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Depressive symptomatology, NT-proBNP levels and health status in patients with heart failure: a prospective observational study

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ABSTRACT

Background Depressive symptoms frequently occur in patients with heart failure (HF). However, research on the relationship between these symptoms and N-terminal pro-brain natriuretic peptide (NT-proBNP), a key biomarker for HF severity and treatment, is scarce and yields inconsistent results.

Aims This study investigates the relationship among depressive symptomatology, NT-proBNP and health status in a cohort of patients with HF. Additionally, it assesses the impact of depressive symptoms on their clinical outcomes.

Methods A cohort of 151 patients with HF was followed for 1 year. The Hospital Anxiety and Depression Scale—Depression (HADS-D) Score was used to assess anxiety and depressive symptoms, and NT-proBNP levels were measured. Health status was evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Results Patients with HADS-D scores>5 points showed significantly higher NT-proBNP levels and lower KCCQ scores at baseline. Over the year, changes in HADS-D scores correlated positively with changes in NT-proBNP levels and negatively with changes in KCCQ scores. A baseline HADS-D score>5 points was significantly associated with an increased risk of the composite outcome of all-cause mortality and HF hospitalisation, even after adjusting for baseline characteristics (adjusted hazard ratio (HR): 2.17; 95% CI 1.05 to 4.48; p=0.036).

Conclusions HADS-D scores are significantly correlated with NT-proBNP levels and health status in patients with HF. A baseline HADS-D score>5 points is significantly associated with an elevated risk for the composite outcome of all-cause mortality and hospitalisation due to HF.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior research has established the prevalence of depressive symptoms in patients with heart failure (HF), but the relationship among depressive symptomatology, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and health status remains understudied. Understanding this relationship is crucial due to the potential impact of depressive symptoms on clinical outcomes in patients with HF.

WHAT THIS STUDY ADDS

⇒ This study highlights significant correlations among depressive symptomatology, NT-proBNP levels and health status in patients with HF. It demonstrates that baseline Hospital Anxiety and Depression Scale—Depression scores>5 points are associated with elevated risks of all-cause mortality and hospitalisation due to HF, even after adjusting for baseline characteristics. These findings shed light on the importance of assessing and addressing depressive symptoms in HF management.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study emphasise the need for routine screening and management of depressive symptoms in patients with HF. Incorporating assessments of depressive symptomatology alongside traditional markers such as NT-proBNP could enhance risk stratification and inform personalised treatment strategies. Addressing depressive symptoms may ultimately improve clinical outcomes and quality of life for patients with HF.

INTRODUCTION

Heart failure (HF) stands as a significant global health concern, impacting 26 million people worldwide, and its prevalence is on the rise.[1] HF not only leads to a decline in functional status and deteriorating quality of life but also results in frequent hospitalisations and high socioeconomic costs.[2–4] Despite improved medical care, mortality rates remain high, with half of all patients succumbing within 5 years of diagnosis.[5] This underscores the need to explore non-conventional risk factors influencing the course of this disease.

Major depression is a common comorbidity in patients with HF, affecting up to 30% of patients with HF depending on screening methods, HF severity and coexisting medical conditions.[6–9] Additionally, many patients with HF experience depressive symptoms.[9] However, the relationship between depressive symptomatology and N-terminal pro-brain natriuretic peptide (NT-proBNP), the most valuable biomarker

for determining severity and tailoring treatment strategies in HF, has only been investigated in a limited number of studies. These studies have produced conflicting results, with no clear correlation established between depressive symptoms and NT-proBNP levels.[10 11] This ambiguity not only impairs our understanding of the relationship between the two conditions but also limits our ability to identify patients at risk and complicates the development of effective treatment strategies. Therefore, this study aims to investigate the relationship between depressive symptomatology and NT-ProBNP levels and health status in patients with HF and assess its impact on their clinical outcomes.

METHODS

Study design

This study represents an observational substudy within the ongoing early palliative care for heart failure (EPCHF) trial, a prospective, controlled, multicentre study comparing standard cardiac care with early palliative care as an add-on to standard care.[12] The present analysis specifically focuses on patients enrolled at the University Hospital Bonn. Inclusion criteria included: (1) age≥18 years old; (2) New York Heart Association≥2; and (3) the ability to follow study instructions and complete all required visits.

Patients were excluded from participation if they: (1) were unable to read, understand or respond to questions in German; (2) were in the intensive care unit, on a ventilator or pre- or post-heart transplant; (3) had a non-cardiac terminal illness; (4) were concurrently participating in another study; or (5) were pregnant, planning for pregnancy or breastfeeding. Additionally, patients who did not attend follow-up visits, complete questionnaires or provide NT-proBNP values were excluded from the analysis. A separate publication details the full rationale and design of the EPCHF trial.[12]

Questionnaires

The Hospital Anxiety and Depression Scale (HADS) is one of the most widely used screening tools for detecting anxiety and depression disorders. With 14 items, each rated on a 4-point scale from 0 to 3, the scale yields maximum scores of 21 for both anxiety and depression. A higher score indicates more severe symptoms.[13]

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a specialised tool for assessing the health status of patients with HF. It includes 23 questions that are categorised into 5 domains: physical and social limitations, symptoms, self-efficacy and quality of life. The Overall Summary Score (OSS) combines all domains except for self-efficacy, while the Clinical Summary Score (CSS) includes only the physical and symptom scores. Scores for all domains and summaries are converted to a range between 0 and 100, with higher scores indicating fewer symptoms and better health status.[14 15]

Outcomes and follow-up

Follow-up examinations were conducted at 3, 6 and 12 months. At each visit, questionnaires, echocardiography and laboratory tests, including NT-proBNP, were administered. Additionally, data on hospitalisations for decompensated HF and mortality were collected. Adherence to and, if necessary, optimisation of HF medical therapy according to the Guidelines of the European Society of Cardiology were ensured at each visit.[16]

Strategies to mitigate research bias

To ensure the reliability and validity of our research findings, we implemented several key strategies to mitigate potential biases. First, all participant data were anonymised to remove any potential bias from researchers, who might otherwise be influenced by personal information, thus ensuring an objective analysis of the data. We also used validated German versions of all questionnaires and provided assistance to participants who needed help, ensuring the accuracy of the data collected. Additionally, we conducted repeated data collection during follow-ups to minimise biases associated with the fluctuating emotional and physical states of participants, as reported through self-assessments. At last, an independent data monitoring committee oversaw the trial's progress to ensure adherence to ethical standards and the integrity of data collection and analysis. These comprehensive measures collectively enhance the trustworthiness of our study, ensuring that our findings are robust and less prone to bias.

Statistical analysis

Depending on the normality of distribution, continuous variables were reported as mean (SD) or as median and interquartile range (IQR), and comparisons were made using either Student's t-tests or Wilcoxon tests. The normal distribution was assessed with Shapiro-Wilk tests. Categorical data were presented as numbers with percentages and analysed using the χ^2 test. The Mann-Whitney U test was applied to compare two independent groups formed by a median split.

Regression models were employed to identify predictors of NT-proBNP percentage change from baseline to the 1 year assessment, adjusting for age, sex, left ventricular ejection fraction (LVEF) and creatinine. Pearson's correlation tests were used to examine the linearity of the association between changes in HADS scores, NT-proBNP percentage changes and KCCQ changes. Time-to-event curves were depicted using the Kaplan-Meier method and compared between groups using the log-rank test. Univariate and multivariable Cox proportional hazard models calculated hazard ratios (HRs) and corresponding 95% CIs for the outcomes. Covariates included in the multivariable model were predefined based on their presumed association with clinical outcomes: anxiety score, age, male sex, body mass index, hypertension, diabetes mellitus, LVEF and creatinine. Statistical significance was set at a two-sided p value<0.05. All analyses were performed using IBM SPSS Statistics V.25.

RESULTS

Study population

A total of 151 patients met the inclusion criteria and were enrolled in this study (figure 1). The mean study duration

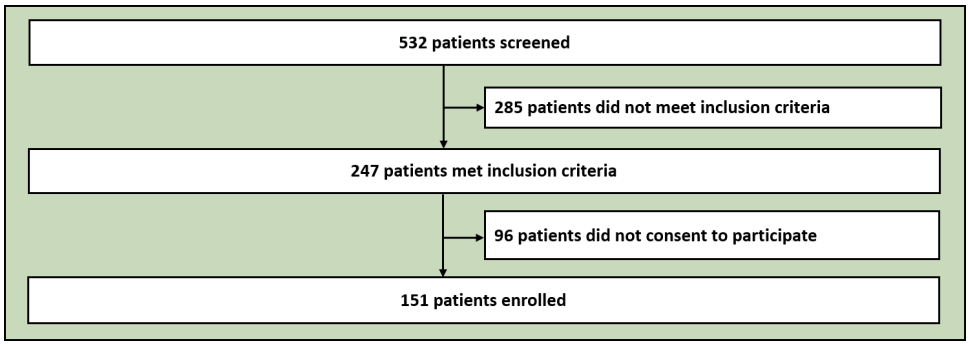

Figure 1 Flowchart of the study.

was 12 months (IQR: 11.6–13). Patients were predominantly men (72%) with a median age of 64 years (IQR: 53–75). An ischaemic aetiology was identified in 86 patients (57%). The median LVEF was 36% (IQR: 30%–45%). The median level of NT-proBNP was 2191 pg/mL (IQR: 854–4915). The median HADS-D score was 5 points (IQR: 3–8), and the median HADS-A score was 5 points (IQR: 2–9). A total of 10 patients (7%) received antidepressants, specifically selective serotonin reuptake inhibitors. The complete demographic and clinical characteristics of the patients are summarised in table 1.

THE RELATIONSHIP WITH NT-PROBNP

A. Depressive symptoms and NT-proBNP: patients with HADS-D scores>5 points exhibited significantly higher

Table 1 Study population

	All	HADS-D>5 points	HADS-D≤5 points	Statistic value	P value
	N=151	N=73	N=78		
Age, years (median (IQR))	64 (53–75)	63 (54–75)	65 (52–76)	0.086*	0.932
Male (%)	108 (72)	54 (74)	54 (69)	0.416†	0.590
BMI, kg/m^2 (median (IQR))	27.2 (23.5–0.9)	27.8 (23.0–33.0)	26.8 (23.5–30.3)	0.585*	0.559
Arterial hypertension (%)	103 (68)	50 (68)	53 (68)	0.005†	1.000
Type 2 diabetes mellitus (%)	40 (26)	25 (34)	15 (19)	4.366†	**0.043**
Lung disease (%)	44 (29)	24 (33)	20 (26)	0.956†	0.373
Coronary artery disease (%)	86 (57)	47 (64)	39 (50)	3.182†	0.100
LVEF, % (median (IQR))	36 (30–45)	36 (30–44)	35 (30–45)	0.425*	0.671
≤40% (%)	102 (68)	49 (67)	53 (68)		
41%–49% (%)	27 (18)	12 (16)	15 (19)		
≥50% (%)	22 (15)	12 (16)	10 (13)		
Serum creatinine, mg/dL (median (IQR))	1.1 (0.9–1.4)	1.0 (0.9–1.5)	1.1 (0.9–1.3)	0.259*	0.796
NT-proBNP, pg/mL (median (IQR))	2191 (854–4915)	2570 (1060–6447)	1884 (744–3331)	2.415*	**0.016**
NYHA functional classification (%)				1.714*	0.087
II	66 (44)	27 (37)	39 (50)		
III	65 (43)	34 (47)	31 (40)		
IV	20 (13)	12 (16)	8 (10)		
Cardiovascular medications (%)					
RASi	139 (92)	64 (88)	75 (96)	3.709†	0.072
Beta-blocker	147 (97)	72 (99)	75 (96)	0.897†	0.621
Diuretics	137 (91)	69 (95)	68 (87)	2.416†	0.162
Furosemide equivalent dose, mg/day (median (IQR))	60 (40–80)	40 (40–80)	80 (40–80)	0.997*	0.319
Aldosterone antagonist (%)	105 (70)	54 (74)	51 (65)	1.313†	0.291
SSRIs (%)	10 (7)	10 (14)	0 (0)	11.443†	**<0.001**

*z value.
† χ^2 BMI.
BMI, body mass index; HADS-D, Hospital Anxiety and Depression Scale—Depression; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional classification; RASi, inhibitors of the renin-angiotensin system; SSRIs, selective serotonin reuptake inhibitors.

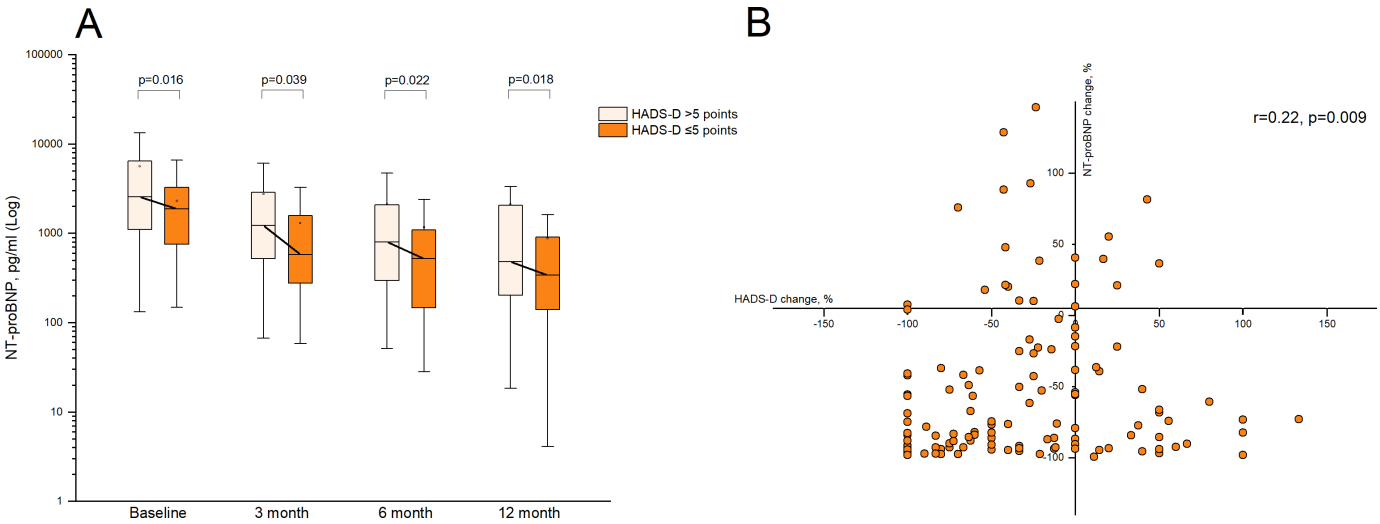

Figure 2 The relationship between HADS-D and NT-proBNP. (A) HADS-D score>5 points was significantly associated with higher NT-proBNP levels. (B) Percentage changes in the HADS-D scores from baseline to 1 year were significantly positively correlated with the percentage changes in NT-proBNP levels. HADS-D, Hospital Anxiety and Depression Scale—Depression; NT-proBNP, N-terminal pro-brain natriuretic peptide.

NT-proBNP levels at baseline compared with those with depression scores≤5 points (2570 pg/mL (IQR: 1060–6447) vs 1884 pg/mL (IQR: 744–3331), respectively) (p=0.016) (figure 2A).

Under HF medical therapy, HADS-D scores decreased to 3 points (IQR: 1–7) at the last assessment after 1 year. The percentage changes in HADS-D scores from baseline to the last assessment after 1 year were significantly positively correlated with the percentage changes in NT-proBNP levels (r=0.22, p=0.009) (figure 2B). In a multivariate regression model, the baseline HADS-D score was shown to be an independent predictor of the percentage change in NT-proBNP levels from baseline to the last assessment (ß=3.91, p=0.030), even after adjustment for age, sex, baseline LVEF and creatinine (ß=4.00, p=0.021) (table 2).

B. Anxiety and NT-proBNP: at baseline, patients with a HADS-A score>5 points had NT-proBNP levels of 1626 pg/mL (IQR: 749–4121), while those with a HADS-A score≤5 points had NT-proBNP levels of 2446 pg/mL (IQR: 1011–4959). There was no statistically significant difference between these two groups (p=0.098) (online supplemental figure 1). Additionally, changes in HADS-A scores did not correlate with percentage changes in NT-proBNP levels from baseline to 1 year (r=0.03, p=0.684).

THE RELATIONSHIP WITH LVEF

A. Depressive symptoms and LVEF: at baseline, there was no significant difference in LVEF values between the two groups with HADS-D scores>5 and ≤5 points (mean (SD): 38 (12)% vs 37 (12)%, respectively), p=0.671 (online supplemental figure 2A). However, the percentage changes in HADS-D scores from baseline to 1 year were significantly and negatively correlated with the changes in LVEF (r= –0.17, p=0.038) (online supplemental figure 2B).

B. Anxiety and LVEF: the mean LVEF score was 37% in both groups with HADS-A>5 and ≤5 points, showing no significant difference (p=0.390). Furthermore, there was no observed correlation between changes in HADS-A scores and changes in LVEF from baseline to 1 year (r= –0.134, p=0.128) (online supplemental figure 3).

Table 2 Multivariate analysis of predictors of percentage changes of NT-proBNP levels

	Coefficient	95% CI	P value
(Constant)	–197.48	–269.70 to –125.25	**<0.001**
Baseline HADS-D, point	4.00	0.61 to 7.39	**0.021**
Age, years	1.28	0.28 to 2.28	**0.012**
Gender	7.56	–23.71 to 38.83	0.633
LVEF, %	0.95	–0.29 to 2.19	0.132
Creatinine, mg/dL	12.32	–16.23 to 40.86	0.395

HADS-D, Hospital Anxiety and Depression Scale—Depression; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

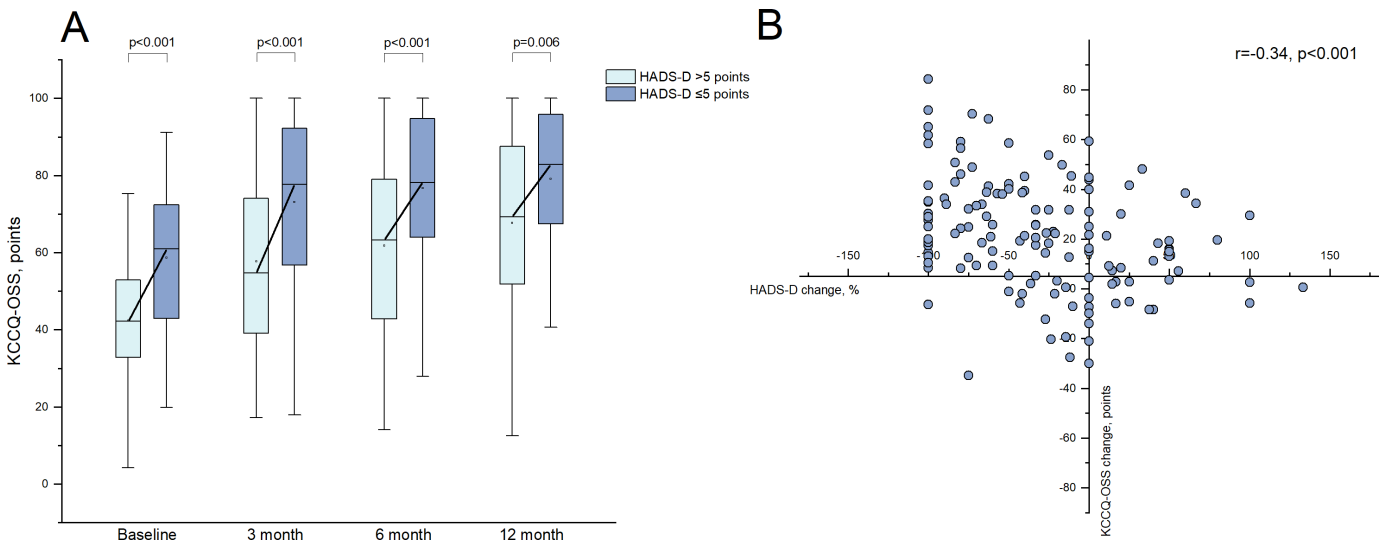

Figure 3 The relationship between HADS-D and KCCQ-OSS. (A) HADS-D score>5 points was significantly associated with higher KCCQ-OSS. (B) Percentage changes in the HADS-D scores from baseline to last assessment were significantly negatively correlated with changes in KCCQ-OSS. HADS-D, Hospital Anxiety and Depression Scale—Depression; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Score.

THE RELATIONSHIP WITH HEALTH STATUS

A. Depressive symptoms and health status: at baseline, patients with an HADS-D score>5 points exhibited a significantly lower KCCQ-OSS of 42 points (IQR: 33–53) and KCCQ-CSS of 48 points (IQR: 38–63) compared with the group with a depression score≤5 points. The latter group reported a KCCQ-OSS of 61 points (IQR: 43–73) and a KCCQ-CSS of 64 points (IQR: 48–76). The difference between the two groups was highly significant at p<0.001 for both KCCQ-OSS and KCCQ-CSS (figure 3A and online supplemental figure 4A). In Pearson's correlation analysis, the percentage change in HADS-D scores from baseline to 1 year was significantly negatively correlated with the changes in KCCQ-OSS (r= –0.34, p<0.001) and KCCQ-CSS (r= –0.20, p=0.021) (figure 3 and online supplemental figure 4B).

B. Anxiety and health status: patients with an HADS-A score>5 points at baseline demonstrated a KCCQ-OSS of 44 points (IQR: 34–59) and a KCCQ-CSS of 53 points (IQR: 40–65). In contrast, those with anxiety scores≤5 points had a KCCQ-OSS of 57 points (IQR: 40–71) and a KCCQ-CSS of 61 points (IQR: 42–75). The difference between the two groups was significant for both KCCQ-OSS (z=3.29, p=0.001) and KCCQ-CSS (z=2.48, p=0.013) (online supplemental figures 5A and 6A).

Moreover, the percentage changes in the HADS-A scores from baseline to the 1 year assessment were significantly negatively correlated with the changes in KCCQ-OSS (r= –0.26, p=0.003) and KCCQ-CSS (r= –0.20, p=0.002) (online supplemental figures 5B and 6B).

IMPACT OF DEPRESSIVE SYMPTOMS ON CLINICAL OUTCOMES

During the follow-up period, 36 patients (24%) were admitted due to cardiac decompensation, and 5 patients (3%) died, resulting in a total of 38 patients (25%) experiencing the composite outcome within 1 year. Patients with a baseline HADS-D score>5 points exhibited a higher incidence of the composite outcome (33% vs 18%; χ^2=4.46, p=0.047; online supplemental figure 7). The Cox proportional hazard analysis demonstrated that a baseline HADS-D score>5 points was associated with a high risk of the composite outcome within 1 year (HR: 1.95; 95% CI 1.01 to 3.78; p=0.047). Furthermore, this association remained consistent even after adjusting for baseline characteristics (adjusted HR: 2.17; 95% CI 1.05 to 4.48; p=0.036) (online supplemental table 1).

DISCUSSION

Main findings

Although the negative impact of depressive symptomatology on the clinical outcomes of HF has been well documented, there is a gap in understanding the relationship between depressive symptoms and NT-proBNP, a pivotal HF marker. This study addresses this gap by revealing a significant correlation among depressive symptoms, NT-proBNP levels and overall health status.

Nevertheless, our findings diverge from some prior studies, such as those conducted by Van den Broek *et al* and Lossnitzer *et al*, where no substantial association between NT-proBNP and depressive symptoms was identified.[10 11] Despite this, these studies confirmed the negative influence of these symptoms on clinical outcomes in patients with HF, aligning with the observations in the present study. These discrepancies may be attributed to the use of different assessment instruments. For instance, Broek *et al* employed the 10-item Center for Epidemiologic Studies Depression Scale, while Lossnitzer *et al* used the 9-item depression module of the Patient Health Questionnaire, covering depressive symptoms over only 2 weeks.

Given the acknowledged influence of depressive symptoms on HF outcomes, it is reasonable to hypothesise a potential relationship between these symptoms and the HF marker

NT-proBNP. This would explain why some patients with HF continue to have high levels of NT-proBNP despite optimal HF management, suggesting that they may be suffering from worsening or unrecognised underlying depression. This aligns with previous studies showing that patients with persistently high levels of NT-proBNP often suffer from unrecognised depressive disorders.[17 18] A drawback of these studies, however, is their limited power, as they examined only a single time point. This work is unique as it documents the relationship between both depression scores and NT-proBNP levels over 1 year. These findings could improve the detection and follow-up of depressive symptoms in this group of patients using a biological marker and may help tailor treatment for both HF and depression.

It is crucial to note that correlation does not necessarily imply causation; rather, it suggests a relationship between two variables, indicating they may mutually influence each other. HF leads to chronic cerebral hypoperfusion, systemic inflammation and endothelial dysfunction, all contributing to cognitive impairment and mental illness.[19] Moreover, HF symptoms restrict physical abilities and impact health status, triggering feelings of hopelessness and sadness that may culminate in depressive symptomatology.[2] Depressive symptoms, in turn, can elevate levels of catecholamine and stress hormones, promoting inflammatory pathways that negatively impact HF progression.[20 21] Additionally, patients with depression and HF who receive treatment with antidepressants face a higher risk of medication non-adherence and are less likely to receive guideline-based drug therapy.[9] This sets up a vicious circle in which both conditions feed into each other. Recognising a significant correlation between these variables is pivotal for breaking this detrimental cycle. This implies that improvements in either cardiac or mental health have the potential to exert positive influences on the other. This dynamic interplay likely accounts for the observed reduction in depression scores in this study, attributed in part to the optimised HF treatment and the reassurance provided to patients through regular follow-ups.

However, the presence of associations between HF and depressive symptoms, in contrast to the lack of a similar relationship with anxiety in this cohort, remains unclear. The literature on the association between anxiety and clinical outcomes in patients with HF is also debated. In a comprehensive meta-analysis investigating the association between anxiety and HF, nearly half of the included studies failed to establish any significant relationship between anxiety and either HF hospitalisation or mortality in patients with HF.[22 23] These findings underscore the critical need for additional research to understand the relationship between mental disorders and HF.

In summary, our study highlights a significant association between depressive symptomatology and NT-proBNP. It emphasises the profound impact of depressive symptoms on clinical outcomes in HF. The valuable insights gained from this research hold the potential to significantly shape a more precisely targeted therapeutic approach for addressing both disorders.

LIMITATIONS

The study's single-centre design may limit the generalisability of the findings, potentially introducing selection bias. Additionally, using self-reported questionnaires to assess depressive symptoms and health status could be influenced by the patients' current emotional and physical states. To address this, we conducted repeated data collection during follow-ups to minimise bias. Although the observation period was extended to 1 year to mitigate temporal biases, this duration may still not fully capture the long-term dynamics among anxiety, NT-proBNP levels and clinical outcomes, indicating the need for longer-term studies.

The reliance on the HADS Questionnaire for assessing anxiety and depression and the KCCQ Questionnaire for health status might introduce measurement bias. Nevertheless, both instruments are extensively validated and recognised for their efficacy in cardiac patients. Future research could enhance robustness by incorporating multiple questionnaires and clinical assessments.

Multivariable regression models were employed to adjust for potential confounders such as age, sex, LVEF and creatinine levels to ensure the robustness and reliability of our findings. However, residual confounding may still influence the results. Future studies should implement more rigorous controls and multivariable adjustments to deepen our understanding of the interactions among HF, mental health and treatment outcomes.

Lastly, as this study is part of the ongoing EPCHF trial, the effects of early palliative care on this patient group have not yet been assessed. The impact of this care on clinical outcomes will be detailed in future reports once more comprehensive data becomes available, providing clearer insights into its benefits.

IMPLICATIONS

Incorporating mental health assessments into regular HF management could lead to better overall outcomes. By recognising the association between depressive symptoms and elevated NT-proBNP levels, clinicians can tailor treatment plans that address both conditions. Regular monitoring of NT-proBNP levels and depressive symptoms could facilitate early detection of worsening HF or depression, allowing for timely interventions and ultimately improving patient care.

CONCLUSIONS

HADS-D scores are significantly correlated with NT-proBNP levels and health status in patients with HF. A baseline HADS-D score>5 points is significantly associated with an elevated risk for the composite outcome of all-cause mortality and hospitalisation due to HF.

Contributors MB collected and interpreted the patient's data and wrote the manuscript. MUB and RC equally provided guidance and oversight throughout the project. All authors contributed to the interpretation of the results and critically reviewed the manuscript. MB acts as the guarantor of this work.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by ethics committee of the University of Bonn with reference number 019/18 (Study code MED2-201604_EPCHF). Participants gave informed consent to participate in the study before taking part. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki by the World Medical Association.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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