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Research article

The impact of comorbidities on the physical and psychological dimension in heart failure patients

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Abstract: Assessing patients' quality of life is frequently used in medical research. Patients diagnosed with heart failure (HF) have reduced exercise tolerance and reduced quality of life due to reduced heart pump function. The objectives of the study are (i) to assess quality of life and comorbidities in HF patients; (ii) to compare quality of life in the physical and psychological domains according to drug treatment followed and (iii) to identify predictors of the two domains assessed. Methods. A cross-sectional study was conducted between February 2023 and May 2024. A total of 169 patients with HF were included and were distributed into two groups: the HF -S/V group (N=64) who received treatment with sacubitril/valsartan and the HF -CT group (N=105) received treatment with conventional therapy. Two questionnaires were used to assess patients: the World Health Organization's Quality of Life Questionnaire (WHOQOL-BREF) questionnaire and the Charlson Comorbidity Index (CCI). Results: The values determined for physical and psy-chological health were significantly lower for Group HF - S/V (51.391 ± 22.232 vs. 61.79 ± 20.04, p=0.002, respectively 59.203 ± 16.871 vs. 64.933 ± 17.448, p=0.038). Approximately 25% of all re-cruited patients distributed in the 2nd CCI category (CCI score 3-4) have an overall poor and moderately poor perception of quality of life vs. 35.5% of patients distributed in the 3rd CCI cate-gory (CCI $\leqslant$ 5); 55% of them belong to the HF - S/V group. A good perception of health status is held by 29 (17.16% of the HF group) of the patients distributed in the 2nd CCI category and 28 (16.56%) have a low and moderate perception. Conclusions: The values for the Physical health domain are moderately low, while the values obtained for the psychological domain show that this domain is less affected. Predictors identified for physical health and psychological well-being are patient age, weight, CCI.

Keywords: heart failure; comorbidities; quality of life; physical dimension; psychological dimension

1. Introduction

Assessing patients' quality of life is increasingly making its way into health research [1]. Heart failure (HF) is considered to be the final stage in the evolution of heart disease. The main cause of HF is myocardial ischemia, along with systemic diseases (chronic obstructive pulmonary disease – COPD, hereditary diseases, etc.), leading to impaired myocardial pump function (according to European Society of Cardiology – ESC guidelines). Risk factors incriminated in favoring the development of HF are high blood pressure (HBP), metabolic and lifestyle factors (diabetes mellitus, dyslipidemia, obesity,

sedentarism, and smoking) [2,3]. Patients who are diagnosed with HF experience reduced exercise tolerance and reduced quality of life due to reduced heart pump function, i.e., decreased O_2 supply at the cellular level. All these lead to increased mortality, repeated hospitalizations and increased hospitalization costs [4,5]. It is considered that any condition (structure or function) that affects left ventricular activity can lead to HF [6]. The incidence of HF is increasing, especially among men [5]. The treatment in HF starts with lifestyle and dietary changes; drug treatment differs according to the stage of HF (New York Heart Association – NYHA class) and left ventricular ejection fraction (LVEF) [7].

The limitation of physical activity influences the quality of life of patients with HF through the occurrence of characteristic symptoms. Pharmaceutical research is focused on the synthesis of innovative drugs to ameliorate symptoms, reduce hospitalizations (and thus costs) and mortality. Only a few drugs approved in HF treatment (USA) are indicated for symptomatic relief; in HF with preserved ejection fraction (HFpEF), no drug is registered for symptomatic relief [8]. Beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs) and isosorbide/hydralazine are used. Since 2015 a new class of drugs, with angiotensin and neprilysin receptor inhibitory action (ARNI), has been approved and put on the market. The first representative of this class is the combination sacubitril with valsartan, approved for the control of HF-specific symptoms [8]. Figure 1 summarizes the drugs according to the endpoints of the studies.

Figure 1. Drugs recommendations in HF.

The objectives of the study were: (i) to assess the quality of life and comorbidities in patients with HF; (ii) to compare the quality of life in the physical and psychological domains according to drug treatment followed and (iii) to identify predictors of the two domains assessed.

2. Results

2.1. General characteristics

The general characteristics of the cohort evaluated are listed in Table 1. The mean age of the patients included in the study was 65.16 ± 11.45 years; 57.40% were male patients. In total, 61.09% of the patients come from rural areas. Comorbidities assessed are BPH, diabetes mellitus, dyslipidemia, peripheral venous disease, dilated cardiomyopathy, chronic kidney disease, lung disease. Statistical analysis shows that about 70% of patients have HF stage II and III according to NYHA, more than 50% have diabetes mellitus; dilated cardiomyopathy was identified in 32.17% of patients, most of the cases belonging to HF-S/V group. Chronic renal and respiratory pathology is present in <25%.

An important feature of HF is LVEF. If LVEF is ≥ 50% (normal) it is considered HFpEF; LVEF ≤ 40% defines HF with reduced ejection fraction (HFrEF). Patients with HF presenting LVEF between 40% - 49% are classified as HF with mildly reduced ejection fraction (HFmrEF).

For achieving the established objectives, the recruited patients were divided into two groups (Group HF-CT, Group HF-S/V), according to the treatment followed. The two groups are homogeneous in terms of age, gender, and background. Differences are related to clinical and paraclinical parameters, namely patients' weight, stages of HF, benign prostatic hyperplasia (BPH), peripheral venous disease, dilated cardiomyopathy, chronic kidney disease, LVEF. Data analysis showed a 95.5% frequency of HF class II and III in

the HF-S/V group vs. 49.51% in the HF-CT group. Stage III BPH was more common in the HF-CT group (13.33% vs. 3.12% in Group S/V). The frequency of LVEF < 40% was 60.94% in Group HF-S/V vs. 0.95% in Group HF-CT.

Table 1. General characteristics of the study groups.

Parameter	Group HF	Group HF-CT	Group HF-S/V	p- value
Age, M, SD (N)	65.16 ± 11.45 (105)	64.057 ± 11.50 (105)	66.96 ± 11.02 (64)	0.159*
Male, N, %	97 (57.40)	56 (53.33)	41 (64.06)	0.171**
Rural area, N (%)	61 (36.10)	33 (31.43)	28 (43.75)	0.106**
Weight	105 (100)	105	64	<0.001**
Normal weight N (%)	29 (17.16)	22 (20.95)	7 (10.94)	0.005**
Overweight N (%)	59 (34.91)	37 (35.23)	22 (34.37)	0.05**
Grade I obesity N (%)	50 (29.59)	28 (26.66)	12 (18.75)	0.01**
Grade II obesity N (%)	24 (14.20)	13 (12.38)	11 (17.18)	0.68**
Grade III obesity N (%)	4 (2.36)	3 (2.85)	1 (1.56)	0.31**
Underweight N (%)	1 (1.18)	1 (0.95)	-	-
HF N (%)	169 (100)	105 (100)	64 (100)	<0.001**
Stage I N (%)	56 (33.14)	53 (50.47)	3 (4.68)	<0.001**
Stage II N (%)	101 (59.76)	49 (46.66)	52 (81.25)	0.08**
Stage III N (%)	12 (7.1)	3 (2.85)	9 (14.06)	0.08**
High blood pressure N (%)	169 (100)	95 (90.47)	49 (76.56)	0.007**
Stage I N (%)	26 (15.39)	20 (19.04)	6 (9.37)	0.006**
Stage II N (%)	102 (60.35)	61 (58.09)	41 (64.06)	0.047**
Stage III N (%)	16 (9.45)	14 (13.33)	2 (3.12)	0.71**
Diabetes mellitus N (%)	94 (55.62)	55 (52.38)	39 (60.93)	0.277**
Dyslipidemia N (%)	140 (82.84)	90 (85.71)	50 (78.12)	0.204**
Peripheral venous disease N (%)	25 (14.79)	11 (10.47)	15 (24.43)	0.002**
Dilated cardiomyopathy N (%)	55 (32.17)	6 (5.71)	49 (76.56)	<0.001**
Chronic kidney disease N (%)	40 (23.67)	18 (17.14)	22 (34.37)	0.020**
Lung disease N (%)	36 (21.30)	25 (23.80)	11 (17.18)	0.308**
LVEF, N (%)	169 (100)	105 (100)	64 (100)	<0.001**
LVEF <40%, N (%)	40 (23.66)	1 (0.95)	39 (60.94)	<0.001**
40 ≤ LVEF < 50%, N (%)	128 (75.74)	103 (98.09)	25 (39.06)	<0.001**
LVEF ≥50%, N (%)	1 (0.59)	1 (0.96)	0 (0)	-

Group HF−CT: patients receiving conventional therapy; Group HF − S/V: patients receiving sacubitril/valsartan, M, SD, M, mean value; SD, standard deviation value; N, total number; PMH, past medical history *p-value t-test; **p-value chi-squared test.

The presence of heart rhythm disorders is presented in Table 2. In the group receiving conventional therapy, 60.95% of patients had no cardiac arrhythmias, vs. 17.19% of patients receiving S/V therapy.

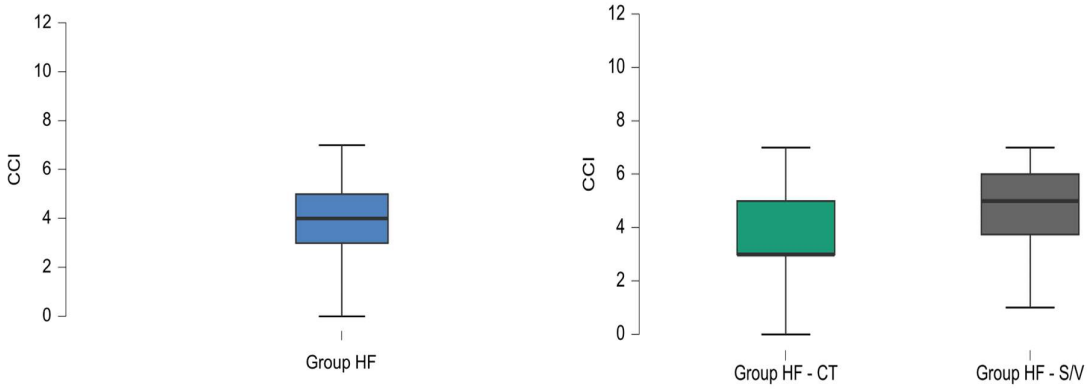
Table 2. Incidence of arrhythmias in the two study groups.

Group	AF	ESSV	ESV	VT unsupported	AFL	Disorders of driving	NO arrhythmias	p
Group HF–CT	13	10	12	0	0	14	64	<0.001
Group HF – S/V	35	3	9	1	1	9	11	

AF – atrial fibrillation, ESSV – supraventricular extrasystoles, ESV – ventricular extrasystoles, VT – ventricular tachycardia, AFL– atrial flutter, p-value chi-square test.

2.2. Comorbidity index

The mean CCI score for Group HF - CT (3.457 ± 1.749) is lower than the cohort mean (3.84 ± 1.83) and significantly lower (p=0.027) than Group HF - S/V (4.438 ± 1.807) (Figure 2).



a. **b.**

Figure 2. CCI score values**. a.** CCI Group HF; **b.** Group HF - CT vs. Group HF - S/V.

The 3rd category (≥5 comorbidities) includes more than 50% of patients in the Group HF - S/V vs. 27.62% in the Group HF - CT; there are statistically significant differences between groups, p=0.002.

Table 3. Contingency Tables of the two groups, according to the number of comorbidities.

Group	Scor ICC		
	1-2	3-4	≥5
Group HF – CT, N (%)	28 (26.7)	48 (45.71)	29 (27.62)
Group HF – S/V, N (%)	10 (15.63)	19 (29.69)	35 (54.68)
Group HF, N (%)	38 (22.48)	67 (39.64)	64 (37.86)

2.3. Quality of life assessment of HF patients

Kolmogorov-Smirnov test was used to assess the homogeneity of dispersion. Non-homogeneous dispersion was determined for the relationship with the environment. Table 4 shows that the mean values are low in all domains of quality of life of HF patients and that there are significant differences between the two groups. The mean value of the Physical health domain for Group HF - CT (61.79 ± 20.04) is good, being higher than both the mean value of the evaluated cohort (57.85 ± 21.44) and the mean value determined for Group HF - S/V (51.39 ± 22.23); both values (Group HF and Group HF - S/V) show a moderate decrease on this dimension. On the psychological domain, the mean values for

Group HF and Group HF - CT are in the range 61-80 (good), while the mean values for Group HF - S/V are moderately low (59.20 ± 16.87).

Table 4. Mean values obtained on the quality-of-life domains.

Dimension	Group	Mean ± SD	p-value
Physical health	Group HF - CT	61.79 ± 20.040	0.002*
	Group HF - S/V	51.391 ± 22.232	
	Group-HF	57.852 ± 21.439	
Psychological	Group HF - CT	64.933 ± 17.448	0.038*
	Group HF - S/V	59.203 ± 16.871	
	Group-HF	62.736 ± 17.406	
Social relationships	Group HF - CT	65.762 ± 12.519	0.024*
	Group HF - S/V	61.266 ± 12.428	
	Group-HF	64.059 ±12.638	
Environment	Group HF - CT	61.333 ± 13.461	<0.001**
	Group HF - S/V	51.719 ± 16.769	
	Group-HF	57.692 ± 15.475	

Figure 3 shows a comparison of cohort-level and two-group averages for the domains set out in the study objectives.

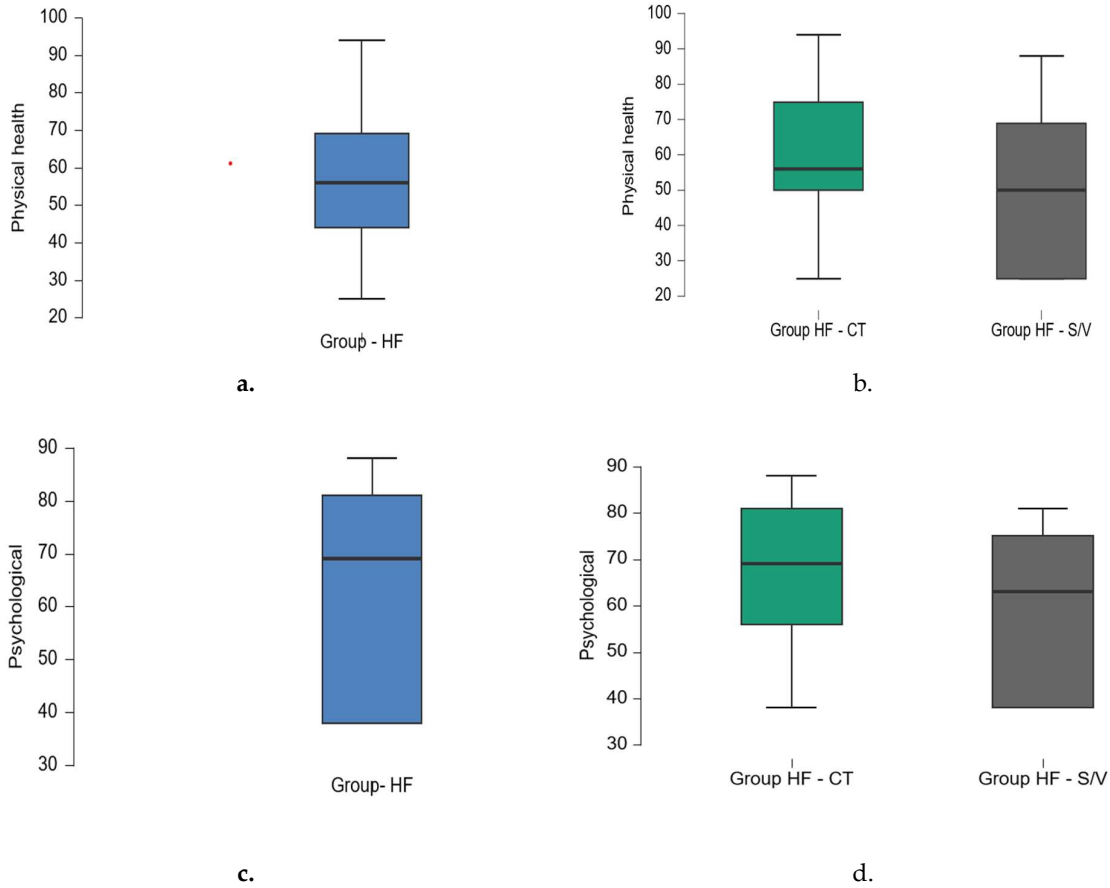


Figure 3. Mean values obtained on the quality-of-life domains: **a.** Mean values obtained on Physical health domain at cohort level; **b.** Mean values obtained on Physical health domain for the two groups; **c.** Mean values obtained on Psychological domain at cohort level; **d.** Mean values obtained on Psychological domain for the two groups.

2.4. Assessment of quality of life according to comorbidity index.

2.4.1. Individual's general perception of quality of life according to CCI

Analysis of the data presented in the Table 5 indicates that 23.8% of Group HF - CT patients in category 1 CCI have a good and very good perception of quality of life vs. 12.5% in Group HF - S/V. Approximately 25% of all recruited patients (Group HF) distributed in the 2nd CCI category (CCI score 3-4) have poor and moderately poor overall quality of life perception vs. 35.5% of patients distributed in the 3rd CCI category (CCI ≤ 5); 55% of them belong to Group HF - S/V.

Table 5. Contingency Tables WHOQOL-BREF Q1 according to CCI category.

CCI category	Group	Answer WHOQOL-BREF Q1 (Likert scale)				Total
		2	3	4	5	
1	HF - CT	0	3	23	2	28
	HF - S/V	1	1	7	1	10
	HF	1	4	30	3	38
2	HF - CT	3	24	21	0	48
	HF - S/V	0	13	6	0	19
	HF	3	37	27	0	67
3	HF - CT	17	10	2	0	29
	HF - S/V	23	10	1	0	34
	HF	40	20	3	0	63
Total	HF - CT	20	37	46	2	105
	HF - S/V	24	25	14	1	64
	HF	44	62	60	3	169

2.4.2. Individual's general perception of their health (Q2) according to CCI

Analysis of the data in Table 6 indicates that 20% of Group HF patients in category 1 CCI have a good and very good perception of their health, of which 75.75% belong to the Group HF - CT group. A good perception of health is held by 29 (17.16 % of Group HF) of the patients distributed to the second CCI category and 28 (16.56 %) have a low and moderate perception. The data show that the responses of patients in the third CCI category emphasize a marked and moderate decrease in health status; 57 (33.72 %) of patients belong to this category, of which, more than half (18.34 %) belong to Group HF - S/V.

Table 6. Contingency Tables WHOQOL-BREF Q2 according to CCI category.

CCI category	Group	Answer WHOQOL-BREF Q2 (Likert scale)					Total
		1	2	3	4	5	
1	Group HF - CT	0	0	3	23	2	28
	Group HF - S/V	0	1	1	7	1	10
	Group HF	0	1	4	30	3	38
2	Group HF - CT	0	3	23	22	0	48
	Group HF - S/V	0	0	12	7	0	19
	Group HF	0	3	35	29	0	67
3	Group HF - CT	0	13	13	3	0	29
	Group HF - S/V	1	21	10	2	0	34
	Group HF	1	34	23	5	0	63
Total	Group HF - CT	0	16	39	48	2	105
	Group HF - S/V	1	22	23	16	1	63
	Group HF	1	38	62	64	3	168

2.5. Predicting quality-of-life

To assess the effects of the treatment in the two groups (Group HF – CT vs. Group HF – S/V), as well as of other factors, on the quality of life of patients with HF, we conducted a series of multiple linear regression analyses. Below, we present the results of regression analyses for the dimensions of physical health, psychological well-being, as measured by WHOQOL-BREF, on the following factors: treatment group, age, gender, area of residence, comorbidities, and LVEF.

2.5.1. Physical health

Table 7 shows the summary statistics of the regression model for physical health**.** The regression model containing the treatment group, age, gender, living area, comorbidities, and FEVS explains 66 % of the total variability in physical health (R_adj^2=0.660). This model is statistically significant [F(27,141)= 13.090, p<0.001], as shown in the table below. Further, we examine the model coefficients to see which of the predictors contribute significantly to the explained variability.

Table 7. Statistics of the regression model for physical health.

Model		Sum of Squares	df	Mean Square	F	p
H_1	Regression	55197.220	27	2044.341	13.090	<0.001
	Residual	22020.082	141	156.171		
	Total	77217.302	168			

In terms of physical well-being, patient age, weight, CCI score and Charlson category are the only statistically significant predictors (Table 8). The treatment group (HF - CT Group, HF - S/V Group) does not show a significant effect on physical health. For age, we found a negative correlation with physical health, as expected. Specifically, we found that when we maintain all other predictors constant, the score on the physical health scale decreases on average by 0.58 points for each 1-year increase in age (or by about 6 points on average for each 10-year increase in age).

The effect of weight (obesity grade III) is negatively correlated with Physical domain. Thus, moving into a higher obesity category will result in a marked decrease in the physical health score (34,249 points). Finally, the effect of the Charlson category on the physical health of HF patients is given by the difference between categories 2 and 3. Specifically, patients with a CCI category 3 show a decrease of 2.93 points, on average, on the physical health scale compared to patients with a CCI category 2. This is a large effect (Cohen's d = - 0.554). In terms of the CCI score, 1 point increase in the score will result in 6.101-point decrease in the physical health score.

Table 8. Statistically significant predictors of physical well-being.

Model		Unstandardized	Standard Error	t	p
H_1	Age	-0.581	0.157	-3.701	**<0.001**
	CCI	-6.101	1.693	-3.604	**<0.001**
	Group (Group HF - S/V)	-0.841	3.598	-0.234	0.816
	LVEF (>50)	14.024	13.786	1.017	0.311
	LVEF (40-50)	0.272	3.091	0.088	0.930
	Residence (urban)	3.605	2.226	1.620	0.108
	Hypertension (II)	-2.918	3.128	-0.933	0.352
	Hypertension (III)	-5.652	4.553	-1.241	0.217
	Hypertension (NO)	-4.082	4.023	-1.015	0.312
	HF_ NYHA (II)	-0.623	2.758	-0.226	0.822
	HF_ NYHA (III)	-4.772	4.704	-1.015	0.312

Weight (II)	2.323	3.333	0.697	0.487
Weight (III)	-34.249	7.191	-4.763	**<0.001**
Weight (NU)	19.310	13.245	1.458	0.147
Diabetes mellitus (NO)	-2.688	2.322	-1.158	0.249
Dyslipidemia (NO)	-4.105	2.809	-1.461	0.146
Chronic kidney disease	10.994	13.170	0.835	0.405
Lung disease (NO)	-4.237	2.964	-1.429	0.155
Dilated cardiomyopathy	1.299	6.569	0.198	0.843
CCI (2)	9.389	3.836	2.448	0.627
CCI (3)	-2.930	6.011	-0.487	**0.016**

The significant effects are depicted in the plots below (Figure 4).

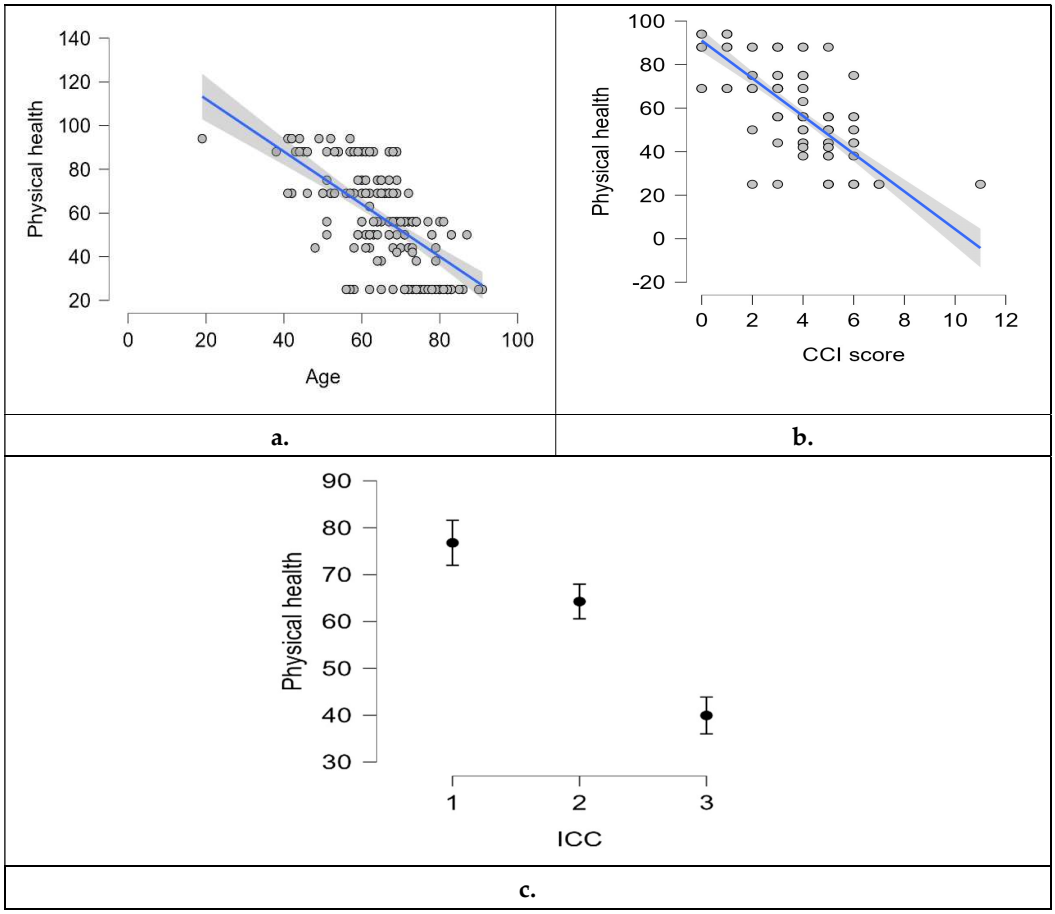


Figure 4. a. Scatter plot of age and physical health, with regression line. **b.** Scatter plot of CCI and physical health, with regression line. **c.** The effect of the Charlson category (CCI) on physical health well-being (error bars with confidence intervals).

2.5.2. Psychological well-being

Table 9 shows the summary statistics of the regression model for psychological well-being. For psychological well-being, the regression model explains 57.8 % of the total variability, and it is statistically significant [F(25,143)=10.197, p<.001], as shown in the table below. Further, we analyzed the model coefficients to see which of the predictors contribute significantly to the explained variability.

Table 9. Statistics of the regression model for psychological well-being.

Model		Sum of Squares	df	Mean Square	F	p
H_1	Regression	32608.203	25	1304.328	10.197	< 0.001
	Residual	18292.330	143	127.918		
	Total	50900.533	168			

Similar to the physical health dimension of quality of life, age, weight (III), and CCI score are significant predictors of psychological well-being (Table 10). In addition, there is a significant effect of high blood pressure (HBP) on this dimension. The treatment group (HF - CT group vs. HF - S/V group) is not significantly associated with psychological well-being. We detail significant effects below.

For age, we found a significant negative correlation with psychological well-being. Specifically, we found that, when keeping all the other predictors fixed (i.e., statistically controlling for the other predictors), the score on the psychological well-being scale decreases by 0.479 points on average, for every 1-year increase in age (or by approximately 5 points on average for every 10-year increase in age).

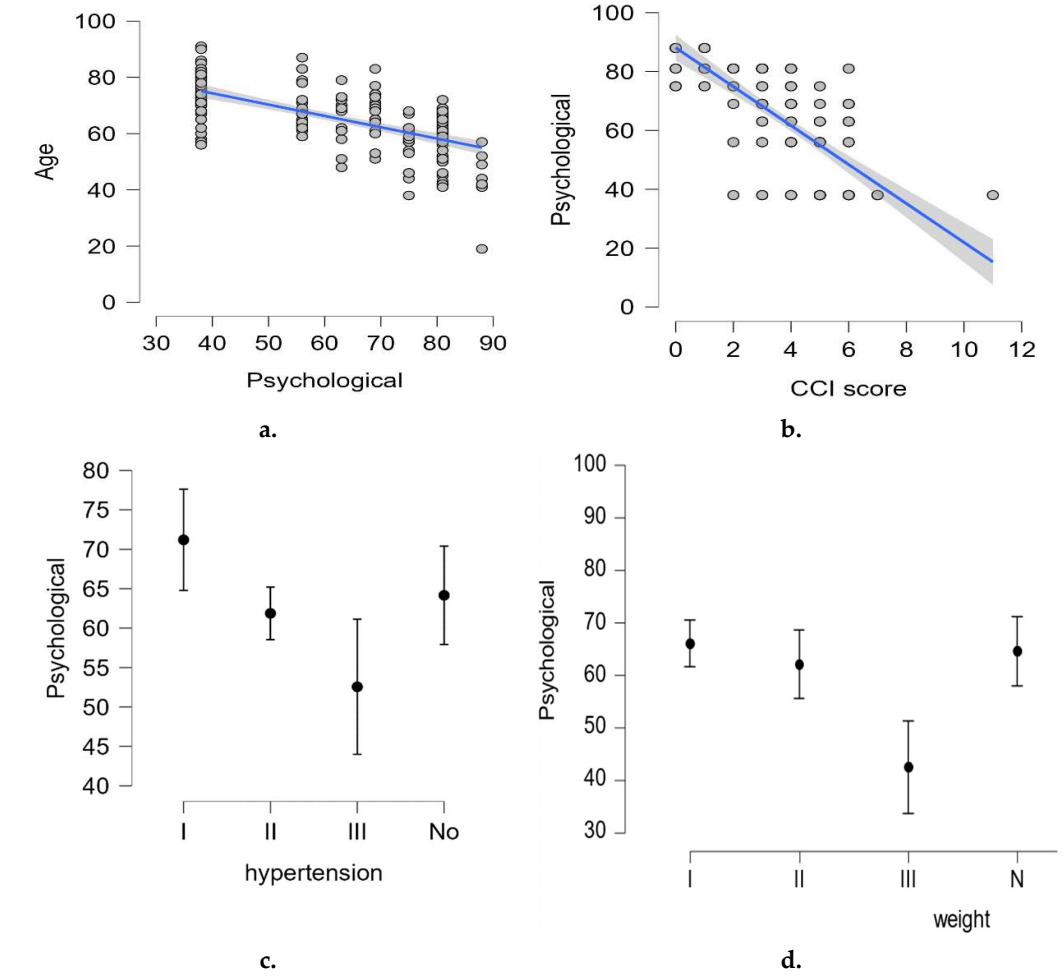
The effect of arterial hypertension on the psychological well-being of patients with HF is given by the difference between the groups of patients without hypertension and those with level III hypertension, as shown above. Thus, the patients with level III hypertension show a decrease in psychological well-being of 10.102 points on average, compared to the patients without hypertension.

Finally, the effect of association of comorbidities, expressed by the CCI score, correlates significantly negatively. Specifically, we found that when all other predictors are fixed (i.e., statistically controlling for the other predictors), the score on the psychological well-being scale decreases on average by 3.575 points for each 1-point increase in the CCI score. The significant effects are depicted in the figure 5.

Table 10. Statistically significant predictors of psychological well-being.

Model		Unstandardized	Standard Error	t	p
H_1	Age	-0.479	0.135	-3.539	**< 0.001**
	CCI score	-3.575	1.449	-2.467	**0.015**
	HF_ NYHA (II)	-2.001	2.487	-0.805	0.422
	HF_ NYHA (III)	-3.777	4.216	-0.896	0.372
	Group (Group HF - S/V)	-0.632	3.206	-0.197	0.844
	Hypertension (II)	-4.511	2.801	-1.611	0.109
	Hypertension (III)	-10.102	3.985	-2.535	**0.012**
	Hypertension (without)	-2.918	3.550	-0.822	0.412
	Diabetes mellitus (without)	-3.435	2.032	-1.690	0.093
	Weight (II)	-1.470	2.962	-0.496	0.620
	Weight (III)	-27.708	6.503	-4.261	**< 0.001**
	Weight (Normoponderal)	0.311	2.857	0.109	0.913
	Weight (Subponderal)	-0.023	8.506	-0.003	0.998
	Weight (Supraponderal)	-1.679	2.335	-0.719	0.473
	Lung disease (without)	-4.783	2.832	-1.689	0.093
	Dyslipidemia (without)	2.376	2.534	0.938	0.350

Chronic kidney disease (without)	-1.796	2.681	-0.670	0.504
Chronic kidney disease	11.895	11.853	1.004	0.317
Dilated cardiomyopathy	0.119	5.893	0.020	0.984
Dilated cardiomyopathy (without)	-1.296	5.750	-0.225	0.822
LVEF (>50)	15.351	12.283	1.250	0.213
LVEF (40-50)	1.132	2.776	0.408	0.684
CCI (2)	4.802	3.456	1.390	0.167
CCI (3)	-4.610	5.414	-0.852	0.396



a. **b.** **c.** **d.**

Figure 5. a. Scatter plot of age and psychological well-being, with regression line. **b.** . Scatter plot of CCI score and psychological well-being, with regression line. **c.** The effect of arterial hypertension on psychological well-being (error bars with confidence intervals). **d.** The effect of the weight on psychological well-being (error bars with confidence intervals).

3. Discussion

Cardiovascular diseases have major effects on the economic burden and global health, and the progression of HF is influenced by interrelated factors [9]. The quality of life of HF patients is closely related to the individual's physical performance, emotional state, and the occurrence of characteristic symptoms [8]. Although great progress has been made in the treatment of HF, control of clinical manifestations, mortality and morbidity is

increased [10]. Self-assessment questionnaires addressed to patients are used in clinical practice, with screening or monitoring role, to assess quality of life (which is a predictor of treatment success) [1], the impact of the symptoms of different diseases on daily activities, emotional state, etc. [11].

The study looked at the correlation of domains assessed by the WHOQOL-BREF questionnaire with the CCI, according to treatment group, HF stages, FEVS values, age, gender.

The analysis shows that the CCI comorbidity index value for Group HF - CT is lower than for Group HF and significantly lower than for Group HF - S/V, which means that the number of comorbidities is lower in the conventional therapy group. The significant difference between groups results from the increased prevalence (more than 50%) of patients with CCI ≥ 5.

The presence of HF leads to decreased quality of life in general and across all domains. At cohort level, moderately low values are on Physical health and Environment domains; a good quality of life was determined on the other two domains (Psychological, Social relationships). The Physical domain is more affected for Group HF - S/V, for which moderate decreases were obtained (51.391 ± 22.23) vs. Group HF - CT (61.790 ± 20.043). On the Psychological domain the situation is similar; the mean values for Group HF - S/V are moderately low (59.203 ± 16.871) vs. the results obtained for Group HF - CT and Group - HF respectively (64.933 ± 17.448, 62.736 ± 17.406).

These differences can be explained by approximately 5 times higher incidence of HF stages III in Group HF - S/V; also, more than 10 times higher frequency of dilated cardiomyopathy. LVEF < 40% present in 60.93%, also plays a role in the reduced physical performance of patients. At the same time, considering the incidence of comorbidities in Group HF - S/V, about 55% of patients have a congestive heart failure (CHF score ≥ 5. Atrial fibrillation is present in 54.69% versus 12.38%. More than 50% of patients included in the HF - CT Group are without heart rhythm disturbances. All these aspects also condition the responses on "individual's general perception of quality of life" and on "individual's general perception of his/her health".

In the study by Tarekegn et al. [12] and published in 2021 (N=469 patients), the decreased quality of life of HF patients across all quality-of-life domains was also highlighted. The decrease was accentuated on the Physical and Environmental health domains, like our study.

In terms of quality-of-life assessment (question Q1) 26.03% of all patients assessed rated their quality of life as poor (11.83% belonging to Group HF - CT vs. 14.20% belonging to Group HF - S/V). Tarekegn et al. obtained similar results, i.e. 31% of patients assessed considered their quality of life as poor [12].

Analyzing the responses related to the general perception of health (Q2), 23.07% (most from Group HF - S/V) were dissatisfied with their health status vs. 43.10% of the patients participating in the study published by Tarekegn et al [12].

Similar results to our study were published by Alharbi M. et el. (2022), quality of life was moderately decreased (N=246 patients); the means obtained on the physical domain were 58.1 vs. 57.852 (our study), respectively for the psychological domain, 63.7 vs. 62.73 [13].

In the meta-analysis published by Moradi et co. (2020) this decrease in the quality of life of HF patients is also supported (25.180 participants). In 14 studies (out of the 70 studies analyzed), the decrease in quality of life was marked in the physical domain and moderate in the mental domain, like the results obtained in our analysis [14].

The published studies have identified several predictors of quality of life, namely: marital status, income and length of IC [12], female gender, older age, comorbidities, advanced symptoms and recent hospitalization [15], smoking, residence and BMI [16]. Physical well-being was negatively correlated with age, residence [12] and positively with lower education level [13].

Compared to our study, age, weight, CCI score and Charlson category were identified as predictors of physical well-being. As expected, older age affects physical activity; statistical analysis shows that for each year, the quality-of-life score decreases by

about 6 points. The association of obesity and comorbidities also affects quality of life with reduced physical well-being. Residency, in this study was not found to be a predictor of physical well-being.

In terms of psychological health, published studies have identified the following as predictors: HF duration [12] and the female gender [13] both factors leading to a low quality of life score on this domain. The review published in 2021 by Levine et al. demonstrates the association between cardiovascular risk factors and psychological health, due to biological mechanisms and behaviors that are triggered [17].

The presence of comorbidities influences all domains of quality, with a greater impact on depression and physical health, an argument also supported by the study published by Hoogwegt et al. (2013, N=401) [18].

The study published by Borumandpour, which was conducted on 147 HF patients, shows that no significant association was found between NYHA class, LVEF and quality of life domains [19], an aspect also found in our study.

Cardiac rehabilitation

Implementing a cardiac rehabilitation exercise program in HF patients over 65 years of age has been shown to improve physical health and quality of life. By improving paraclinical parameters (lipid and carbohydrate profile), physical training favours a superior control of HF-associated comorbidities [20], an important aspect in increasing the quality of life of patients [21]. At the same time, benefits have also been found on psychological well-being, an important component of quality of life [20]. Meta-analysis by Chen Z. et al. (2022) highlights the benefits of cardiac rehabilitation, with effects on cardiac function, 6-minute walk test (6MWT) and readmission rates [22].

Strengths and Limitations of the Study

The study was designed to assess the two dimensions of quality of life, namely the physical health and the psychological health. A strength of the study is that, to our knowledge, it is the first study in Romania in which the dimensions of physical well-being and psychological well-being have been comparatively assessed according to the treatment followed for HF. Another strength of the study is the large number of patients included in the study.

The limitations are related to the cross-sectional design of the study and the lack of long-term, dynamic evaluation of these dimensions. Among the potential predictive factors identified in other studies, marital status, income and education level were not analyzed. The fact that it was conducted in a single center is another limitation of the study.

4. Materials and Methods

4.1. Database

Patient recruitment took place between February 2023 and May 2024. The cross-sectional study was applied to 261 patients with HF who were admitted to the Avram Iancu Clinical Hospital Oradea. After applying the selection criteria, 169 patients remained. The selection of subjects was followed by the formation of two groups:

- Group I - which includes patients under treatment with Sacubitril/Valsartan and will be referred to as the HF - S/V Group, N=64;

- Group II - which includes patients on conventional treatment (diuretics, converting enzyme inhibitors, beta-blockers, ARBs and anti-aldosterone diuretics), HF - CT Group, N=105.

4.2. Inclusion/exclusion criteria

Patients with a definite diagnosis of HF for more than six months (confirmation by a certified cardiologist), with New York Heart Association (NYHA) stages I-III, hemodynamically stable were recruited. The associated comorbidities assessed were acute

myocardial infarction, renal and digestive pathology, diabetes mellitus and its complications, chronic pulmonary and liver diseases, stroke, neoplasms.

The exclusion criteria were as follows: age under 18 years, decompensated forms of cardiac or non-cardiac pathology of recruited patients. Also, incomplete data were not considered in data processing.

Of the 261 patients recruited, 169 patients remained in the study. The allocation by study groups is summarized in the Figure 6.

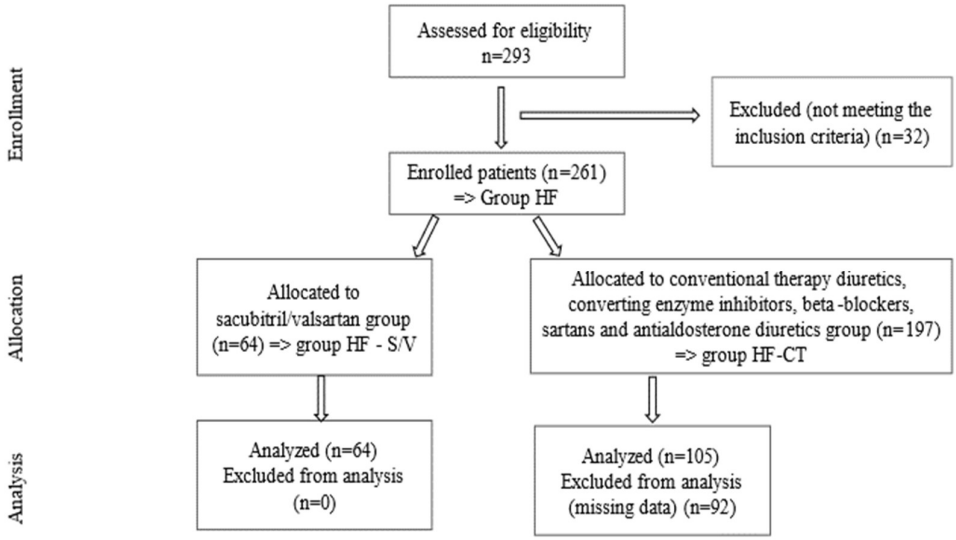


Figure 6. CONSORT flow diagram of the study.

4.3. Sample size

To calculate the sample size of patients we used the formula n = t2 pq/(x2 + t2 pq/N). The variables for the calculation were: p - probability of occurrence of the phenomenon, 0p1, q - counter-probability, q = 1-p, t - probability factor, x - error limit, N - community volume. We consider n to be maximum if the value of the product pq is maximum (p = q = 0.5). Assuming a probability of 95%, the corresponding t-value is 1.96. A bounding error of 0.1 has been set. If N is large, above 10 000 (in our case N = 221), the ratio t2 pq/N is neglected. N = 96 is obtained; the formula applies to studies where the target characteristic is an alternative [6].

4.4. Study tools.

Two questionnaires were used in this cross-sectional survey: the WHOQOL-BREF questionnaire (license ID: 202300206) to assess quality of life and the CCI to assess associated comorbidity.

The WHOQOL-BREF consists of 26 items [23]; the questionnaire allows the overall assessment of quality of life, as well as by quality-of-life dimensions: physical, psychological, social and environmental [24]. The characteristics of this questionnaire (cross-culturality, self-administrability, self-assessment of individuals' well-being) allow its use in different contexts [25]. The first two items (Q1 and Q2) refer to the "individual's general perception of quality of life" and the "individual's general perception of their health". The domains Physical health and Psychological health are the ones followed in this study. The physical health assessment consists of 7 questions related to physical pain, ability to perform daily activities, sleep, energy, movement and work capacity. The psychological health assessment (6 questions) refers to the state of joy, contentment, concentration, sadness, anxiety, depression. The quantification of each item is done with the Likert scale [23].

The value 100 represents the best possible health status and 0 represents the worst possible health status. To calculate the WHOQOL-BREF score for each domain we used

the online questionnaire [26]. The quality of life is divided into 5 categories: very poor (0-20), poor (21-40), moderate (41-60), good (61-80), very good (80-100) [27].

The most common non-cardiac comorbidities are diabetes mellitus [28], chronic kidney disease, peripheral vascular disease [29] and dementia. Prevalence and incidence of cognitive impairment and dementia in HF –are systematically reviewed using meta-analysis, specifically meta-regression. The CCI, now considered the gold standard, is calculated according to the number of comorbidities and their severity. CCI is useful for clinical evaluation and to "delineate major diagnostic and prognostic differences between subgroups of patients with the same medical diagnosis" [30]. In this study, three grades of comorbidity severity were considered: mild (1-2), moderate (3-4) and severe (≥5) [31]. For the most accurate calculation of the results, the CCI questionnaire data were processed with the online questionnaire [32].

4.5. Ethical approval

The research was conducted following the World Medical Association Declaration of Helsinki guidelines. The approval of the ethics committee of the Faculty of Medicine and Pharmacy, University of Oradea (CEFMF/02/19.05.2022) was obtained for this research. Participation in the study was voluntary, the patients signing a consent form prior their inclusion in the study.

4.6. Statistical analysis

JASP version 0.18.1 [33] was used for statistical processing of the data. The Kolmogorov-Smirnov test was used to assess the distribution of variables. The tests used were Student's (t-test) and Mann-Whitney U, depending on the homogeneity/non-homogeneity of the dispersion between the two groups. Statistical significance was considered 0.05. The mean values of the determined parameters, and the frequency intervals were compared. The chi-square test was used to assess significant differences between the frequency data of the two groups. Multiple linear regression model was used to identify factors that influenced the physical-psychological performance of patients correlated with comorbidity index.

5. Conclusions

The quality of life of HF patients is low. Approximately one third of HF patients have a low to moderately low perception of quality of life and health. The values for the Physical health domain are moderately low, while the values obtained for the psychological domain show that this domain is less affected. Predictors identified for physical health and psychological well-being are patient age, weight, and CCI.

Author Contributions: Conceptualization, Diana-Carina Iovanovici, Delia Mirela Tit, Mirela Marioara Toma and Carmen Delia Nistor – Cseppento; Data curation, Diana-Carina Iovanovici; Formal analysis, Diana-Carina Iovanovici, Mirela Marioara Toma and Delia Mirela Tit; Investigation, Diana-Carina Iovanovici and Ioan Andrei Antal; Methodology, Simona Gabriela Bungau, Mirela Marioara Toma, Bombonica Gabriela Dogaru and Carmen Delia Nistor – Cseppento; Resources, Delia Mirela Tit; Software, Carmen Delia Nistor – Cseppento; Supervision, Simona Gabriela Bungau, Bombonica Gabriela Dogaru and Delia Mirela Tit; Validation, Simona Gabriela Bungau; Visualization, Anamaria Lavinia Purza, Mirela Marioara Toma and Ioan Andrei Antal; Writing – original draft, Diana-Carina Iovanovici, Anamaria Lavinia Purza, Bombonica Gabriela Dogaru, Ioan Andrei Antal and Carmen Delia Nistor – Cseppento; Writing – review & editing, Mirela Marioara Toma, Simona Gabriela Bungau and Anamaria Lavinia Purza. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Oradea (CEFMF/02/19.05.2022).

Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study."

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

Conflicts of Interest: The authors declare no conflict of interest.

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