 0.193, p < 0.0001**
Haemoglobin (g/dL)	**r = −0.191, p < 0.0001**	**r = −0.241, p < 0.0001**	sc = −0.014 p = 0.67	**sc = −0.102, p = 0.0032**

All values with logANP and logBNP and logCreat.
Bold numbers indicate significance at $p < 0.05$.

with NT-proBNP but after adjustment for GRF, age became insignificant. Moertl et al. measured MR-proANP, BNP and NT-proBNP in 797 patients with chronic HF. In their multiple linear regression analysis they showed LVEF, glomerular filtration rate (GFR) and ankle edema to be independent predictors of all the natriuretic peptides but age and BMI were not [11]. Their findings are thus in accordance with our data, and we agree with their statement that age and sex may not be relevant in patients with HF in whom factors such as ventricular function, volume status, and renal function become more relevant [11].

Natriuretic peptides are secreted from cardiomyocytes in response to excessive cardiac wall stretch and induce vasodilatation and natriuresis. By doing so, natriuretic peptides aid in lowering blood pressure and cardiac afterload and help to increase the cardiac output at the same time. Therefore, it is not uncommon that patients with higher NYHA class have higher biomarker values due to the advanced stress on the heart. In our study, a trend was found between MR-proANP, NT-proBNP and NYHA class which has also been shown by Masson et al. [22]. With increasing NYHA class the values of MR-proANP and NT-proBNP increased accordingly. However, significance was not observed for all NYHA stages. This was mainly because the patient distribution was not balanced in all individual NYHA stages. A similar mechanism can be used to explain the association between LVEF and natriuretic peptides. In patients with impaired LVEF, the left ventricle does not empty sufficiently. This leads to ventricular volume overload and an elevated end-diastolic pressure. This brings about stretching of the left ventricular wall and an associated release of cardiac biomarkers. With increasing restriction of LVEF, the volume fraction of non-ejected blood volume increases, which in turn is reflected in an increased stretching of the cardiac walls and increased secretion of natriuretic peptides [32]. We found a significant inverse relationship between MR-proANP, NT-proBNP and LVEF, a result with has previously also been reported by Elmas et al. [33] in 102 patients with coronary artery disease and Eggers et al. [34] in 999 community-dwelling subjects aged 70 years participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study.

In the present study, a significant correlation between serum creatinine and MR-proANP as well as NT-proBNP was observed. Patients with increasing creatinine values had significantly higher values of MR-proANP and NT-proBNP. This finding is in agreement with several previous studies [11,22,35,36,37]. When looking at haemoglobin, we were able to show that haemoglobin may have an influence on NT-proBNP levels in a multivariable setting, but not MR-proANP. In our study, anaemic had significantly higher MR-proANP and NT-proBNP values than patients with normal haemoglobin values, which may also be viewed as more advanced HF. In multivariable regression, the association between haemoglobin and NT-proBNP remained significant, while MR-proANP became insignificant. When looking just at anaemia, we found MR-proANP and NT-proBNP levels to be slightly higher in anaemic women than in anaemic men. This might be caused by the different cut-off points used to define anaemia for men and women. An association between NT-proBNP and haemoglobin was also found by Desai et al. in their analysis of 189 anaemic patients with coronary heart disease form the Heart and Soul Study [38]. Here lower haemoglobin values were linearly associated with higher mean levels of log NT-proBNP. Hogenhuis et al. also found a significant negative association between both BNP and NT-proBNP and haemoglobin in a cohort of 541 patients hospitalised for HF [30] and a study on 137 diastolic HF patients equally showed a significant inverse relationship between BNP and haemoglobin ($p < 0.0001$) [39]. Anaemia is repeatedly seen in patients with HF. Estimates of the incidence of anaemia in patients with HF vary considerably from 4 up to 61% and are related to clinical characteristics of the studied population [40]. The reason of anaemia in patients with HF could be caused by renal damage due to restricted cardiac function [41] or iron deficiency evoked by decreased intestinal iron uptake caused by elevated pro-inflammatory cytokines blocking the absorption [40].

HF is a common disease with an excepted rise in prevalence over the next decades. It still is a disease with a limited life expectancy, thus early diagnosis and treatment is essential. The diagnosis based on physical examination and symptoms can be vague and echocardiography might not be available everywhere at any time. Therefore, the determination of natriuretic peptides for diagnostic and risk stratification purposes in patients with acute and chronic HF has gained increasing importance in recent years and is now mentioned in the guidelines for HF [2,9]. BNP and NT-proBNP are already well-established cardiac biomarkers. MR-proANP gained more recognition after introduction of a new measurement method a few years back. Natriuretic peptides are released from cardiomyocytes due to increased wall stretching and are subject to influencing factors. Those have been investigated for BNP and NT-proBNP in various studies. For MR-proANP there has been little information. Our study was designed to investigate the confounding factors of MR-proANP in comparison with the findings for NT-proBNP. We found that MR-proANP and NT-proBNP share many influencing factors. MR-proANP values increase with rising NYHA class, decreasing renal function, are higher in patients with reduced LVEF and decrease with increasing BMI and haemoglobin values. The results for NT-proBNP were similar, additionally it also showed a correlation between NT-proBNP and haemoglobin. Age and gender did not have an effect on the natriuretic peptide values in our cohort.

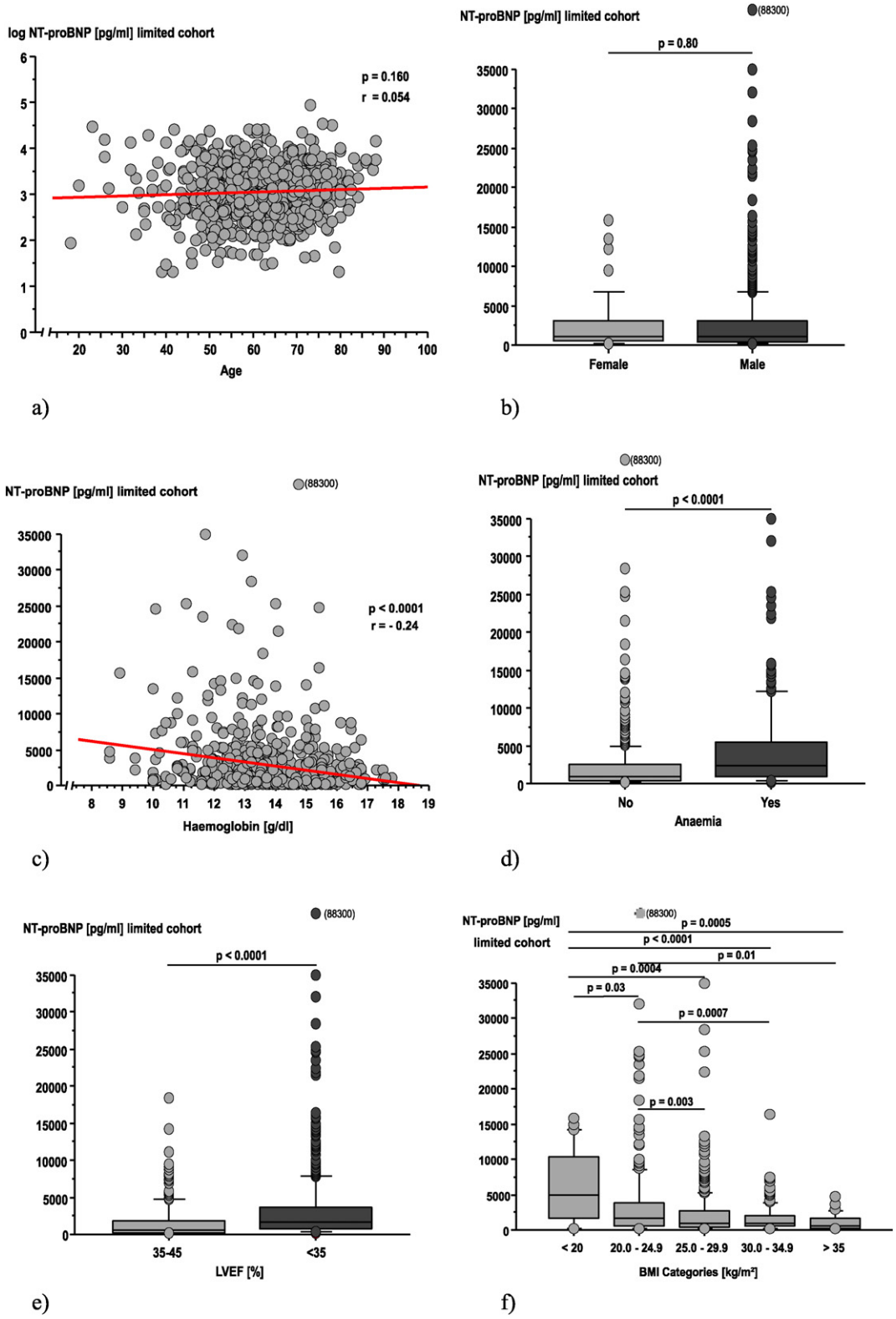

Fig. 3. Relationship between logNT-proBNP and age (a), NT-proBNP and gender (b), NT-proBNP and haemoglobin (c), NT-proBNP and anaemia (d), NT-proBNP and LVEF (e) and NT-proBNP and BMI by categories (f).

5. Conclusions

In conclusion, MR-proANP is subject to the same influencing factors as NT-proBNP, except for haemoglobin, which only remained independently associated with NT-proBNP. Anaemia is frequently seen in patients with HF, therefore further studies will be needed to determine whether NT-proBNP needs to be adjusted for anaemia before interpreting results. Since MR-proANP seems not to be influenced by haemoglobin values, it might be more reliable in the diagnosis of HF in anaemic patients.

Table 4
Biomarker values and anaemia.

Gender	Female (n = 42)			Male (n = 642)		
	Anaemia			Anaemia		
	Yes (n = 13)	No (n = 29)	p value	Yes (n = 148)	No (n = 494)	p value
MR-proANP [pmol/L]	510.5 ± 574.4	208.3 ± 131.0	**0.0097**	413.0 ± 350.0	260.4 ± 239.0	<**0.0001**
NT-proBNP [pg/mL]	5108.0 ± 5621.0	1517.0 ± 1522.3	**0.0025**	4551.8 ± 6084.0	2278.7 ± 5096.0	<**0.0001**

Bold numbers indicate significance at $p < 0.05$.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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