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The Role of Biomarkers in Predicting Cognitive Impairment in Elderly Patients with Heart Failure

Kalp Yetersizliği Olan Yaşlı Hastalarda Bilişsel Bozukluğu Öngörmede Biyobelirteçlerin Rolü

ABSTRACT

Objective: This study explores the impact of sST2, Growth Differentiation Factor 15 (GDF-15), and clinical factors on cognitive dysfunction in elderly patients with heart failure with reduced ejection fraction (HFrEF).

Methods: A cohort of 101 chronic stable HFrEF patients aged over 65 years old participated in the study. Cognitive functions were assessed using the Montreal Cognitive Assessment (MoCA) test and the Mini Mental State Examination (MMSE). Levels of sST2, GDF-15, and N-terminal pro b-type natriuretic peptide (NT-proBNP) were also measured.

Results: Notably higher levels of NT-proBNP and GDF-15 were observed in the group with cognitive dysfunction, whereas sST2 levels were similar between the groups. The cognitive dysfunction group consisted of older patients. A higher proportion of patients with normal cognitive function had received influenza vaccinations. Furthermore, GDF-15 levels inversely correlated with MMSE score. Right ventricular diameter was negatively correlated, while hemoglobin levels were positively correlated with both MoCA and MMSE scores. Logistic regression analysis identified increased GDF-15 levels, older age, and advanced New York Heart Association (NYHA) classes as predictors of higher cognitive dysfunction risk, whereas influenza vaccination was linked to a reduced risk of cognitive dysfunction.

Conclusion: Cognitive dysfunction in elderly patients with heart failure may be influenced by factors such as age, right ventricular enlargement, anemia, NYHA functional class, and levels of GDF-15 and NT-proBNP.

Keywords: Cognitive dysfunction, GDF-15, heart failure, NT-proBNP, sST2

ÖZET

Amaç: Bu çalışmanın amacı, düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) olan yaşlı hastalarda bilişsel işlev bozukluğunda rol oynayan klinik faktörleri ve sST2 ve GDF-15'in rolünü araştırmaktır.

Yöntem: Çalışmaya 65 yaş üstü 101 kronik DEF-KY hastası dahil edildi. Hastaların bilişsel işlevlerini değerlendirmek amacıyla Montreal Kognitif Değerlendirme Testi (MoCA) ve Mini Mental Durum Testi (MMSE) uygulandı ve sST2, GDF-15 ve NT-proBNP düzeyleri ölçüldü.

Bulgular: NT-proBNP [1845 (831-6387) vs. 1310 (590-2830), *P* = 0.01, sırasıyla] ve GDF-15 [2.19 (1.10-4.25) vs. 1.43 (0.87-2.34), *P* = 0,042, sırasıyla] düzeyleri bilişsel işlev bozukluğu olan grupta anlamlı derecede yüksek iken sST2 (1297±604 vs.1199±422, *P* = 0,34, sırasıyla) düzeyi gruplar arasında benzer bulundu. Bilişsel işlev bozukluğu olan hastalar daha ileri yaştaydı. İnfluenza aşısı olan hastaların oranı bilişsel fonksiyonları normal olan grupta daha yüksek bulundu. GDF-15 düzeyleri MMSE puanı ile negatif korelasyon gösterdi (r = -0,257, *P* = 0,009). MoCA (r = -0,325, *P* = 0,001) ve MMSE (r = -0,282, *P* = 0,005) skorları ile sağ ventrikül çapı negatif, hemoglobin düzeyleri ise pozitif korelasyon gösterdi. Lojistik regresyon analizinde yüksek GDF-15 (OR = 1,264, %95 GA = 1,009-1,583) düzeyleri, ileri yaş (OR = 1,100, %95 GA = 1,012-1,195) ve yüksek NYHA (OR = 5,328, %95 GA = 2,033-13,962) sınıfı artmış bilişsel işlev bozukluğu riskiyle ilişkili bulundu.

Sonuç: Kalp yetersizliği olan yaşlı hastalarda bilişsel işlev bozukluğu yaş, sağ ventriküler dilatasyon, anemi, NYHA fonksiyonel sınıfı, GDF-15 ve NT-proBNP düzeyi ile ilişkili olabilir.

Anahtar Kelimeler: Bilişsel işlev bozukluğu, GDF-15, kalp yetersizliği, NT-proBNP, sST2

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Ayça Arslan[1]
Ahmet Çelik[2]
Oben Döven[2]

[1]*Department of Cardiology, Kafkas University Medical Faculty, Kars, Türkiye*
[2]*Department of Cardiology, Mersin University Medical Faculty, Mersin, Türkiye*

Corresponding author:
Ayça Arslan
✉ hivda.arslan@hotmail.com

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Heart failure (HF) is one of the most common chronic diseases globally, associated with increased mortality and morbidity, frequent hospitalization, a diminished quality of life, and reduced functional status. The risk of cognitive impairment in HF patients is double that of age-matched control groups.[1,2] Cognitive dysfunction, potentially reversible, is commonly observed in older patients with HF[3], with incidence rates ranging from 30% to 80%, depending on the study population.[4,5] Since the 1970s, when the co-existence of HF and brain failure was first identified, the relationship between HF and cognitive impairment has been extensively studied using various neuropsychological tests.[5] Cognitive disorders in HF patients can complicate the management of heart disease due to impacts on learning, working memory, recall, attention, executive function, and psychomotor speed.[4] Recent studies indicate specific deficits in attention and memory among these patients.[6] Research by Zuccala et al.[7] identified cognitive impairment as an independent prognostic marker in older HF patients. Rozzini et al.[8] reported a six-month mortality rate of 19% in hospitalized elderly U.S. patients without cognitive impairment, which rose to 35.6% when cognitive impairment was also present.

The last decade has seen increased use of biomarkers in managing HF. N-terminal pro b-type natriuretic peptide (NT-proBNP) is linked to cognitive impairment in cerebrovascular disease.[9] High levels of NT-proBNP in HF patients are thought to indicate a risk of developing cognitive dysfunction.[10] Additionally, soluble ST2 (sST2) is released from heart cells in response to myocardial stress.[11] Higher concentrations of sST2 in chronic HF have been associated with increased severity of HF, higher risks of death or cardiac transplantation, sudden cardiac death, cardiovascular events, and hospitalization due to heart disease.[12-14] A study found that serum sST2 levels were significantly higher in patients with mild cognitive impairment compared to healthy controls (15). Furthermore, sST2 has been shown to correlate with BNP, NT-proBNP, and proBNP in patients with heart failure with reduced ejection fraction (HFrEF).[13] Growth Differentiation Factor-15 (GDF-15), a member of the transforming growth factor-β family first reported in 1997, is continuously expressed in the liver and increases in concentration under cardiac stress, such as overpressure load.[16] In the Framingham study, GDF-15 was associated with all-cause mortality, HF, and major cardiovascular events.[17] The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) study found that among 1,935 patients with chronic stable HFrEF, elevated levels of GDF-15 and changes in these levels were linked to poor cardiovascular outcomes and reduced survival.[18] GDF-15 is considered a marker of age-related cognitive impairment and brain structural deficiencies.[19] However, the relationship between sST2, GDF-15, and cognitive dysfunction in patients with HF has not been established.

Patients with both cognitive dysfunction and HF face challenges in recognizing their symptoms and adhering to HF treatment, which can lead to worsening symptoms, increased hospitalization risks, and mortality.[7,8] Therefore, identifying cognitive impairment in HF patients is vital. This study aims to explore the roles of sST2, GDF-15, and NT-proBNP in cognitive impairment among elderly patients with HFrEF.

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
esPAP	Estimated systolic pulmonary artery pressure
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure
TAPSE	Tricuspid annular plane systolic excursion

Materials and Methods

This single-center prospective study received approval from the Ethics Committee of Mersin University (decision dated May 25, 2018, number 2018/216). A total of 101 chronic stable HFrEF patients aged over 65 were consecutively included in the study and followed at our University Cardiology Clinic from November 1, 2018, to January 30, 2020. The inclusion and exclusion criteria for the study are detailed below.

Inclusion Criteria:

1. Patients with a history of chronic HFrEF classified as New York Heart Association (NYHA) Class I–III and on standard HF therapy.
2. Patients aged 65 years or older.
3. Patients with an ejection fraction (EF) of 40% or less, as measured by echocardiography.
4. Patients who have provided written informed consent.

Exclusion Criteria:

1. Patients experiencing acute HF or acute pulmonary edema.
2. Patients classified as NYHA Class IV.
3. Patients who have undergone coronary artery bypass grafting, percutaneous coronary angioplasty, or experienced a myocardial infarction within the last three months.
4. Patients with an estimated glomerular filtration rate (GFR) of 30 mL/min/1.73 m^2 or less.
5. Patients who did not provide written informed consent.
6. Patients with active and/or chronic liver disease.
7. Patients with electrolyte abnormalities.
8. Patients with a history of cerebrovascular disease.
9. Patients diagnosed with dementia and/or Alzheimer's disease.
10. Patients with a history of malignancy within the past five years.
11. Patients with an active infection.

Chronic kidney failure is defined as a reduction in kidney function lasting three months or more prior to the study, with a GFR below 90 mL/min per 1.73 m^2. Patients are considered diabetic if they have been treated for diabetes, have had fasting glucose levels above 126 mg/dL in two consecutive measurements, or have an HbA1c level greater than 6.5%. Ischemic etiology is recognized as the development of left ventricular dysfunction due to coronary artery disease, including events like myocardial infarction or revascularization. Vitamin B12 deficiency is defined as having a vitamin B12 level less than 129 pg/mL.

A comprehensive transthoracic echocardiographic examination was conducted after obtaining written consent from HFrEF patients who met the inclusion criteria. All echocardiographic measurements were performed using a transthoracic approach in the left lateral decubitus position. M-mode and 2-D measurements were obtained from the parasternal long axis view. The left ventricular ejection fraction (LVEF) was determined using the modified Simpson method. Measurements of mitral E and A waves, lateral and septal E' velocities, left atrial volume, right ventricular diastolic diameter, tricuspid annular plane systolic excursion (TAPSE), and estimated systolic pulmonary artery pressure (esPAP) were all taken during the examination of the four apical chambers.

Blood samples were collected from each participant in the study to determine their levels of sST2 and GDF-15. After collection, the samples were left to stand for 15 minutes before being centrifuged at 5000 rpm for another 15 minutes. The serum obtained from the centrifugation was stored at -80°C until analysis. The levels of GDF-15 (SEC034Hu, Uscn, Wuhan, China) and sST2 (E-EL-h1615, Elabscience, USA) were quantified using the DSX™ four-plate automated ELISA Processing System mikroELISA device (Dynex Technologies, Virginia, USA) with specific Enzyme-Linked Immunosorbent Assay (ELISA) kits. The absorbance values representing the concentrations of the standards for both parameters were measured, and the concentrations of the samples were calculated using the curve and equation derived from the graph drawn. The measurement range for GDF-15 spanned from 0.156 to 10 ng/mL, and for sST2, it ranged from 31.25 to 2000 pg/mL.

To assess the cognitive functions of the patients, 11 questions from the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE) were administered, focusing on orientation, memory, attention and calculation, language, and recall. An additional point was added to the MoCA scores of participants with ≤ 12 years of education to mitigate the influence of educational background on the results. Based on the results of the screening tests, patients were categorized into two groups: those with normal cognitive function and those with cognitive dysfunction. Patients who scored 21 or higher on the MoCA[20] and 24 or higher on the MMSE, both out of a total of 30 points[21], were classified as having normal cognitive function. Conversely, patients scoring below 21 on the MoCA and/or below 24 on the MMSE were categorized as having cognitive dysfunction. According to the MMSE, 27 patients were identified with cognitive dysfunction, while the MoCA identified 42.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 21 (IBM Corporation, Armonk, NY). Continuous data were presented as means for normally distributed variables and medians for non-normally distributed variables. Categorical data were reported as numbers (percentages). Group comparisons were performed using Student's t-tests or Analysis of Variance (ANOVA) for normally distributed continuous data, and Mann-Whitney U tests or Kruskal-Wallis H tests for non-normally distributed continuous data. Pearson's χ^2 tests were used for categorical data. The probability rate and 95% fit intervals were calculated via single logistic regression analysis for all factors affecting the endpoints. Pearson's correlation analysis was utilized for analyzing correlations. A p-value of < 0.05 was considered statistically significant.

Results

The study included 101 patients with HFrEF. These patients were divided into two groups based on the results of cognitive screening tests (the MoCA and MMSE): those with cognitive dysfunction and those without. The demographic and clinical features of the patients are summarized in Table 1. The mean age for patients with cognitive dysfunction was 72.5 ± 5.3, compared to 70.2 ± 4.5 for those without cognitive dysfunction ($P = 0.022$) (Table 1). There were no gender differences between the groups. The prevalence of ischemic etiology, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney failure, smoking, and chronic obstructive pulmonary disease was similar across both groups. The proportion of NYHA Class III patients was significantly higher in the group with cognitive dysfunction, whereas the proportion of NYHA Class I patients was significantly higher in the group with normal cognitive function ($P < 0.001$) (Table 1).

Echocardiographic data are also detailed in Table 1. The right ventricular diastolic diameter was significantly larger in patients with cognitive dysfunction (3.9 ± 0.6 vs. 3.6 ± 0.5, $P = 0.005$). Other parameters such as LVEF, mitral E/A ratio, E/e' mean, TAPSE, esPAP, and the left atrial volume index (LAVI) were similar between the groups (Table 1).

Biochemical data of the patients are presented in Table 1. Hemoglobin levels were higher in patients without cognitive dysfunction. NT-proBNP and GDF-15 levels were found to be significantly higher in the cognitive dysfunction group ($P = 0.01$ and $P = 0.042$, respectively), while sST2 levels did not differ between groups (Table 1). Table 2 presents the rates of previous cardiovascular drug use among the patients. The use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), acetylsalicylic acid, new oral anticoagulants, digoxin, loop diuretics, thiazide diuretics, ivabradine, and vitamin K antagonists was similar between the groups. However, the influenza vaccination rate was found to be higher in the group with normal cognitive functions (17.4% vs. 36.4%, $P = 0.035$, respectively).

Table 3 displays a correlation analysis of clinical and biochemical parameters with the MoCA and MMSE test scores. The MoCA score was found to have a highly significant

Table 1. Demographic Characteristics, Echocardiographic Parameters, and Biochemical Parameters of Patients Between Groups

Variables	Cognitive Dysfunction Group (n=46)	Normal Cognitive Function Group (n=55)	*P*
Age (years), ± std	72.5 ± 5.3	70.2 ± 4.5	0.022
Women (%)	21.7	14.5	0.34
Ischemic Etiology (%)	80	77.8	0.78
Diabetes Mellitus (%)	50.0	50.9	0.92
Hypertension (%)	45.7	58.2	0.21
Hyperlipidemia (%)	26.1	20.0	0.47
Chronic Kidney Disease (%)	23.9	21.8	0.80
COPD (%)	6.5	16.4	0.13
Smoking (%)	17.4	10.9	0.35
Sinus Rhythm (%)	73.9	74.5	0.96
LBBB (%)	13	21.8	0.25
fQRS (%)	26.7	38.2	0.22
ICD (%) CRT (%)	28.3 2.2	29.1 7.3	0.76
NYHA Class 1 Class 2 Class 3	 2.2 71.7 26.1	 25.5 67.3 7.3	<0.001
Hospitalization for HF in 1st year (%)	34.8	21.8	0.14
LVEF (%)	29.5 ± 7.5	31.0 ± 6.9	0.30
Mitral E/A Ratio, Median (25th-75th Percentile)	0.75 (0.50-1.60)	0.85 (0.59-1.43)	0.55
Mean E/e' Ratio	13.1 ± 5.5	12.1 ± 5.3	0.37
LAVI (ml/m²)	42.4 ± 23.3	35.1 ± 17.7	0.09
LVEDV (ml)	145 ± 68	155 ± 73	0.51
TAPSE (cm)	18.6 ± 3.7	18.9 ± 4.1	0.73
esPAP (mmHg)	42 ± 16	41 ± 17	0.81
RVDD (cm)	3.9 ± 0.6	3.6 ± 0.5	0.005
AST (U/L)	19.0 (14.7-24.5)	18.50 (16.00-23.25)	0.29
ALT (U/L)	14.0 (11.0-23.0)	17.00 (12.75-25.25)	0.54
Serum Albumin (g/dl)	3.8 ± 0.4	4 ± 0.3	0.06
Hemoglobin (g/dl)	12.7 ± 1.9	13.4 ± 1.5	0.05
Serum Creatinine (mg/dl)	1.03 ± 0.44	0.99 ± 0.33	0.59
eGFR (ml/min/1.73 m²)	81.9 ± 30.4	84.3 ± 28.3	0.68
Ferritin (ng/ml)	46.0 (30.1-72.2)	49.85 (24.50-84.50)	0.88
Vitamin B12 Deficiency (%)	12.8	21.2	0.3
Folic Acid (ng/ml)	9.4 ± 4.2	9.5 ± 3.4	0.92
GDF-15 (ng/ml)	2.19 (1.10-4.25)	1.43 (0.87-2.34)	0.042
sST2 (pg/ml)	1297 ± 604	1199 ± 422	0.34
NT-proBNP (ng/L)	1845 (831-6387)	1310 (590-2830)	0.01

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; COPD, Chronic Obstructive Pulmonary Disease; CRT, Cardiac Resynchronization Therapy; eGFR, Estimated Glomerular Filtration Rate; esPAP, Estimated Systolic Pulmonary Artery Pressure; fQRS, Fragmented QRS; GDF-15, Growth Differentiation Factor-15; HF, Heart Failure; ICD, Implantable Cardioverter Defibrillator; LAVI, Left Atrial Volume Index; LBBB, Left Bundle Branch Block; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal Pro Brain Natriuretic Peptide; NYHA, New York Heart Association; RVDD, Right Ventricular Diastolic Diameter; sST2, Soluble ST2; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Table 2. Previous Cardiovascular Medical Treatment of Patients

Variables	Cognitive Dysfunction Group (n=46)	Normal Cognitive Function Group (n=55)	*P*
ACEi/ARB (%)	52.2	58.2	0.54
Digoxin (%)	19.6	21.8	0.78
MRA (%)	50	40	0.31
ASA (%)	50	56.4	0.52
Loop Diuretic (%)	58.7	50	0.38
Thiazide Diuretic (%)	19.6	29.1	0.27
Ivabradine (%)	10.9	16.4	0.42
NOAC (%)	28.3	20	0.33
Vitamin K Antagonist (%)	6.5	7.3	0.88
Influenza Vaccine (%)	17.4	36.4	0.035
Pneumococcal Vaccine (%)	39.1	43.6	0.64

ACEi, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; ASA, Acetylsalicylic Acid; MRA, Mineralocorticoid Receptor Antagonist; NOAC, Non-vitamin K Antagonist Oral Anticoagulant.

Table 3. Correlation Analysis of Clinical and Biochemical Parameters with MoCA and MMSE Tests

		GDF-15	sST2	NT-proBNP	eGFR	Age	RVDD	Hb	MoCA	MMSE
GDF-15	r	1	0.186	0.555**	-0.432**	0.154	0.402**	-0.484**	-0.174	-0.257**
	p		0.063	0.000	0.000	0.124	0.000	0.000	0.081	0.009
sST2	r	0.186	1	0.209*	-0.189	-0.003	0.114	-0.024	0.017	-0.067
	p	0.063		0.036	0.058	0.979	0.268	0.815	0.865	0.502
NT-proBNP	r	0.555**	0.209*	1	-0.310**	0.116	0.325**	-0.348**	-0.213*	-0.245*
	p	0.000	0.036		0.002	0.250	0.001	0.000	0.033	0.014
eGFR	r	-0.432**	-0.189	-0.310**	1	-0.92**	-0.032	0.308**	-0.016	0.031
	p	0.000	0.058	0.002		0.003	0.755	0.002	0.871	0.757
Age	r	0.154	-0.003	0.116	-0.292**	1	0.037	-0.121	-0.174	-0.114
	p	0.124	0.979	0.250	0.003		0.717	0.228	0.082	0.254
RVDD	r	0.402**	0.114	0.325**	-0.032	0.037	1	-0.290**	-0.325**	-0.282**
	p	0.000	0.268	0.001	0.755	0.717		0.004	0.001	0.005
Hb	r	-0.484**	-0.024	-0.348**	0.308**	-0.121	-0.290**	1	0.229*	0.236*
	p	0.000	0.815	0.000	0.002	0.228	0.004		0.021	0.018
MoCA	r	-0.174	0.017	-0.213*	-0.016	-0.174	-0.325**	0.229*	1	0.892**
	p	0.081	0.865	0.033	0.871	0.082	0.001	0.021		0.000
MMSE	r	-0.257**	-0.067	-0.245*	0.031	-0.114	-0.282**	0.236*	0.892**	1
	p	0.009	0.502	0.014	0.757	0.254	0.005	0.018	0.000	

eGFR, Estimated Glomerular Filtration Rate; GDF-15, Growth Differentiation Factor-15; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NT-proBNP, N-terminal Pro-brain Natriuretic Peptide; RVDD, Right Ventricular Diastolic Diameter; sST2, Soluble ST2.

positive correlation with the MMSE score (r = 0.892, P < 0.001). GDF-15 levels negatively correlated with MMSE scores (Figure 1A). Both GDF-15 and sST2 levels showed a significant positive correlation with NT-proBNP levels (Figure 2). The right ventricular diameter had a significant negative correlation with both MoCA and MMSE scores (Figure 1B). Hemoglobin levels were positively correlated with the MoCA and MMSE scores (Figure 1C). The results of logistic regression analysis assessing the impact of cognitive dysfunction in patients with chronic HFrEF are summarized in Table 4. Univariate logistic regression analysis indicated that higher levels of GDF-15 are associated with an increased risk of cognitive dysfunction. We observed that patients who had received the influenza vaccine within the past year exhibited better cognitive functions. Additionally, older age and a higher NYHA class were associated with increased cognitive dysfunction.

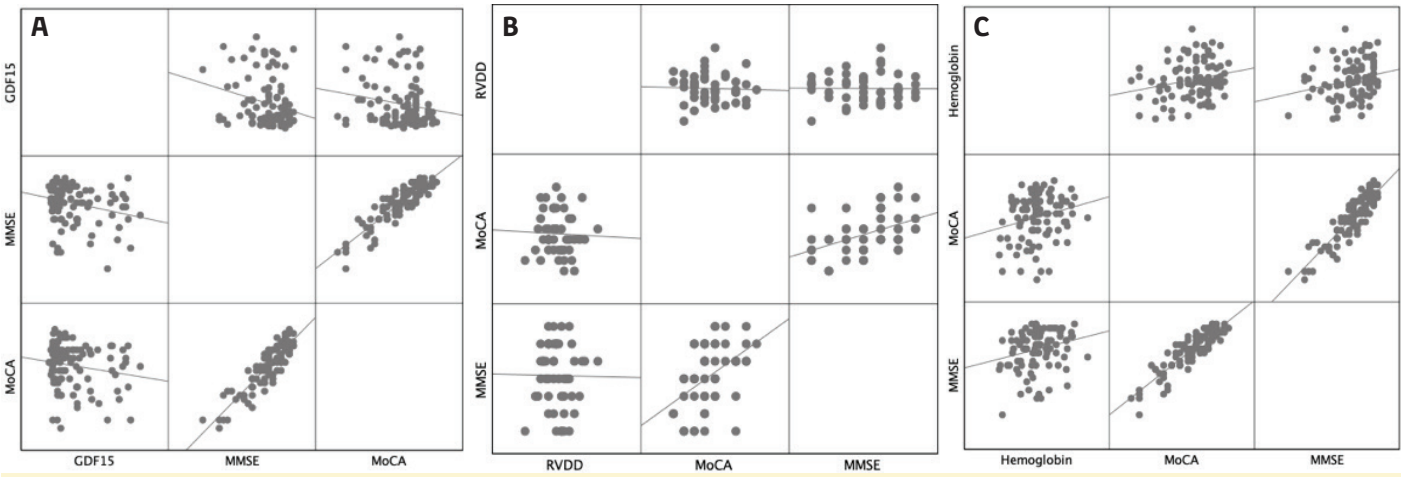

Figure 1. Scatter dot plots illustrating the relationships between GDF-15 (A), RVDD (B), hemoglobin (C), and MoCA and MMSE.
MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; RVDD, Right Ventricular Diastolic Diameter.

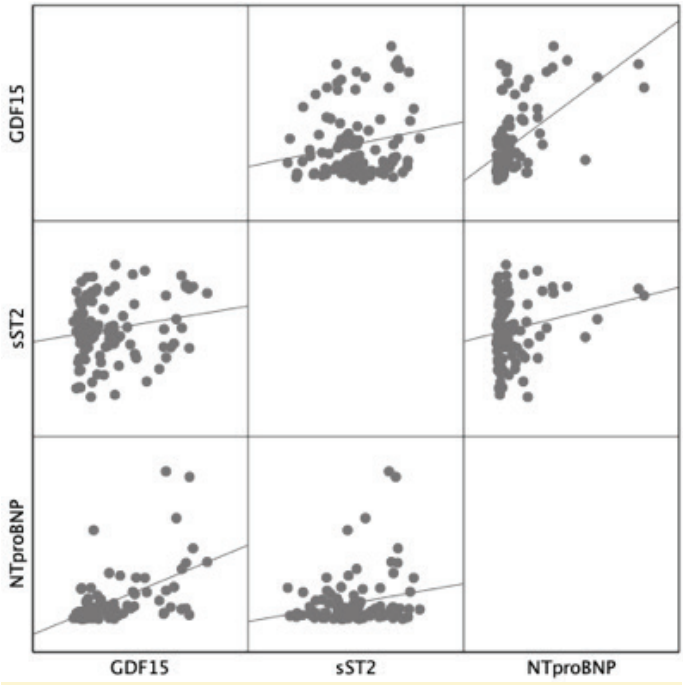

Figure 2. Scatter dot plot depicting the relationships among GDF-15, sST2, and NT-proBNP.
GDF-15, Growth Differentiation Factor-15; NT-proBNP, N-terminal Pro-Brain Natriuretic Peptide; sST2, Soluble ST2.

Table 4. Evaluation of Significant Parameters Related to Cognitive Dysfunction with Univariate Logistic Regression Analysis

	OR	95% CI
GDF-15	1.264	1.009-1.583
Age	1.100	1.012-1.195
RVDD	3.001	1.336-6.742
Hemoglobin	0.799	0.631-1.011
NYHA Class	5.328	2.033-13.962
Influenza Vaccine	0.368	0.144-0.943

GDF-15, Growth Differentiation Factor-15; NYHA, New York Heart Association; RVDD, Right Ventricular Diastolic Diameter.

Discussion

In this study, we identified factors such as age, NYHA class, right ventricular diastolic diameter, GDF-15 levels, NT-proBNP levels, influenza vaccination status, and hemoglobin levels as significant indicators of cognitive dysfunction in chronic HFrEF patients aged 65 years and older. This study is the first in the literature to delineate the parameters associated with cognitive impairment in this specific patient population.

Previous research has consistently linked older age with cognitive dysfunction in HF patients.[22-24] For example, Sterling et al.[25] found that HF patients aged 73.14 ± 8.73 years showed signs of cognitive dysfunction, whereas those aged 69.81 ± 8.94 years did not. Furthermore, Kim and Son reported that individuals over 80 years old had a 3.2 times greater risk of cognitive impairment compared to younger cohorts.[26] Although our study only included patients aged 65 and over, the mean age was significantly higher in the group with cognitive dysfunction, indicating that older HF patients may struggle with medication adherence due to memory issues. Given the importance of regular medication intake for maintaining stability in HF, exploring new treatments or interventions to address cognitive dysfunction in this population is crucial.

In contrast, a study conducted with 100 patients aged 18 years and over with HF by Dong et al.[10] showed no differences in cognitive impairment based on NYHA classes. Similarly, another study reported that the prevalence of cognitive dysfunction was 60% in NYHA Class I symptomatic patients and 72.4% in NYHA Class III symptomatic patients, though these differences were not statistically significant.[27] However, another research involving 113 participants with HF found that those with NYHA Class III-IV HF were more cognitively impaired than those with NYHA Class II ($P < 0.0001$).[28] This supports the findings of our study, suggesting a positive correlation between higher NYHA classes

and cognitive dysfunction. The studies collectively discuss two key pathophysiological hypotheses: cerebral hypo-perfusion and multiple cardiogenic emboli. These conditions may co-occur, making it challenging to determine which specifically causes impaired cognition in HF patients. It is important to note that this cerebral malfunction has been found to be reversible after correcting cardiac output in heart-transplant patients.[29]

We observed that cognitive functions were improved in patients who received the influenza vaccine within the last year. It is well-documented that annual influenza vaccination reduces hospitalization rates among HF patients.[30,31] While there is evidence to suggest a positive effect of the influenza vaccine on cognitive functions, studies specifically examining this effect in HF patients are limited. For instance, animal research has shown that nonspecific immunity induced by an inactivated influenza vaccine can modify Alzheimer's pathology and enhance cognitive performance in the early stages of Alzheimer's disease in a mouse model.[32] Additionally, a study by Liu and colleagues found a significantly lower risk of dementia in vaccinated HF patients compared to those who were not vaccinated. This study focused on patients over 60 years old, involving 20,509 individuals with HF. Of these, 10,797 patients received the influenza vaccine at least once, while the remaining 9,712 did not receive the vaccine during the 12-year follow-up period. The vaccinated group had a 35% lower risk of developing dementia compared to the unvaccinated group, and a 55% lower risk among those vaccinated more than three times.[33] In this study, we demonstrated that patients with HF who received the influenza vaccine had a lower risk of cognitive dysfunction. However, to more definitely ascertain the impact of influenza vaccination on cognitive function in HF patients, further extensive studies involving long-term follow-up and a larger cohort of patients who received influenza vaccination are necessary.

The association between cognitive dysfunction and NT-proBNP levels in HF patients is well-established in the literature.[10] For example, one study found that cognitive dysfunction, as detected by the MMSE, was associated with elevated plasma BNP levels in decompensated HF patients.[23] Consistent with these findings, our study revealed higher NT-proBNP levels in patients with cognitive dysfunction. Our correlation analysis further indicated a significant negative correlation between NT-proBNP levels and scores on both the MoCA and MMSE tests. In addition to NT-proBNP, we investigated the potential roles of GDF-15 and sST2 in determining cognitive dysfunction in HF patients. Research has shown that GDF-15 levels are elevated in patients with HFrEF and that higher levels are linked to increased mortality risk.[16,18,34,35] It has been established that GDF-15 holds significant clinical value in patients with acute myocardial infarction.[36] Furthermore, in the Valsartan Heart Failure Study (ValHeFT), baseline levels of GDF-15 were found to correlate positively with mortality.[37] Studies have also linked GDF-15 with impaired cognitive functions.[19,38] In another study, it was found that the mean GDF-15 levels were significantly higher in patients with Parkinson's disease.[38] In our study, we noted that both GDF-15 and NT-proBNP levels were significantly elevated in patients with cognitive dysfunction who had chronic stable HFrEF. Increased GDF-15 levels were associated with a higher risk of cognitive dysfunction. To our knowledge, this is the first study to explore the role of GDF-15 in cognitive dysfunction among patients with chronic stable HFrEF. Additionally, a study found that serum levels of sST2 were significantly higher in patients with mild cognitive impairment compared to healthy controls.[15] However, we did not find a correlation between sST2 levels and cognitive dysfunction in patients aged 65 and older with HFrEF.

Anemia is a common comorbidity in patients with HF and is associated with long-term deteriorating outcomes. Few studies have investigated the relationship between anemia and cognitive impairment in HF. One study reported that among patients with HF aged over 60 years, the prevalence of cognitive impairment was higher in those with anemia.[26] Another study identified an important relationship between cognitive status scores and anemia.[39] Pulignano et al.[40] found that anemia was associated with lower scores on the MMSE, and the prevalence of cognitive impairment was lower in patients with hemoglobin levels above 15 g/dL. Additionally, a large in-hospital HF study conducted by Zuccala et al.[41] involving 1,511 patients demonstrated that the prevalence of cognitive dysfunction was linked to anemia. Their findings suggested that normalizing hemoglobin levels during hospitalization correlated with improved cognitive performance at discharge. Although the specific mechanisms driving the development of anemia in HF are unclear, there is evidence to suggest that renal dysfunction, along with neurohormonal and proinflammatory cytokine activation in heart failure, contribute to the onset of chronic disease anemia.[42] The mechanisms by which anemia adversely affects HF outcomes are not completely clear. The increased myocardial workload associated with anemia can lead to left ventricular hypertrophy and left ventricular enlargement.[43] This may result in long-term cerebral hypoperfusion and impair cognitive functions. Alternatively, anemia might directly exacerbate the effects of hypoperfusion on cerebral metabolism, further reducing cognitive function.[44] There are few studies investigating the link between anemia and cognitive impairment in HF. In this study, we observed that patients with cognitive dysfunction had lower hemoglobin levels. Consequently, screening for anemia in patients with HF could be crucial for assessing the risk of cognitive impairment in elderly patients.

Limitations

This study faced two main limitations: it had a small sample size and lacked a control group to compare the cognitive functions of non-HF patients.

Conclusion

Our findings indicate that both the average age and anemia rates were significantly higher in the group with cognitive dysfunction. Additionally, right ventricular enlargement was identified as a factor associated with cognitive dysfunction. NT-proBNP and GDF-15 can be utilized alongside cognitive assessment tests to identify cognitive dysfunction in patients over 65 years old with HFrEF.

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