Depressive symptomatology and NT-proBNP and Health status in Heart Failure

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Research Article

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Abstract

**Background:** Although depression symptoms are common among heart failure (HF) patients, there is little consensus regarding the relationship between depressive symptoms and NT-proBNP, the key HF marker. Therefore, this study aimed to investigate this relationship and assess the impact of depressive symptoms on the health status and clinical outcomes of HF patients.

**Methods:** 151 patients with HF were enrolled in the study and followed up for one year. Depressive symptoms and health status were assessed by the Hospital Anxiety and Depression Scale (HADS-D) and the Kansas City Cardiomyopathy Questionnaire (KCCQ), respectively.

**Results:** At baseline, the median HADS-D score was 5 (3 - 8) points. Patients with HADS-D scores > 5 points had significantly higher NT-proBNP levels ($p = 0.043$), and significantly lower KCCQ-OSS and KCCQ-CSS ($p < 0.001$ for both KCCQ scores).

From baseline to the last assessment after one year the percentage changes in the HADS-D scores were significantly positively correlated with the percentage changes in the levels of NT-proBNP ($r = 0.22$, $p = 0.009$). It was also significantly negatively correlated with the changes in KCCQ-OSS ($r = -0.34$, $p < 0.001$) and KCCQ-CSS ($r = -0.19$, $p = 0.021$).

Moreover, baseline HADS-D score was an independent predictor of the percentage changes in NT-proBNP from baseline to the last assessment ($\beta = 3.91$, $p = 0.03$), even after adjustment for age, sex, baseline LVEF and creatinine ($\beta = 3.99$, $p = 0.02$).

In a Cox regression analysis baseline HADS-D score had a significant impact on the cardiovascular mortality, which remained consistent even after adjustment for age, sex, and baseline LVEF, NT-proBNP and creatinine (hazard ratio = 1.18, 95% CI = 1.0 – 1.4, $p = 0.048$).

**Conclusions:**

1. There is a significant correlation between depressive symptoms, NT-proBNP, and health status in HF patients.

2. Baseline HADS-D score has a significant impact on the cardiovascular mortality in HF patients.

**Introduction**

Heart failure (HF) is a major global health concern affecting 26 million people worldwide, and its prevalence is on the rise.\(^1\) It not only leads to poor functional status and deteriorating quality of life (QOL), but also to frequent hospitalizations and high socioeconomic costs.\(^2\) Not to mention that, despite improved medical care, mortality rates remain high, with half of all patients dying within five years of diagnosis.\(^2\) This reinforces the need to explore further non-conventional risk factors that may influence the course of this disease.
Major depression is a common comorbidity in patients with HF. Depending on the method of screening, the severity of HF, and co-existing medical conditions, it can reach up to 40%. While, even more, are affected by depressive symptoms. 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 been investigated by only a limited number of studies. Furthermore, these studies yielded conflicting results with no clear correlation between depressive symptoms and NT-proBNP levels. 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, the aim of this study was to investigate the relationship between depressive symptomatology and NT-ProBNP levels in HF patients and to assess its impact on their health status and clinical outcomes.

**Methodology**

**Study design:**

This was an observational substudy of the still ongoing EPCHF trial (Early Palliative Care for Heart Failure). The EPCHF trial is a prospective, controlled, multicenter study comparing standard cardiac care with early palliative care as an add-on to the standard care. This current work analyzed the patients enrolled in the Department of Internal Medicine and Cardiology at University Hospital Bonn. Inclusion criteria included: (a) age \( \geq 18 \) years old, (b) NYHA \( \geq 2 \), and (c) the ability to follow the study instructions and to complete all the required visits.

Patients were excluded from participation in this study if they: (a) were unable to read, understand, or respond to questions in German, (b) were in the intensive care unit, on a ventilator, or pre- or post-heart transplant, (c) non-cardiac terminal illness, (d) were simultaneously participating in another study, or (e) were pregnant, planning for pregnancy, or nursing. Patients who did not attend the follow-up visits, did not complete the questionnaires, or did not have NT-proBNP values were also excluded from the analysis. There is a separate publication detailing the full rationale and design of the EPCHF Trail.

Regular data monitoring was performed to ensure the precision and quality of the data collected. All patients provided their informed consent to the study, which was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki of the World Medical Association.

**Questionnaires:**

The Hospital Anxiety and Depression Scale (HADS) is one of the most widely used screening tools to help identify anxiety and depression disorders in people with a physical illness. It contains 14 items summed up into two scales: anxiety and depression. Each item is rated on a four-point scale, giving maximum
scores of 21 for anxiety and depression. A higher score reflects a higher degree of anxiety and depressive symptoms.\textsuperscript{11}

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a specialized questionnaire that assesses health status in patients suffering from HF. It consists of 23 questions divided into five domains: physical and social limitations, symptoms, self-efficacy, and QOL. The overall summary score (OSS) combines all domains except that of self-efficacy. The clinical summary score (CSS) includes only the physical and symptoms scores. All domains and summary scores were converted to a score range between 0 and 100, with higher scores indicating fewer symptoms and better health status.\textsuperscript{12,13}

**Follow up:**

Follow-up examinations were performed at 3, 6, 9, and 12 months in the outpatient clinic of the University Hospital Bonn. At each visit, vital signs, physical examination, questionnaires, ECG, echocardiography, and laboratory tests including NT-proBNP were performed. At each visit, adherence to and, if necessary, optimization of HF medical therapy according to the Guidelines of the European Society of Cardiology (ESC) was ensured.\textsuperscript{14} All patients were also followed for the first hospitalization for decompensated HF and cardiovascular mortality.

**Statistical analysis:**

Statistical analysis was performed using IBM® SPSS® Statistics 25 (Chicago, IL, United States). Categorical variables were reported as counts (percentages), while continuous variables were reported as mean ± standard deviation if normally distributed, or as median and interquartile range if not normally distributed. Normal distribution and homogeneity of variance were tested before the statistical analysis using Shapiro-Wilk tests. The Mann-Whitney U test was used to compare the differences between two independent groups created by a median split. Regression models were performed to identify predictors of NT-proBNP percentage change from baseline to the last assessment while adjusting for age, sex, EF, and creatinine. Pearson's correlation tests were performed to examine the linearity of the association between HADS-D and NT-proBNP percentage changes and KCCQ changes. Cox regression analysis was used to investigate the impact of the baseline depression score on the cardiovascular mortality while adjusting for age, sex, and baseline LVEF, NT-proBNP and creatinine. A two-tailed p-value < 0.05 was considered statistically significant.

**Results**

**Study population:**

A total of 151 patients met the inclusion criteria and were enrolled in this study. The last assessment took place after 12 (11.6–13) months. Patients were mainly men (71.5%) with a mean age of 64 (20–88) years. An ischemic etiology was found in 86 (57%) of patients. The median left ventricular ejection fraction (LVEF) was 36 (30–45) %. The median level of NT-proBNP was 2191 (132–42434) pg/ml. A total
of ten patients (5.8%) received antidepressants. Selective serotonin reuptake inhibitors (SSRIs) were the only antidepressant drugs prescribed. The complete demographic and clinical patients` characteristics are summarized in Table 1.
<table>
<thead>
<tr>
<th>Variables</th>
<th>All (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>64 (20–88)</td>
</tr>
<tr>
<td>Male sex – n. (%)</td>
<td>108 (71.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.22 (14.84–55.98)</td>
</tr>
<tr>
<td>Arterial hypertension – n. (%)</td>
<td>103 (68.2)</td>
</tr>
<tr>
<td>Diabetes mellitus Type 2 – n. (%)</td>
<td>40 (26.5)</td>
</tr>
<tr>
<td>Lung disease – n. (%)</td>
<td>44 (29.1)</td>
</tr>
<tr>
<td>Ischemic heart failure – n. (%)</td>
<td>86 (57)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td></td>
</tr>
<tr>
<td>Median –%</td>
<td>36 (30–45)</td>
</tr>
<tr>
<td>≤ 40% – n. (%)</td>
<td>102 (67)</td>
</tr>
<tr>
<td>41 bis 49 – n. (%)</td>
<td>27 (18)</td>
</tr>
<tr>
<td>≥ 50 – n. (%)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Serum creatinine – mg/dl</td>
<td>1.05 (0.50–4.30)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>2191 (132–42434)</td>
</tr>
<tr>
<td>NYHA functional classification</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>66 (43.7)</td>
</tr>
<tr>
<td>III</td>
<td>65 (43)</td>
</tr>
<tr>
<td>IV</td>
<td>20 (13.2)</td>
</tr>
<tr>
<td>Cardiovascular premedication</td>
<td></td>
</tr>
<tr>
<td>RASi – n. (%)</td>
<td>139 (92.1)</td>
</tr>
<tr>
<td>Beta blocker – n. (%)</td>
<td>147 (97.4)</td>
</tr>
<tr>
<td>Diuretics – n. (%)</td>
<td>109 (72.2)</td>
</tr>
<tr>
<td>Aldosterone antagonist – n. (%)</td>
<td>105 (69.5)</td>
</tr>
<tr>
<td>SSRIs – n. (%)</td>
<td>10 (5.8)</td>
</tr>
</tbody>
</table>

*N: number, BMI: body mass index, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association functional classification, RASi: Inhibitors of the renin-angiotensin system, SSRIs: selective serotonin reuptake inhibitors.*

The relationship with NT-proBNP:
A.) Depressive symptoms and NT-proBNP: At baseline, the median HADS-D score was 5 (3–8) points. Patients with HADS-D scores > 5 points had significantly higher NT-proBNP levels of 2570 (1060–6447) pg/ml compared to NT-proBNP values of 1884 (744–333) pg/ml in those with depression scores ≤ 5 points (p = 0.043) (Fig. 1A).

Furthermore, the percentage changes in the HADS-D scores from baseline to the last assessment after one year were significantly positively correlated with the percentage changes in the levels of NT-proBNP (r = 0.22, p = 0.009) (Fig. 1B).

In a multivariate regression model, 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 (β = 3.91, p = 0.03), even after adjustment for age, sex, baseline LVEF and creatinine (β = 3.99, p = 0.02) (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>-197.475</td>
<td>-269.701</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline HADS-D, point</td>
<td>3.998</td>
<td>0.609</td>
<td>7.387</td>
</tr>
<tr>
<td>Age, year</td>
<td>1.283</td>
<td>0.281</td>
<td>2.284</td>
</tr>
<tr>
<td>Gender</td>
<td>7.558</td>
<td>-23.710</td>
<td>38.826</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.951</td>
<td>-0.291</td>
<td>2.193</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>12.315</td>
<td>-16.232</td>
<td>40.862</td>
</tr>
</tbody>
</table>

CI: confidence interval, HADS: Hospital Anxiety and Depression Scale, LVEF: left ventricular ejection fraction

B.) Anxiety and NT-proBNP: At baseline, the median HADS-A score was 5 (2–9) points. Patients with HADS-A scores > 5 points had NT-proBNP levels of 1626 (749–4121) pg/ml. Patients with HADS-A scores ≤ 5 points had NT-proBNP levels of 2446 (1011–4959) pg/ml. There was no statistically significant difference between the two groups (p = 0.09) (Supplementary Fig. 1A). Additionally, changes in HADS-A scores did not correlate with percentage changes in NT-proBNP levels (p = 0.77).

The relationship with LVEF:

A.) Depressive symptoms and LVEF: At baseline, there was no significant difference between the LVEF values of the two groups with HADS-D scores > 5 and ≤ 5 points (LVEF = 38 ± 12% and 37 ± 12%, respectively), p = 0.09. (Fig. 2A). However, the percentage changes in the HADS-D scores from baseline to last assessment were significantly negatively correlated with the changes in LVEF (r = -0.17, p = 0.038) (Fig. 2B).
B.) Anxiety and LVEF: The mean LVEF score was 37% in both groups with HADS-A > 5 and ≤ 5 points, \(p = 0.4\). No correlation was observed between changes in HADS-A scores and changes in LVEF from baseline to last assessment, \(p = 0.13\) (Supplementary Fig. 2).

The relationship with health status:

A.) Depressive symptoms and health status: At baseline, patients with a HADS-D score > 5 points had a significantly lower KCCQ-OSS of 42 (33–53) points and KCCQ-CSS of 48 (38–63) points compared to the group with a depression score ≤ 5 points, who had KCCQ-OSS of 61 (43–73) points and KCCQ-CSS of 64 (48–76) points. The difference between the two groups was highly significant at \(p < 0.001\) for both KCCQ-OSS and -CSS (Fig. 3A and Fig. 4A).

In a Pearson’s correlation analysis, the percentage change in HADS-D scores from baseline to last assessment was significantly negatively correlated with the changes in KCCQ-OSS (\(r = -0.34, p < 0.001\)) and KCCQ-CSS (\(r = -0.19, p = 0.021\)) (Fig. 3B and Fig. 4B).

B.) Anxiety and health status: Patients with a HADS-A score > 5 points at baseline had KCCQ-OSS of 44 (34–59) points and a KCCQ-CSS of 53 (40–65) points. Those with anxiety scores ≤ 5 points had a KCCQ-OSS of 57 (40–71) points and a KCCQ-CSS of 61 (42–75) points. The difference between the two groups was significant for both KCCQ-OSS (\(p < 0.001\)) and KCCQ-CSS (\(p = 0.013\)) (Supplementary Fig. 3A and Fig. 4A).

The percentage changes in the HADS-A scores from baseline to last assessment were also significantly negatively correlated with the changes in KCCQ-OSS (\(r = -0.26, p = 0.003\)) and KCCQ-CSS (\(r = -0.2, p = 0.02\)) (Supplementary Fig. 3B and Fig. 4B).

Impact of depressive symptoms on patients' outcomes

During the follow-up period, 39 (26%) of patients were admitted due to cardiac decompensation and nine (6%) died, five (3%) because of cardiovascular reasons, two (1%) for non-cardiovascular reasons, and two (1%) with unknown causes. Under optimal HF medical therapy, HADS-D scores changed from 5 (3–8) points at baseline to 3 (1–7) points at the last assessment. In a Cox regression analysis baseline HADS-D score had a significant impact on the cardiovascular mortality (hazard ratio = 1.2, 95% CI = 1.04–1.45, \(p = 0.018\)). This impact remained consistent even after adjustment for age, sex, and baseline LVEF, NT-proBNP and creatinine (hazard ratio = 1.18, 95% CI = 1.0–1.4, \(p = 0.048\)) (Table 3).
### Table 3
Impact of the baseline HADS-D score on the cardiovascular mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Monovariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Baseline HADS-D, points</td>
<td>1.2</td>
<td>1.04–1.45</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.03</td>
<td>0.96–1.1</td>
</tr>
<tr>
<td>Gender</td>
<td>33.9</td>
<td>0.009–132066</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.92</td>
<td>0.83–1</td>
</tr>
<tr>
<td>Baseline NT-proBNP, pg/mL</td>
<td>1</td>
<td>1–1</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dl</td>
<td>2.66</td>
<td>1.1–6.3</td>
</tr>
</tbody>
</table>

*HR: Hazard ratio, CI: confidence interval, HADS: Hospital Anxiety and Depression Scale, LVEF: left ventricular ejection fraction*

### Discussion

Although depressive symptomatology has long been known to negatively impact the clinical outcomes of HF patients, little is known about the relationship between depressive symptoms and NT-proBNP, the most valuable marker of HF. This study provides evidence that there is a significant correlation between depressive symptoms and NT-proBNP as well as health status and clinical outcomes in HF patients.

However, these results are not consistent with those of some other studies. Van den Broek et al. (2011) and Lossnitzer et al. (2020), for example, found no significant association between NT-proBNP and depressive symptoms, despite demonstrating that these symptoms negatively impact clinical outcomes in HF patients similar to this one. However, inconsistent findings can be partially attributed to the use of different assessment instruments for affective symptoms: Broek et al. (2011) used the 10-item Center for Epidemiologic Studies Depression Scale (CES-D), while Lossnitzer et al. (2020) applied the nine-item depression module of the Patient Health Questionnaire (PHQ-9), which covers depressive symptoms in the past two weeks. In addition, given that depressive symptoms are able to affect HF outcomes, it would be reasonable to assume that they also have some relationship with the HF marker NT-proBNP. This may explain why some HF patients continue to have high levels of NT-proBNP despite optimal HF management, suggesting that they may be suffering from worsening affective symptoms or unrecognized underlying depression. That would be in line with previous studies showing that patients suffering from depressive disorders often have higher levels of NT-proBNP. A drawback of these studies, though, is their limited power, as they examined only a single time point. This work is thus unique as it also tracked changes over one year. These findings could therefore improve the detection of clinically relevant depressive symptoms in this group of patients by a biological marker and may help monitor and adjust antidepressant treatment.
It is important to note that correlation does not necessarily imply causation. A correlation simply indicates that there is a relationship between two variables, meaning that they may affect each other. HF leads to chronic cerebral hypoperfusion, systemic inflammation, and endothelial dysfunction, all of which lead to cognitive impairment and mental illness. Moreover, HF symptoms limit physical abilities and affect health status, causing feelings of hopelessness and sadness that can culminate in depressive symptomatology. Depressive symptoms, in turn, may increase levels of catecholamine and stress hormones and promote inflammatory pathways, all of which have a negative impact on HF progression. In addition, depressed HF patients treated with antidepressants are at higher risk for medication non-adherence and less likely to receive guideline-based drug therapy. It is then a vicious circle in which both conditions feed into each other.

Identifying a significant correlation between both variables can therefore be advantageous in breaking this vicious circle, as it is supposed to work both ways. This implies that improving either cardiac or mental health could enhance the status of the other. It is likely that this would explain the reduction in depression scores observed in this study, which could partly be attributed to the optimization of HF treatment as well as the reassurance provided to patients through regular follow-ups and telephone support.

However, the mechanisms by which affective symptoms and HF influence each other are complex and poorly understood. This also applies to this study, as no clear explanation can be found for the presence of these associations with depressive symptoms, but not with anxiety. The literature on the association between anxiety and HF is insufficient, and the findings are conflicting. In a meta-analysis of 20 studies, only 10 found an association between anxiety and cardiovascular disease. Another meta-analysis that found a significant association between anxiety and poor cardiac outcomes also noted that this relationship disappeared when the analysis was adjusted for other medical variables, suggesting that its original findings may have been largely driven by these cofactors.

Taken together, the current study found a significant association between depressive symptomatology and NT-proBNP, in contrast to anxiety. It also highlights the significant impact of depressive symptoms on clinical outcomes in HF. These findings may help develop a tailored therapeutic approach for both disorders.

**Limitations**

This was a single-center study, so the results cannot be generalized. In addition, it may be that a one-year observation period is not long enough to capture associations between anxiety, NT-proBNP levels, and clinical outcomes. Similar studies with longer time frames would help confirm these findings.

Another limitation is the use of only one screening questionnaire to assess anxiety and depression. Multiple questionnaires should have been used to confirm these results. Furthermore, the assessment of psychopathology by a self-report questionnaire has to be distinguished from the clinical diagnosis of an
affective or anxiety disorder. However, the objective of the study was to simulate daily practice with an easy-to-use but scientifically recommended screening instrument. In future studies, different questionnaires alongside clinical assessments should be compared to find out the one best suited for this group of patients.

Finally, This study was a sub-study from the EPCHF trial. Since the EPCHF trial is still in progress, the current work was unable to assess the effects of early palliative care on this group of patients. However, this study was only aimed to investigate the relationship between depression, NT-proBNP and health status. The impact of early palliative care on clinical outcomes will be published separately once the data are available.

Conclusions

1. There is a significant correlation between depressive symptoms, NT-proBNP, and health status in HF patients.

2. Baseline HADS-D score has a significant impact on the cardiovascular mortality in HF patients.

Abbreviations

CES-D = Center for Epidemiologic Studies Depression Scale

EPCHF = Early Palliative Care for Heart Failure

HADS = Hospital Anxiety and Depression Scale

HF = heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical score

KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire overall score

LVEF = left ventricular ejection fraction

PHQ-9 = Nine-item depression module of the Patient Health Questionnaire

QOL = quality of life

RASi = Inhibitors of the renin-angiotensin system

NT-pro BNP = N-Terminal pro-brain natriuretic peptide

Declarations
Ethics approval:
The study was carried out in accordance with the ethical standards set forth in the Declaration of Helsinki. It was approved by the Ethics Committee of the University of Bonn and assigned the reference number MED2-201604_EPCHF

Consent for publication:
Not applicable

Availability of data and materials:
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:
The authors declare that they have no competing interests.

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Authors’ contributions:
Mahmoud Balata collected and interpreted the patient’s data and wrote the manuscript.
Ralf Westenfeld supervised the study.
Marwa Hassan analyzed the data.
Roman Pfister supervised the study.
Sebastian Zimmer supervised the study.
Georg Nickenig supervised the study.
Marc Ulrich Becher and Rupert Conrad equally provided guidance and oversight throughout the project.
All authors contributed to the interpretation of the results and critically reviewed the manuscript.

Acknowledgements:
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References


**Figures**
Figure 1

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 last assessment were significantly positively correlated with the percentage changes in NT-proBNP levels.

Figure 2

A: No significant difference in LVEF values between patients with HADS-D scores > 5 and ≤ 5 points.

B: Percentage changes in the HADS-D scores from baseline to last assessment were significantly negatively correlated with changes in LVEF.
Figure 3

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.

Figure 4

A: HADS-D score > 5 points was significantly associated with higher KCCQ-CSS.

B: Percentage changes in the HADS-D scores from baseline to last assessment were significantly negatively correlated with changes in KCCQ-CSS.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.pdf
- SupplementaryFigure2.pdf
- SupplementaryFigure3.pdf
- SupplementaryFigure4.pdf