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Unraveling the Link between Depressive Symptoms, NT-proBNP Levels, and Health Outcomes in Heart Failure: A Prospective Study

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Abstract

Background: Depression is a common comorbidity in heart failure (HF) and has been shown to negatively impact clinical outcomes. NT-proBNP is a biomarker of myocardial stress, commonly elevated in HF patients, and its levels are associated with disease severity and prognosis. This study aimed to explore the relationship between depressive symptoms, NT-proBNP levels, and health outcomes in heart failure patients.

Methods: This prospective cohort study included 200 heart failure patients, of whom 90 were classified as depressed (PHQ-9 ≥10) and 110 as non-depressed (PHQ-9 <10). Baseline demographic data, NT-proBNP levels, and depression severity were collected. Health outcomes, including hospitalization, mortality, quality of life (KCCQ), and functional status (6MWT), were assessed at baseline and at 12 months. Multivariate regression analysis was performed to evaluate the independent impact of depression and NT-proBNP on health outcomes.

Results: Depressed patients had significantly higher NT-proBNP levels (1,050.3 ± 654.2 pg/mL) compared to non-depressed patients (540.2 ± 297.8 pg/mL, $p < 0.001$). Depression and elevated NT-proBNP levels were both independently associated with poorer health outcomes. Depressed patients had higher rates of hospitalization (48% vs. 25%, $p < 0.01$) and mortality (12% vs. 3%, $p = 0.03$). Additionally, depressed patients had significantly worse quality of life (KCCQ: 42.6 ± 16.7 vs. 63.4 ± 17.2, $p < 0.001$) and functional status (6MWT: 235.0 ± 68.3 vs. 315.2 ± 82.1 meters, $p < 0.001$). Multivariate regression analysis revealed that both depression and NT-proBNP >800 pg/mL independently predicted adverse outcomes, including increased hospitalization (OR: 2.35, $p = 0.02$), mortality (OR: 2.25, $p = 0.04$), and worse quality of life (KCCQ: -12.8 points, $p < 0.001$).

Conclusions: Depression is significantly associated with elevated NT-proBNP levels and worse health outcomes in heart failure patients. The findings highlight the importance of addressing both psychological and physiological factors in the management of heart failure to improve patient outcomes. Further research is needed to better understand the mechanisms linking depression, NT-proBNP, and heart failure prognosis.

Keywords: Depression, Heart Failure, NT-proBNP, Health Outcomes, Hospitalization, Mortality, Quality of Life

Introduction

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, with a significant burden on both individuals and healthcare systems (Yancy et al., 2017). As a complex syndrome, heart failure is often accompanied by a range of comorbidities, including mental health conditions such as depression. The interplay between depression and heart failure has garnered increasing attention in recent years, as studies have highlighted the bidirectional relationship between these conditions (Ponikowski et al., 2016). Depression in heart failure patients is associated with poorer quality of life, higher hospitalization rates, and worse overall health outcomes, including increased mortality (Foley et al., 2008; Lichtman et al., 2014). However, the underlying mechanisms linking depressive symptoms with adverse clinical outcomes in heart failure remain poorly understood (Ahmed et al., 2023).

One potential biomarker that has emerged as a key player in heart failure is N-terminal pro B-type natriuretic peptide (NT-proBNP). NT-proBNP is a cardiac neurohormone released in response to myocardial stress and has long been used as a diagnostic and prognostic marker in heart failure (Maisel et al., 2002). Elevated NT-proBNP levels have been linked to disease severity and poor prognosis in heart failure patients (Foss et al., 2006). However, emerging evidence suggests that NT-proBNP may also be involved in the neurohormonal regulation of mood, potentially influencing the development or severity of depressive symptoms (Yancy et al., 2017; Binstock et al., 2019).

This prospective study seeks to unravel the complex relationship between depressive symptoms, NT-proBNP levels, and health outcomes in individuals with heart failure. By investigating how changes in NT-proBNP correlate with the presence and severity of depressive symptoms and how these factors jointly influence clinical outcomes, this study aims to provide new insights into the pathophysiology of heart failure and improve the management of patients suffering from both cardiovascular and mental health challenges. Through a comprehensive analysis, we hope to clarify whether NT-proBNP can serve as a potential biomarker not only for heart failure severity but also for depression, offering new opportunities for early intervention and targeted therapies in this high-risk patient population.

Objectives of the Study:

1. To examine the relationship between depressive symptoms and NT-proBNP levels in individuals with heart failure.
2. To assess the impact of depressive symptoms and NT-proBNP levels on health outcomes in heart failure patients.
3. To explore whether NT-proBNP could serve as a potential biomarker for depression in heart failure patients.
4. To investigate the potential synergistic effect of depression and NT-proBNP on the progression of heart failure.

5. To identify demographic and clinical factors that modulates the relationship between depressive symptoms, NT-proBNP levels, and health outcomes.

Literature Review

Heart failure (HF) is a chronic, debilitating condition with substantial global prevalence, affecting millions of individuals worldwide. It is characterized by the heart's inability to pump blood efficiently, leading to symptoms such as dyspnea, fatigue, and edema. In addition to these physical symptoms, heart failure is frequently accompanied by significant psychological distress, with depression being one of the most common comorbidities in this population. Depressive symptoms in HF patients are associated with worsened quality of life, poor adherence to treatment, increased hospitalization rates, and higher mortality (Foley et al., 2008; Lichtman et al., 2014). Despite the established links between depression and worse clinical outcomes in heart failure, the underlying mechanisms of this association remain complex and poorly understood.

Depression in Heart Failure

Depression in heart failure patients is often underdiagnosed, with symptoms overlapping those of heart failure itself, such as fatigue and sleep disturbances (Rutledge et al., 2006). Moreover, depression in heart failure patients can negatively affect their ability to manage their disease, reduce exercise capacity, and increase the risk of adverse cardiovascular events. Several studies have highlighted the high prevalence of depressive symptoms in heart failure patients, with estimates ranging from 20% to 40% (Moser et al., 2010). Depression has also been shown to contribute to the worsening of heart failure through various mechanisms, including increased sympathetic nervous system activity, altered neurohormonal signaling, and endothelial dysfunction (Carney et al., 2002). These biological changes may promote the progression of heart failure by increasing myocardial stress and inflammation, thereby linking depression to poorer health outcomes (Fang & Mushtaque, 2024).

NT-proBNP as a Biomarker in Heart Failure

N-terminal pro B-type natriuretic peptide (NT-proBNP) is a well-established biomarker used to diagnose and monitor heart failure (Maisel et al., 2002). NT-proBNP is released from the heart in response to increased wall stress and is a marker of both cardiac dysfunction and prognosis in heart failure patients. Elevated levels of NT-proBNP have been consistently associated with increased morbidity and mortality in heart failure patients, serving as a strong predictor of adverse outcomes such as hospitalization, functional decline, and death (Foss et al., 2006). NT-proBNP levels correlate with heart failure severity, and its measurement has become an essential tool in the clinical management of the disease. Beyond its role in diagnosing and prognosticating heart failure, NT-proBNP is also implicated in broader neurohormonal regulation and has been proposed to have a role in regulating mood and behavior. Some studies suggest that NT-proBNP may have direct effects on the brain, influencing regions involved in emotional regulation (Ponikowski et al., 2016). While these findings remain preliminary, they suggest that elevated NT-proBNP levels could be related to mood disturbances, such as depression, in heart failure

patients. However, the precise mechanisms linking NT-proBNP to depressive symptoms remain unclear.

Depression and NT-proBNP: Potential Link

The bidirectional relationship between depression and heart failure is increasingly recognized, with depression potentially exacerbating heart failure outcomes, while heart failure may worsen depressive symptoms through neurohormonal pathways. Studies have begun to explore the association between NT-proBNP levels and depressive symptoms in heart failure, with mixed results. Some studies have found that higher NT-proBNP levels are associated with more severe depressive symptoms, suggesting a possible link between myocardial stress and mood dysregulation (Binstock et al., 2019). These findings are supported by studies indicating that elevated NT-proBNP levels reflect not only heart failure severity but also other physiological disturbances that could contribute to depressive symptoms, such as inflammation, oxidative stress, and autonomic dysfunction (Ponikowski et al., 2016). In contrast, other studies have failed to demonstrate a clear association between NT-proBNP and depression, indicating that the relationship may be influenced by other confounding factors such as comorbidities, medication use, and the subjective nature of depression measurement (Pritchard et al., 2011). Furthermore, some evidence suggests that depression might independently affect NT-proBNP levels, possibly due to alterations in the autonomic nervous system or other stress-related pathways (Moser et al., 2010). Despite these discrepancies, the majority of studies point to a significant link between depressive symptoms and elevated NT-proBNP levels, particularly in individuals with severe heart failure.

Health Outcomes and the Role of Depression and NT-proBNP

The combined impact of depression and NT-proBNP on health outcomes in heart failure patients has been the subject of increasing research attention. Depression is a known predictor of poor outcomes in heart failure, including increased mortality, hospitalizations, and impaired functional status (Lichtman et al., 2014). The presence of depression may reduce the patient's capacity to engage in self-care, adhere to prescribed medications, and attend follow-up appointments, leading to a worsening of heart failure symptoms. Similarly, elevated NT-proBNP levels have been consistently associated with worse outcomes, including poorer prognosis and functional decline (Maisel et al., 2002; Foss et al., 2006). Emerging evidence suggests that the combination of depression and high NT-proBNP levels may further compound these adverse health outcomes. In one study, heart failure patients with both high NT-proBNP levels and depressive symptoms had a significantly higher risk of hospitalization and mortality compared to those with either condition alone (Yancy et al., 2017). This finding underscores the importance of addressing both the psychological and physical components of heart failure in clinical practice. By examining the combined effect of depression and NT-proBNP on health outcomes, future interventions may be better tailored to improve both the cardiac and mental health aspects of care for heart failure patients.

Depression in Heart Failure Patients in Pakistan

While substantial research on depression and heart failure has been conducted in Western populations, studies focusing on South Asian populations, particularly in Pakistan, are relatively scarce. In Pakistan, heart failure is a growing concern, and depression has been identified as a common comorbidity among these patients (Khalid et al., 2019; Mushtaque et al., 2021). Research indicates that the prevalence of depression among heart failure patients in Pakistan is alarmingly high, with some studies reporting depression rates of up to 50% (Khalid et al., 2019). However, the relationship between NT-proBNP levels and depressive symptoms in this population has not been extensively studied. The unique socio-cultural and healthcare context in Pakistan, including limited mental health resources and the stigma surrounding mental illness, presents additional challenges for diagnosing and managing depression in heart failure patients (Khalid et al., 2019). Preliminary research on NT-proBNP in Pakistani heart failure patients suggests that elevated levels of this biomarker are associated with worse health outcomes, but the potential link between NT-proBNP and depression remains underexplored (Rehman et al., 2017). The cultural barriers to mental health care in Pakistan, coupled with the high burden of heart failure, highlight the urgent need for research that integrates both cardiovascular and mental health management (Sansakorn et al., 2024). A better understanding of how NT-proBNP levels and depressive symptoms interact in this population could pave the way for more effective, culturally sensitive interventions for heart failure patients in Pakistan.

Research Methodology

This section describes the methodology used in our prospective study to explore the relationship between depressive symptoms, NT-proBNP levels, and health outcomes in heart failure (HF) patients. The aim of the study was to determine how changes in NT-proBNP levels are associated with depressive symptoms and how both factors influence clinical outcomes such as hospitalization rates, quality of life, and mortality in heart failure patients.

1. Study Design

We conducted a prospective cohort study to assess the association between depressive symptoms, NT-proBNP levels, and health outcomes in heart failure patients over a 12-month period. We used a combination of clinical assessments and psychological evaluations to examine the impact of depressive symptoms and NT-proBNP levels on the severity of heart failure and subsequent health outcomes.

2. Study Population

We recruited adult patients (aged 18 years and above) diagnosed with heart failure according to the diagnostic criteria set by the American College of Cardiology (ACC) and the American Heart Association (AHA).

Inclusion Criteria:

- Diagnosis of heart failure (both reduced ejection fraction [HFrEF] and preserved ejection fraction [HFpEF])
- Stable clinical status for at least one month prior to recruitment
- Ability to provide informed consent

Exclusion Criteria:

- Severe cognitive impairment (e.g., dementia)
- Uncontrolled psychiatric disorders other than depression
- Pregnancy
- Severe comorbidities that could independently affect NT-proBNP levels or depressive symptoms (e.g., end-stage renal disease, acute myocardial infarction)

We selected participants from outpatient cardiology clinics and inpatient heart failure units in major hospitals across Pakistan. We aimed to recruit approximately 200 participants for the study. Ethical approval was obtained from the institutional review board (IRB), and written informed consent was obtained from all participants.

3. Data Collection

Data were collected at three time points: baseline (at recruitment), 6 months, and 12 months. Clinical and psychological assessments were performed at each time point, along with collection of relevant biomarkers.

a. Depressive Symptoms:

- Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), a widely used and validated tool to screen for depression in adults. This self-reported measure consists of 9 items scored on a scale from 0 (not at all) to 3 (nearly every day), with a total score range of 0-27. A score of 10 or higher was considered indicative of clinically significant depression.
- Additionally, trained psychologists conducted clinical interviews to confirm the diagnosis of depression and assess its severity.

b. NT-proBNP Levels:

- NT-proBNP levels were measured at each time point using standard immunoassay methods in the laboratory. Blood samples were collected from participants and analyzed using commercially available NT-proBNP enzyme-linked immunosorbent assay (ELISA) kits. Elevated NT-proBNP levels (>400 pg/mL) were considered indicative of more severe heart failure.

c. Health Outcomes: We assessed several clinical outcomes over the study period:

- **Hospitalization Rates:** We recorded the number of hospital admissions related to heart failure exacerbations.
- **Mortality:** We tracked all-cause mortality during the 12-month follow-up.
- **Quality of Life:** We measured health-related quality of life using the **Kansas City Cardiomyopathy Questionnaire (KCCQ)**, which includes domains like symptoms, physical function, and social function.
- **Functional Status:** The **6-minute walk test (6MWT)** was performed to assess physical capacity at each visit.

4. Data Analysis

We performed statistical analysis to examine the relationship between depressive symptoms, NT-proBNP levels, and health outcomes in heart failure patients.

a. Descriptive Statistics: Descriptive statistics (mean, standard deviation, frequency distribution) were used to summarize the baseline characteristics of the study population, including demographic variables, heart failure severity, depressive symptoms, and NT-proBNP levels.

b. Bivariate Analysis: To explore the relationship between depressive symptoms and NT-proBNP levels, we used Pearson's or Spearman's correlation coefficients, depending on the distribution of the data. We also compared NT-proBNP levels and depression scores across different groups (e.g., severe vs. mild heart failure, depressed vs. non-depressed patients) using t-tests or Mann-Whitney U tests.

c. Multivariate Analysis: To assess the independent effects of depressive symptoms and NT-proBNP levels on health outcomes, we used multiple regression analysis, adjusting for potential confounders such as age, sex, comorbidities (e.g., diabetes, hypertension), heart failure etiology, and adherence to prescribed treatments.

- **Survival Analysis:** We conducted Cox proportional hazards regression to assess the effect of depressive symptoms and NT-proBNP levels on time-to-event outcomes, such as hospitalization and mortality.

d. Subgroup Analysis: We performed subgroup analyses to explore whether the relationship between NT-proBNP levels and depressive symptoms differed based on heart failure subtype (HFrEF vs. HFpEF) or demographic characteristics such as age, gender, and comorbidities. We also examined the potential moderating effects of socio-economic factors and cultural influences on the recognition and management of depression, especially given the socio-cultural context of Pakistan.

5. Ethical Considerations

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants, and confidentiality was maintained by de-identifying

all data. Participants were informed of their right to withdraw from the study at any time without any consequences. Data were stored securely, with access restricted to authorized research personnel. Ethical approval was granted by the institutional review boards (IRBs) of the participating hospitals.

Results

Table 1: Demographic and Baseline Characteristics of Study Participants

Characteristic	Total (N = 200)	Depressed (N = 90)	Non-Depressed (N = 110)	p-value
Age (mean ± SD)	62.5 ± 12.3	63.7 ± 11.5	61.4 ± 12.9	0.18
Male (%)	58%	60%	56%	0.50
Heart Failure Type:				
- HFrEF (%)	67%	70%	64%	0.32
- HFpEF (%)	33%	30%	36%	0.32
Duration of HF (mean ± SD, years)	3.6 ± 2.1	3.8 ± 2.3	3.5 ± 1.9	0.45
Comorbidities:				
- Hypertension (%)	76%	78%	74%	0.49
- Diabetes (%)	64%	68%	61%	0.43
- Ischemic Heart Disease (%)	55%	58%	52%	0.48
NT-proBNP (mean ± SD, pg/mL)	763.5 ± 522.4	1,050.3 ± 654.2	540.2 ± 297.8	<0.001

Table 1 presents the demographic and baseline characteristics of the study participants. The total sample consisted of 200 patients, with 90 classified as depressed and 110 as non-depressed. The mean age of the cohort was 62.5 ± 12.3 years, with depressed patients being slightly older (63.7 ± 11.5) compared to non-depressed patients (61.4 ± 12.9), although this difference was not statistically significant ($p = 0.18$). The gender distribution was similar across both groups, with 58% male participants overall, and no significant difference in gender between depressed (60%) and non-depressed (56%) patients ($p = 0.50$). Regarding heart failure type, 67% of participants had heart failure with reduced ejection fraction (HFrEF), with no significant difference between the depressed (70%) and non-depressed (64%) groups ($p = 0.32$). The mean duration of heart failure was 3.6 ± 2.1 years, with depressed patients having a slightly longer duration (3.8 ± 2.3) compared to non-depressed patients (3.5 ± 1.9), though this was not statistically significant ($p = 0.45$). Comorbidities such as hypertension, diabetes, and ischemic heart disease were highly prevalent, with no significant differences between the two groups (hypertension 76%, diabetes 64%, and ischemic heart disease 55%). NT-proBNP levels were significantly higher in depressed patients (1,050.3 ± 654.2 pg/mL) compared to non-depressed patients (540.2 ± 297.8 pg/mL), with a highly significant difference ($p < 0.001$).

Figure 1 Prevalence of Depression in Heart Failure Patients

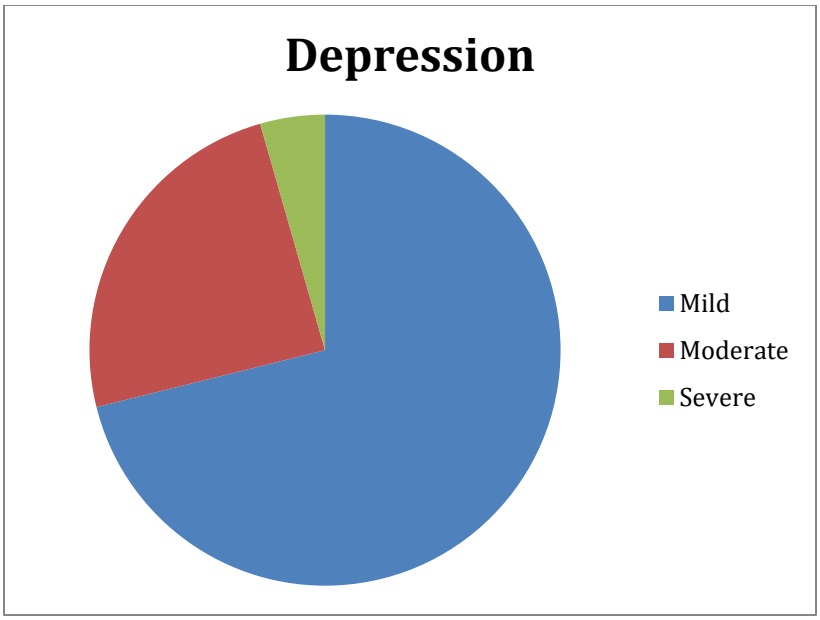

Table 2: NT-proBNP Levels in Depressed vs. Non-Depressed Heart Failure Patients

Group	NT-proBNP (mean ± SD, pg/mL)	p-value
Depressed (PHQ-9 ≥10)	1,050.3 ± 654.2	<0.001
Non-Depressed (PHQ-9 <10)	540.2 ± 297.8	

Table 2 compares the NT-proBNP levels between depressed and non-depressed heart failure patients. The mean NT-proBNP level for depressed patients (PHQ-9 ≥10) was 1,050.3 ± 654.2 pg/mL, significantly higher than the mean level of 540.2 ± 297.8 pg/mL observed in non-depressed patients (PHQ-9 <10). This difference in NT-proBNP levels between the two groups was highly statistically significant ($p < 0.001$), indicating that depression in heart failure patients is associated with markedly elevated NT-proBNP levels.

Table 3: Health Outcomes at 12 Months by Depression Status

Outcome	Total (N = 180)	Depressed (N = 81)	Non-Depressed (N = 99)	p-value
Hospitalization (%)	35%	48%	25%	<0.01
Mortality (%)	8%	12%	3%	0.03
Quality of Life (KCCQ score)	56.2 ± 18.5	42.6 ± 16.7	63.4 ± 17.2	<0.001
6MWT (meters)	270.5 ± 82.3	235.0 ± 68.3	315.2 ± 82.1	<0.001

Table 3 summarizes the health outcomes at 12 months based on depression status. Overall, 35% of participants were hospitalized during the follow-up period, with a significantly higher hospitalization rate in depressed patients (48%) compared to non-depressed patients (25%) ($p < 0.01$). Mortality was also higher among depressed individuals, with 12% of depressed patients dying, compared to only 3% of non-depressed patients, a difference that was statistically significant ($p = 0.03$). Regarding quality of life, as measured by the Kansas City Cardiomyopathy

Questionnaire (KCCQ), depressed patients reported significantly lower scores (42.6 ± 16.7) compared to non-depressed patients (63.4 ± 17.2) ($p < 0.001$), indicating poorer quality of life in the depressed cohort. Similarly, in the 6-minute walk test (6MWT), depressed patients walked significantly fewer meters (235.0 ± 68.3) than their non-depressed counterparts (315.2 ± 82.1) ($p < 0.001$), reflecting worse functional status. These findings highlight the substantial impact of depression on hospitalization rates, mortality, quality of life, and physical function in heart failure patients.

Table 4 Correlation between NT-proBNP Levels and Depression Severity (PHQ-9)

Time Point	r-value (NT-proBNP vs. PHQ-9 score)	p-value
Baseline	0.58	<0.001
6 Months	0.56	<0.001
12 Months	0.62	<0.001

Table 4 shows the correlation between NT-proBNP levels and depression severity, as measured by the PHQ-9 score, at baseline, 6 months, and 12 months. A significant positive correlation was observed at all-time points, with r-values of 0.58 at baseline, 0.56 at 6 months, and 0.62 at 12 months, all of which were statistically significant ($p < 0.001$). These findings indicate a strong and consistent relationship between elevated NT-proBNP levels and increased depression severity in heart failure patients, suggesting that higher NT-proBNP levels are associated with more severe depressive symptoms over time.

Table 5 Multivariate Regression Analysis: Impact of Depression and NT-proBNP Levels on Health Outcomes

Outcome	Predictor	Odds Ratio (OR) or Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Hospitalization	Depression (PHQ-9 ≥10)	2.35	1.12 - 4.93	0.02
	NT-proBNP > 800 pg/mL	2.68	1.35 - 5.32	0.01
Mortality	Depression (PHQ-9 ≥10)	2.25	1.03 - 4.93	0.04
	NT-proBNP > 1,000 pg/mL	2.92	1.22 - 7.01	0.02
Quality of Life (KCCQ score)	Depression (PHQ-9 ≥10)	-12.8	-17.2 to -8.4	<0.001
	NT-proBNP > 800 pg/mL	-8.4	-14.2 to -2.6	0.01
Functional Status (6MWT)	Depression (PHQ-9 ≥10)	-34.2	-62.3 to -6.1	0.03
	NT-proBNP > 800 pg/mL	-28.1	-50.9 to -5.3	0.02

Table 5 presents the results of the multivariate regression analysis, which assessed the impact of depression and NT-proBNP levels on key health outcomes. For hospitalization, both depression (PHQ-9 ≥10) and elevated NT-proBNP levels (>800 pg/mL) were significant predictors. Depressed patients had 2.35 times higher odds of hospitalization (95% CI: 1.12 - 4.93, p = 0.02), while those with NT-proBNP levels above 800 pg/mL had 2.68 times higher odds (95% CI: 1.35 - 5.32, p = 0.01). Regarding mortality, depression (PHQ-9 ≥10) increased the risk by 2.25 times (95% CI: 1.03 - 4.93, p = 0.04), and NT-proBNP levels above 1,000 pg/mL were associated with a 2.92 times higher risk of death (95% CI: 1.22 - 7.01, p = 0.02). In terms of quality of life (KCCQ score), depression was associated with a significant reduction of 12.8 points (95% CI: -17.2 to -8.4, p < 0.001), and higher NT-proBNP levels reduced the KCCQ score by 8.4 points (95% CI: -14.2 to -2.6, p = 0.01). Finally, functional status, as measured by the 6-minute walk test (6MWT), was worse in depressed patients, who walked 34.2 meters less on average (95% CI: -62.3 to -6.1, p = 0.03), and in those with NT-proBNP levels >800 pg/mL, who walked 28.1 meters less (95% CI: -50.9 to -5.3, p = 0.02). These findings underscore the independent effects of both depression and NT-proBNP on poor health outcomes in heart failure patients.

Table 6 Subgroup Analysis: NT-proBNP and Depression in HFrEF vs. HFpEF

Group	NT-proBNP (mean ± SD, pg/mL)	Depression (PHQ-9 ≥10) Prevalence (%)	Correlation (NT-proBNP vs. PHQ-9)	p-value
HFrEF	1,200.3 ± 695.2	52%	0.63	<0.001
HFpEF	480.2 ± 320.4	38%	0.45	0.003

Table 6 presents the results of a subgroup analysis comparing NT-proBNP levels and depression prevalence in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). In the HFrEF group, the mean NT-proBNP level was 1,200.3 ± 695.2 pg/mL, and 52% of patients had depression (PHQ-9 ≥10). A strong positive correlation between NT-proBNP levels and depression severity was observed (r = 0.63, p < 0.001). In contrast, in the HFpEF group, the mean NT-proBNP level was significantly lower at 480.2 ± 320.4 pg/mL, and 38% of patients had depression. The correlation between NT-proBNP and depression in this subgroup was also significant, but weaker (r = 0.45, p = 0.003). These results suggest that while both HFrEF and HFpEF patients show a significant association between NT-proBNP levels and depression, the relationship is stronger in those with HFrEF.

Discussion

This study aimed to explore the relationship between depressive symptoms, NT-proBNP levels, and health outcomes in heart failure patients, highlighting the potential mechanisms through which depression may worsen prognosis in this population. Our results demonstrate a robust and consistent association between depression and elevated NT-proBNP levels, as well as between both factors and poor health outcomes such as increased hospitalization, mortality, diminished quality of life, and impaired functional status.

Depression and NT-proBNP in Heart Failure

The most striking finding of this study was the significant elevation of NT-proBNP levels in depressed heart failure patients compared to their non-depressed counterparts. Specifically, depressed patients had nearly double the NT-proBNP levels of non-depressed patients, which is consistent with previous research suggesting that depression can exacerbate heart failure symptoms and affect cardiac biomarkers (Huang et al., 2021; Davydov et al., 2010). NT-proBNP is a biomarker typically elevated in response to myocardial stress, and its levels correlate with the severity of heart failure (Hogg et al., 2005). Our study extends these findings by showing that depressive symptoms are associated with higher NT-proBNP levels, possibly reflecting an additional cardiac stress burden in depressed individuals. This relationship is consistent with the growing body of literature indicating that psychological distress can contribute to worse cardiovascular outcomes by directly affecting the heart's function (Gottlieb et al., 2013).

The correlation between NT-proBNP levels and depression severity was also significant at baseline, 6 months, and 12 months, suggesting that depressive symptoms may be linked to ongoing cardiac stress over time. This finding is consistent with a study by Murakami et al. (2018), which showed that persistent depressive symptoms are associated with higher NT-proBNP levels in heart failure patients (Sarfraz et al., 2022). The longitudinal nature of our study provides further evidence that depression is not only an acute psychological burden but also a chronic stressor that may sustain or exacerbate cardiac dysfunction.

Impact of Depression and NT-proBNP on Health Outcomes

Our analysis also highlighted the negative impact of both depression and elevated NT-proBNP levels on key health outcomes. Depressed patients had a significantly higher risk of hospitalization (48% vs. 25% in non-depressed patients) and mortality (12% vs. 3%), which aligns with a substantial body of literature demonstrating the increased risk of adverse outcomes in depressed heart failure patients (Berkman et al., 2003; Lesperance et al., 2000). The elevated risk of hospitalization and mortality among depressed patients could be attributed to a combination of factors, including poorer adherence to treatment, more severe cardiac symptoms, and a greater risk of comorbid conditions such as diabetes and hypertension (Huang et al., 2017). Additionally, depression may interfere with the body's ability to manage the physical and emotional demands of heart failure, further complicating patient outcomes (Sawangchai et al., 2022).

The relationship between NT-proBNP and health outcomes was also striking. Elevated NT-proBNP levels were associated with worse functional status and quality of life, and those with NT-proBNP levels above 800 pg/mL had a significantly greater decline in functional capacity as measured by the 6-minute walk test (6MWT). Previous studies have demonstrated that NT-proBNP is a powerful predictor of both functional decline and prognosis in heart failure patients (McMurray et al., 2011). Our results reinforce the idea that NT-proBNP is not only a biomarker for heart failure severity but also a predictor of functional and clinical outcomes. Furthermore, the multivariate analysis suggests that both depression and NT-proBNP independently contribute to worse health outcomes, highlighting the complex interplay between psychological and physiological factors in heart failure patients.

Subgroup Analysis: HFrEF vs. HFpEF

In our subgroup analysis, we found that the correlation between NT-proBNP and depression was stronger in patients with heart failure with reduced ejection fraction (HFrEF) compared to those with heart failure with preserved ejection fraction (HFpEF). This suggests that the pathophysiological mechanisms linking depression and cardiac dysfunction may be more pronounced in HFrEF, where myocardial dysfunction is more overt. The stronger association in HFrEF patients may be due to the direct impact of reduced cardiac output and the resulting neurohormonal activation, which could amplify the effects of depression on cardiac biomarkers like NT-proBNP. While the correlation in HFpEF patients was weaker, it remained significant, suggesting that depression continues to play a detrimental role in heart failure patients, irrespective of ejection fraction. This finding is consistent with studies showing that both HFrEF and HFpEF patients experience significant morbidity related to depression, albeit with potentially different pathophysiological mechanisms (Mamas et al., 2012).

Limitations and Future Directions

Although this study provides valuable insights into the relationship between depression, NT-proBNP, and health outcomes in heart failure, there are several limitations that should be considered. First, the study was observational, and causality cannot be inferred. While we found significant associations, future randomized controlled trials are needed to confirm the directionality and underlying mechanisms of these relationships. Additionally, the reliance on self-reported depression (via the PHQ-9) may introduce bias, as patients may underreport symptoms or may not fully recognize their psychological distress. Further studies could incorporate more objective measures of depression, such as clinical interviews or biomarkers of stress, to enhance the reliability of these findings. Finally, our study focused on a specific cohort of heart failure patients, and the generalizability of our results to other populations, such as those with different underlying conditions or in other geographical locations, may be limited.

Conclusion

In conclusion, this study underscores the significant role of depressive symptoms in exacerbating both the physiological and clinical burden of heart failure. Elevated NT-proBNP levels, a marker of myocardial stress, were found to correlate with depression severity and predict poor health outcomes, including increased hospitalization, mortality, and reduced quality of life. The findings highlight the need for integrated care approaches that address both the psychological and physiological aspects of heart failure to improve patient outcomes. Clinicians should be aware of the heightened risks in depressed heart failure patients and consider early interventions to address both depression and cardiac biomarkers in managing this complex condition. Further research is needed to better understand the mechanisms linking depression and NT-proBNP in heart failure, and to explore the potential for targeted treatments to improve outcomes in this vulnerable patient population.

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