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ORIGINAL RESEARCH ARTICLE

Cognitive performance is associated with worse prognosis in patients with heart failure with reduced ejection fraction

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Abstract

Aims Heart failure (HF) is a complex clinical syndrome with multiple comorbidities. Cognitive impairment, stress, anxiety, depression, and lower quality of life are prevalent in HF. Herein, we explore the interplay between these parameters and study their value to predict major adverse cardiovascular events (MACEs) and health-related quality of life (HrQoL) in patients with HF with reduced ejection fraction using guideline recommended assessment tools.

Methods and results We conducted a longitudinal study using a sample of 65 patients from two hospitals. A battery of tests was applied to assess cognition [Montreal Cognitive Assessment (MoCA)], stress (Perceived Stress Scale-10), anxiety, and depression (Hospital Anxiety and Depression Scale) at baseline. MACEs were registered using clinical records. HrQoL was estimated using the Kansas City Cardiomyopathy Questionnaire (KCCQ). A descriptive statistical analysis was conducted, and multiple linear and Cox regression models conducted to determine the predictive value of neurocognitive parameters and HrQoL in MACE. Both MoCA [hazard ratio = 0.906 (0.829–0.990); P = 0.029] and KCCQ scores were predictors of MACE, but not of overall mortality. Anxiety, depression, and stress scores did not predict MACE. However, anxiety (β = −0.326; P = 0.012) and depression levels (β = −0.309; P = 0.014) were independent predictors of the KCCQ score.

Conclusions The MoCA score and HrQoL were predictors of MACE-free survival. Anxiety and depression were good predictors of HrQoL, but not of MACE-free survival.

Keywords Cognitive impairment; Heart failure; Quality of life; Major adverse cardiovascular events; Montreal Cognitive Assessment (MoCA)

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Introduction

Patients with heart failure (HF) have a worst health-related quality of life (HrQoL) when compared with healthy populations and patients with other chronic diseases.[1] HF has a multisystemic impact, including mental health. Several studies show that HF is associated with a high prevalence of neuropsychological disorders such as depression,[2] anxiety,[3] psychological stress,[4] and cognitive impairment (CI).[5] Evidence suggests that some of these factors are associated with prognosis. For example, patients with a higher prevalence of depressive symptoms are at higher risk of mortality and poorer HF outcomes.[6,7] Recently, the OPERA-HF study investigated the prognostic value of psychosocial factors in HF and showed that moderate-to-severe depression, anxiety, and CI increase the risk of repeated admissions.[8] Despite the importance of these findings, the sample was composed of both patients with reduced and preserved ejection

fraction, which adds heterogeneity to the analysis. Besides, the tool used to assess cognitive performance on this trial was not amongst the ones suggested by the European Society of Cardiology.[9] In fact, using different tools to assess cognitive performance and the heterogeneity of the populations studied may justify the wide range of CI prevalence reported in HF (25% to 80% across studies).[5,10–12] The European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF suggest the screening of CI using specific instruments such as the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination.[9] While these two tools were validated in clinical studies, MoCA identifies clinical relevant CI more often than Mini-Mental State Examination.[13,14] However, no previous study has followed HF with reduced ejection fraction (HFrEF) patients over time using guideline-recommended tools to assess both CI and HrQoL.

In this context, the current report aims to further explore the interplay between neuropsychological parameters, HrQoL, and prognosis in a sample of ambulatory patients with HFrEF.

Methods

We performed a longitudinal observational study using a convenience sample composed of 65 outpatients with HFrEF under follow-up in the cardiology department of two hospitals in the North of Portugal (Guimarães and Barcelos).

The inclusion criteria were (i) HF patients under follow-up in an outpatient clinic, (ii) clinically stable and under maximum tolerated medical treatment without medication changes in the last 6 months, and (iii) left ventricular ejection fraction $<40\%$ in transthoracic echocardiogram (Simpson biplane method). The exclusion criteria were (i) hospitalization for HF decompensation in the previous 6 months, (ii) history of clinical stroke, and (iii) CI due to neuropsychiatric diseases or individuals unable to complete the questionnaires (severe visual or auditory deficits).

The participants were submitted to a battery of four scales/questionnaires to assess depressive and anxiety symptoms, cognitive function, perceived stress, and quality of life. Herein, we analyse the health outcomes of these patients during a 2 year follow-up (July 2016 to June 2018).

The battery of scales/questionnaires was composed by MoCA,[15,16] for cognitive performance evaluation; Kansas City Cardiomyopathy Questionnaire (KCCQ)[17,18] for quality of life, Perceived Stress Scale-10[19,20] to assess psychological stress and the Hospital Anxiety and Depression Scale (HADS)[21,22] to assess anxiety and depression. Previously, validated Portuguese versions of each questionnaire were used.

MoCA is a cognitive screening instrument with greater sensitivity than the Mini-Mental State Examination to detect neurocognitive deficits, namely, mild CI.[14] It assesses different cognitive domains: attention, concentration, executive functions, memory, language, visual-constructional skills, conceptual thinking, calculations, and orientation; its maximum score is 30 points. We use the cut-off for mild CI according to the MoCA Portuguese version, as validated and normalized by Freitas and colleagues.[16,23]

Regarding the HADS-A and HADS-D scales, we used the following cut-offs: normal if value <8, abnormal if >10, and borderline if 8–10.[21] For Perceived Stress Scale-10, values above 19 indicate high levels of perceived stress.[20]

A clinical interview was also performed to assess the New York Heart Association (NYHA) class and overall symptoms. Clinical data were retrieved from the clinical records of the patients.

For the follow-up, the primary endpoint was major adverse cardiovascular event (MACE)-free survival time. MACE was defined as the composite of cardiovascular (CV) hospitalizations, CV emergency department admissions, and CV deaths. A more comprehensive characterization was also performed including the total number of hospitalizations, the total number of emergency department visits, and the current clinical status based on the clinical record of the last outpatient clinic visit. During the follow-up period, medical treatment changes were allowed according to the clinical judgement of the assistant cardiologists. A systematic recording of medical compliance was not performed.

All participants signed the informed consent and the study received approval from the Ethics Committees of both hospitals. The Declaration of Helsinki,[24] the Council of Europe's Convention on Human Rights,[25] and Biomedicine and the Council for International Organizations of Medical Science's guidelines[26] were strictly followed.

Results

Baseline evaluation

The cohort was composed of 83% male participants, with an average age of 63 years old and 5.6 years of school (*Table* 1). The aetiology of HF was ischemic disease in 63% of the patients (52% had a previous myocardial infarction). About 62% were in NYHA class II at the beginning of the follow-up. Anxiety had been previously diagnosed in 17% of patients and depression in 9%. On the cognitive evaluation, 92% of the patients were classified as having mild CI. The scores in anxiety and depressive scales reached the clinical cut-off of abnormal in 45% and 48% of the patients. Thirty-seven per cent of patients presented a 'high level of perceived stress'.

One of the objectives of this work was to understand how the neuropsychological parameters are related to each other. These results are displayed in *Table* 2. Given the importance

Table 1 Characterization of the cohort: medical background and heart failure

Characteristic	*N* (%)
Gender (male)	54 (83.10%)
Age (years)	*M* = 62.92 (SD = 11.25)
Years of school	*M* = 5.57 (SD = 3.35)
None	1 (1.5%)
1–2	0 (0.0%)
3–4	41 (63.1%)
5–8	13 (20.0%)
9–12	6 (9.2%)
13+	4 (6.2%)
Living alone	3 (4.6%)
Smoking status	9 (13.8%)
Alcohol consumption	29(23.8%)
Physical activity	19 (29.2%)
Height(m)	*M* = 1.66 (SD = 0.081)
Weight (kg)	Mdn = 72 (IR = 16)
BMI (kg/m^2)	26.43 (SD = 5.22)
Normal weight	27 (41.5%)
Abdominal perimeter (cm)	*M* = 98.85 (SD = 12.4)
Medical background	
Diabetes mellitus	29 (44.6%)
Hypertension	37 (56.9%)
Dyslipidaemia	54 (83.1%)
Atrial fibrillation	33 (50,7%)
Myocardial infarction	34 (52.3%)
Depression	6 (9.2%)
Anxiety	11 (16.9%)
Thyroid disease	6 (9.2%)
COPD/asthma	15 (23.1%)
Sleep disorders	
OSA	3 (4.6%)
Cheyne–Stokes	4 (6.2%)
Heart failure aetiology (ischemic)	41 (63.0%)
Time of disease (>1 year)	58 (89.4%)
NYHA functional class	
I	12 (18.50%)
II	40 (61.50%)
III	13 (20.00%)
Pro-BNP (pg/mL)	M = 1294 (IR = 3593)
Rhythm (atrial fibrillation)	10 (15.40%)
Left bundle branch block	48 (73.80%)
Transthoracic echocardiogram	
LVEF	M = 28.6 (SD = 7.6)
35–40%	16 (24.6%)
<35%"/>	49 (75.4%)
LA diameter	M = 45.4 (SD = 6.2)
E/E' ratio	M = 14.1 (SD = 6.9)
E/A ratio	M = 69.7 (SD = 25.6)
LV end diastolic diameter	M = 62.4 (SD = 7.8)
LV end diastolic volume	Mdn = 137 (IR = 64)
Mitral regurgitation	
No/Mild	51 (84.60%)
Moderate/severe	10 (15.40%)
Tricuspid regurgitation	
No	56 (91.8%)
Moderate	5 (8.20%)
Right ventricular dysfunction	48 (73.8%)
Heart failure pharmacologic therapy	
ACEI or ARA	65 (100%)
Beta-adrenergic blockers	60 (92.3%)
Aldosterone antagonists	53 (81.5%)
Diuretics	46 (70.8%)
Nitrates	5 (77%)
Digoxin	18 (27.7%)
Ivabradine	7 (10.8%)
Other pharmacologic therapy	
Warfarin	17 (26.2%)
Acetylsalicylic acid	36 (55.4%)
DAOCs	16 (24.6%)

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Table 1 (continued)

Characteristic	*N* (%)
OADs	20 (30.8%)
Insulin	12 (18.5%)
Statin	49 (75.4%)
Fibrate	2 (3.1%)
PPI	38 (58.5%)
Electronic device	
None	27 (41.5%)
ICD	21 (32.3%)
CRT	17 (26.2%)

Cognitive and psychometric assessment Questionnaire	Score Mean ± SD	Category	*N* (%)
MoCA[a]	17.22 ± .86	MCI	59 (92.2)
HADS-Anxiety[b]	7.53 ± 4.45	Anxiety	19 (29.7)
		Borderline	10 (15.4)
HADS-Depression[b]	7.03 ± 4.38	Depression	12 (18.5)
		Borderline	19 (29.2)
PSS-10[c]	17.77 ± 6.334	Perceived stress	24 (36.9)

ACEI, angiotensin-converting-enzyme inhibitor; ARA, angiotensin II receptor antagonists; BMI, body mass index; CRT, cardiac resynchronization therapy; *df*, degrees of freedom; DOACs, direct-acting oral anticoagulants; EF, ejection fraction; ICD, implantable cardioverter defibrillator; IR, interquartile range; LVEF, left ventricular ejection fraction; M, mean; MCI, mild cognitive impairment; Mdn, median; NYHA, New York Heart Association; OAD, oral antidiabetic drugs; Pro-BNP, pro-brain-type natriuretic peptide; PPI, proton pump inhibitor; *phi*, phi coefficient; *r*, Pearson's correlation presented as *r*(*df*); *rs*, Spearman's rho, presented as *rs*(*df*); SD, standard deviation; $^{*}P < 0.001$

[a]MoCA, Montreal Cognitive Assessment, mild cognitive impairment cut-off: <24, 7 points, adjusted to the Portuguese population for all ages and years of school.

[b]HADS, Hospital Anxiety and Depression Scale, Anxiety (HADS-A) and Depression (HADS-D) subscales, pathological score if >10 points, borderline score if ranging 8 to 10 points.

[c]PSS-10, Perceived Stress Scale, score ≥20 indicative of high level of perceived stress.

of gender, age, and school years in anxiety, depression, and cognitive performance, these parameters were included in the analysis. We found a significant association between anxiety and depression ($r(64) = 0.559$; $P < 0.001$); perceived stress and anxiety ($r(64) = 0.357$; $P < 0.001$); and perceived stress and depression ($r(64) = 0.252$; $P = 0.045$). There was also a significant correlation between age and school years ($r(65) = -0.611$; $P < 0.001$); and between depression and school years ($r(64) = 0.229$; $P = 0.048$). MoCA scores were significantly associated with the number of school years (rMoCA$(64) = 0.436$; $P < 0.001$) and age (rMoCA$(64) = -0.556$; $P < 0.001$). Psychometric scores, such as anxiety, depression, and perceived stress, as well as KCCQ scores, demonstrated no association with cognitive performance.

Major adverse cardiovascular event-free survival and mortality

As shown in *Table* 3, 40% of the patients had at least one MACE during the follow-up period. From all MACE, 14.5% were CV hospitalizations, 69% were CV emergency department visits, and 15.4% were CV-related deaths. The average time for the first MACE event was 255 days. The overall mortality rate of our cohort was 13.8%; in the first year of follow-up, the mortality rate was 7.7%, and in the second year, it was 6.2%.

As previously referred on the Methods section, we used Cox regression models to search for predictors of

Table 2 Correlations between neuropsychological parameters, age, gender, and school year

Parameter	HADS-Anxiety	HADS-Depression	MoCA	PSS10	Age	Gender
HADS-Depression	0.559** (64)					
MoCA	−0.037 (63)[b]	−0.178 (63)[b]				
PSS-10	0.357** (64)	0.252* (64)	0.0112 (63)[b]			
Age	−0.042 (64)[b]	0.158 (64)	−0.556** (64)	−0.011 (65)[b]		
Gender[a]	−0.148 (64)[b]	−0.225 (64)[b]	0.17 (64)[b]	−0.061 (65)[b]	−0.114 (65)[b]	
Years of scholarity	−0.006 (64)[b]	−0.229* (64)	0.436** (64)	0.12 (64)[b]	−0.611** (65)	0.206 (65)[b]

HADS, Hospital Anxiety and Depression Scale; MoCA, Montreal Cognitive Assessment; PSS-10, Perceived Stress Scale.

$^{*}P < 0.05$.

$^{**}P < 0.001$.

[a]Gender, reference category: female.

[b]Spearman's rho.

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Table 3 Characteristics of the MACE

Characteristic Days to event	Mean (SD)
Days to MACE	255.00 (214.84)
Days to first hospitalization	267.27 (219.76)
Days to first CV hospitalization	289.00 (230.68)
Days to first ED event	193.85 (157.39)
Days to first ED CV event	300.80 (231.36)
Days to death	312.78 (195.24)
Number of events	***n*** **(%)/Mean (SD)**
MACE	26 (40.0%)/0.40 (0.49)
MACE CV hospitalizations	4 (15.4%)
MACE ED-CV	18 (69.2%)
MACE Death	4 (15.4%)
Hospitalizations	61 (100%)/0.94 (1.39)
Non elective hospitalizations	48 (78.7%)/0.74 (1.33)
CV hospitalizations	32 (52.5%)/0.49 (1.09)
ED	144 (100%)/2.22 (3.05)
ED-CV	42 (29.2%)/0.65 (1.26)
ED–non-CV	102 (70.8%)/1.55 (2.17)
	N **(Mortality rate)**
Death	9 (13.8%)

CV, cardiovascular; ED, emergency department; SD, standard deviation; MACE, major adverse cardiovascular event.

MACE-free survival. We used a stepwise forward selection method that included the following variables: age, gender, years of school, MoCA, HADAS-A, HADS-D, and KCCQ. On the univariate analysis, MoCA and KCCQ were the only variables significantly associated with MACE-free survival (*Table* 4). These two were combined on a model that was statistically significant for predicting MACE-free survival. In this model, a 1-point increase in MoCA score was associated with a decreased risk of MACE [hazard ratio (HR) = 0.906; 95% confidence interval (CI) = 0.829–0.990; $P = 0.029$] independently of the KCCQ score. While significant, the association between KCCQ score and MACE-free survival was weak (HR = 0.986; CI = 0.973–0.999; $P = 0.031$). The model did not survive correction for further addition of other variables. It is important to highlight that we used MoCA scores as a continuous variable, which makes it independent of the categorization of the clinical entity (mild CI or dementia).

We used a similar approach to search for predictors of mortality. On the univariate analysis, age and KCCQ were the only variables associated with mortality. However, KCCQ lost significance when adjusted for age. As so, age persisted as the main predictor of mortality (HR = 1.091; CI = 1.012–1.177; $P = 0.017$).

Table 4 Cox-regressions for MACE-free survival and the neuropsychological parameters scores

Model	MACE-free survival[a]	
	HR (95% CI)	*P* value
Univariable Cox regression model		
MoCA	0.894 (0.819–0.977)	0.012
KCCQ	0.982 (0.969–0.996)	0.011
Multivariable Cox regression model		
MoCA	0.906(0.829–0.990)	0.029
KCCQ	0.986 (0.973–0.999)	0.031
Final overall model ($\chi^2 = 12.220$; $df = 2$; $P = 0.002$)		

CI, confidence interval; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiovascular event; MoCA, Montreal Cognitive Assessment;.
There was no association between MACE-free survival and age ($P = 0.101$), gender ($P = 0.734$, HADS-A ($P = 0.665$), HADS-D ($P = 0.391$), and years of school ($P = 0.709$).

Health-related quality of life evaluation

Health-related quality of life was assessed by the KCCQ. Its overall summary score mean was 64.3 ± 24.7 points; the domains, 'self-efficacy' and 'knowledge', 'symptoms frequency', and 'symptoms burden', showed the higher scores (means of 87.5; 72.9 and 71.5, respectively).

To better understand the strength of the relationship between KCCQ and the other battery test scores, we performed a Pearson's correlation (*Table* 5) that demonstrated a significant correlation between KCCQ levels and anxiety ($R(65) = -0.390$), depression ($R(65) = -0.378$), and perceived stress ($R(64) = -0.333$) levels.

To determine if anxiety, depression, and perceived stress are predictors of HrQoL, we performed a multilinear regression model. As shown in *Table* 5, this model was able to explain 38.8% of the variance of the KCCQ score ($F(3.60) = 12.704$, $P < 0.001$). Also, both anxiety ($\beta = -0.326$; $P = 0.012$) and depression ($\beta = -0.309$; $P = 0.014$) scores were independently associated with worst HrQoL.

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Table 5 Inferential analysis to explore the correlation between KCCQ score and neuropsychological parameters and MACE-free survival

A. Pearson correlation coefficients between neuropsychological parameters and KCCQ score	KCCQ Pearson coefficient (*R*); (*N*)
MoCA	0.074 (64)
HADS-A	−0.390** (65)
HADS-D	−0.378** (65)
PSS-10	−0.333** (64)
Age	−0.049 (65)
Years of school	0.082 (65)

B. Multiple linear regression models between HADS-A, HADS-D, PSS-10, and KCCQ score	KCCQ score		
	B [CI 95%]	SE	Beta
HADS-A	−1.642 [−2.915;-0.369]	0.636	−0.326*
HADS-D	−1.580 [−2.828;-0.331]	0.624	−0.309*
PSS	−0.490 [−1.255;0.275]	0.382	−0.139
F.R^2 and R^2 adjusted	F(3.60) = 12.704**; 0.388; 0.358		

CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiovascular event; MLRM, Multivariate Linear Regression Model; MoCA, Montreal Cognitive Assessment; PSS-10, Perceived Stress Scale; SE, standard error.
*$P < 0.05$.
**$P < 0.001$.
[a]Adjusted for age.
The Pearson's correlation demonstrates a significant correlation between KCCQ levels and anxiety ($R(65) = -0.390$), depression ($R(65) = -0.378$) and perceived stress ($R(64) = -0.333$) levels. The MLRM was able to explain 38.8% of the variance of the KCCQ score ($F(3.60) = 12.704$, $P < 0.001$). Also, both anxiety ($\beta = -0.326$; $P = 0.012$) and depression ($\beta = -0.309$; $P = 0.014$) were independently associated with worst quality of life. On the longitudinal evaluation, KCCQ was a predictor of MACE-free survival when adjusted to age.

Discussion

In this study, we explored the value of neuropsychological assessment tools to predict events and quality of life in patients with HF. Our data show that both lower MoCA and KCCQ scores are predictors of MACE-free survival. These results are in line with other studies showing that lower scores in MoCA and KCCQ are associated with poor health outcomes in adults with HF.[27–31] A possible explanation for this finding is that lower MoCA and KCCQ scores reflect greater severity of HF and consequently worst outcome; another explanation, especially for the predictive value of MoCA, is that mild CI may be associated with poorer self-care and therapeutic compliance, although we did not explore this topic on our study. Recently, the OPERA-HF study[8] found that psychosocial variables (presence of frailty, moderate-to-severe depression, and moderate-to-severe anxiety) were independently associated with both the first and recurrent adverse events in patients with HF. In that study, the presence of CI was independently associated only with an increased risk of recurrent events.[8] However, a direct comparison with our study cannot be performed for several reasons. First, the tool used on OPERA-HF to assess cognitive performance is different from the ones herein used; second, the cohort of OPERA-HF included patients with preserved ejection fraction, and finally, the events accounted for the referred study were not only CV events, unlike the criteria used in our study that was restricted to MACE. Another noteworthy finding of our study was the very high prevalence of CI (92%). This may be explained not only by the severity of HF on our cohort (patients with reduced ejection fraction) but also by the high prevalence of alcohol consumption and low-level of academic education.

The pathophysiology of CI in HF is not completely understood,[5] but some studies suggest that the reduction in cerebral blood flow, alterations of cerebrovascular reactivity, and modification of baseline levels of blood pressure[1] play an important role. Neuroanatomical changes such as reduced regional cortical thickness,[5] smaller grey matter volume,[32] and reduction of hippocampus volume[33,34] have been well documented. Of notice, an important finding of the current study was the lack of significant association between MoCA score and clinical parameters (such as NYHA class, Pro-BNP and left ventricular ejection fraction). The same holds for the HrQoL component. The perception of patients of their own HrQoL was not associated with cognitive performance. There are controversial findings in the literature about this topic with some studies reporting a negative impact of CI in quality of life,[30] while others show no association.[31]

The present study did not find any significant association between CI and depression, anxiety, or stress, which is contrary to findings from other studies, where a consistent association between depression and cognition has been reported.[35,36] One possible explanation for this lack of association may be that in patients with HFrEF, cardiac dysfunction is the dominant cause for CI, diluting the effects of other factors such as education or depression. However, a different study design is needed to address this question (p.e. case–control study).

On our cohort, anxiety and depressive symptoms were not associated with CI or MACE but were correlated with the worst quality of life reinforcing the importance of screening and managing anxious and depressive symptoms in patients with HF. The efficacy of pharmacological and non-pharmacological strategies to treat depression is yet to be completely determined in patients with HF.[37] Further studies are needed to clarify the best approach to tackle neuropsychological disorders in these patients.

The current study presents limitations. The major limitation is the size of the cohort, although it should be highlighted that this study population represents a subgroup of patients with HFrEF under follow-up in a hospital

outpatient setting. While this brings specificity to the current study, it makes it impossible to determine if the results can be extrapolated to other populations of patients, such as those with HF with preserved or mid-range EF or who do not attend follow-up at the hospital. Another limitation was the descriptive nature of the study, which does not allow determining the mechanisms underlying the predictive value of MoCA and KCCQ scores for MACE-free survival time. Finally, external factors in patient selection may have influenced the results, such as the willingness to participate in the study.

In summary, our study concludes that the prevalence of mild CI is very high in patients with HFrEF and, of greater clinical relevance, MoCA, and KCCQ scores predict MACE-free survival. On the contrary, anxiety and depression performed poorly to predict MACE-free survival but were good predictors of quality of life in this cohort. Overall, these results highlight the importance of neuropsychological and HrQoL parameters in the management of patients with HFrEF.

Statistical analysis

A descriptive analysis was conducted. For quantitative variables, the average and standard deviation, (if normal distribution) and the median and IR (if non-normal distribution) were used. For categorical variables, the absolute and relative (%) frequencies are presented. A two-sample *t*-test was used to study the differences between provenience hospital groups and between cohorts, for quantitative variables. To study differences between groups and association between categorical variables, the χ^2 was used, or the Fisher's exact test, when one of χ^2 test assumptions was violated. Pearson's χ^2 test was used whenever possible.

To measure the strength of associations between quantitative variables, the Pearson correlation was used, or Spearman's rho if any assumption was violated.

To determine which variables predicted MACE-free survival time in this sample, we used Cox regression analysis. To determine which variables predicted KCCQ, we performed a univariate analysis followed by a multiple linear regression model.

Statistical differences were considered significant when P value < 0.05. Data were analysed using the software IBM SPSS version 24.0.

Conflict of interest

None declared.

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References

1. Bauer LC, Johnson JK, Pozehl BJ. Cognition in heart failure: an overview of the concepts and their measures. *J Am Acad Nurse Pract* 2011; **23**: 577–585.
2. Chapa DW, Akintade B, Son H, Woltz P, Hunt D, Friedmann E, Hartung MK, Thomas SA. Pathophysiological relationships between heart failure and depression and anxiety. *Crit Care Nurse* 2014; **34**: 2.
3. Vongmany F, Hickman LD, Lewis J, Newton PJ, Phillips JL. Anxiety in chronic heart failure and the risk of increased hospitalizations and mortality: a systematic review. *Eur J Cardiovasc Nurs* 2016; **15**: 478–485.
4. Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, Kutner M, Vaccarino V. Meta-analysis of mental stress—induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol* 2014; **114**: 187–192.
5. Leto L, Feola M. Cognitive impairment in heart failure patients. *J Geriatr Cardiol* 2014; **11**: 316–328.
6. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, Blazing MA, Gaulden LH, Califf RM, Krishnan RR, O'Connor CM. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004; **110**: 3452–3456.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006; **48**: 1527–1537.
8. Sokoreli I, Pauws SC, Steyerberg EW, de Vries GJ, Riistama JM, Tesanovic A, Kazmi S, Pellicori P, Cleland JG, Clark AL. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. *Eur J Heart Fail* 2018; **20**: 689–696.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200.

10. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007; **9**: 440–449.
11. Alagiakrishnan K, Mah D, Ahmed A, Ezekowitz J. Cognitive decline in heart failure. *Heart Fail Rev* 2016; **21**: 661–673.
12. Currie K, Rideout A, Lindsay G, Harkness K. The association between mild cognitive impairment and self-care in adults with chronic heart failure. *J Cardiovasc Nurs* 2015; **30**: 382–393.
13. Hawkins MA, Gathright EC, Gunstad J, Dolansky MA, Redle JD, Josephson R, Moore SM, Hughes JW. The MoCA and MMSE as screeners for cognitive impairment in a heart failure population: a study with comprehensive neuropsychological testing. *Heart Lung* 2014; **43**: 462–468.
14. Cameron J, Worrall-Carter L, Page K, Stewart S, Ski CF. Screening for mild cognitive impairment in patients with heart failure: Montreal cognitive assessment versus mini mental state exam. *Eur J Cardiovasc Nurs* 2013; **12**: 252–260.
15. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *JAGS* 2015; **53**: 695–69920.
16. Freitas S, Simões MR, Martins C, Vilar M, Santana I. Estudos de adaptação do *Montreal Cognitive Assessment* (MoCA) para a população portuguesa. *Avaliação Psicológica* 2010; **9**: 345–357.
17. Green PC, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000; **35**: 1245–1255.
18. Nave-Leal E, Pais-Ribeiro J. Estudo de validação da versão portuguesa do Kansas City Cardiomyopathy Questionnaire. *Actas do 7° congresso nacional de psicologia da saúde* 2008; 191–194.
19. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**: 385–396.
20. Trigo M, Canudo N, Branco F, Silva D. Estudo das propriedades psicométricas da Perceived Stress Scale (PSS) na população portuguesa. *Psychologica* 2010; **53**: 353–378.
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **77**: 361–370.
22. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychol Health Med* 2007; **12**: 225–237.
23. Freitas S, Simões MR, Alves L, Santana I. Montreal Cognitive Assessment (MoCA): normative study for the Portuguese population. *J Clin Exp Neuropsychol* 2011; **33**: 989–996.
24. Convenção para a Protecção dos Direitos do Homem e da Dignidade do Ser Humano Face às Aplicações da Biologia e da Medicina: Convenção sobre os Direitos do Homem e da Biomedicina (Conselho da Europa 1997). Resolução da Assembleia da República n.° 1/2001, Diário da República – I Série A, n° 2, 3 de Janeiro de 2001. https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98 accessed 01 July 2020.
25. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: CIOMS; 2013.
26. European Medicines Agency, Good clinical practice. 2000; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004343.pdf accessed 20 January 2020.
27. Pereira VH, Costa PS, Santos NC, Cunha PG, Correia-Neves M, Palha JA, Sousa N. Adult body height is a good predictor of different dimensions of cognitive function in aged individuals: a cross-sectional study. *Front Aging Neurosci* 2016; **8**: 217.
28. Huynh QL, Negishi K, Blizzard L, Saito M, De Pasquale CG, Hare JL, Leung D, Stantone T, Sanderson K, Venna AJ, Marwick TH. Mild cognitive impairment predicts death and readmission within 30 days of discharge for heart failure. *Int J Cardiol* 2016; **221**: 212–217.
29. Gathright EC, Fulcher MJ, Dolansky MA, Gunstad J, Redle JD, Josephson R, Moore SM, Hughes JW. Cognitive function does not impact self-reported health-related quality of life in heart failure patients. *J Cardiovasc Nurs* 2016; **31**: 405–411.
30. Pressler SJ, Subramanian U, Kareken D, Perkins SM, Gradus-Pizlo I, Sauvé MJ, Ding Y, Kim J, Sloan R, Jaynes H, Shaw RM. Cognitive deficits and health-related quality of life in chronic heart failure. *J Cardiovasc Nurs* 2015; **25**: 189–198.
31. Gallagher R, Sullivan A, Burke R, Hales S, Sharpe P, Tofler G. Quality of life, social support and cognitive impairment in heart failure patients without diagnosed dementia. *Int J Nurs Pract* 2016; **22**: 179–188.
32. Alosco ML, Brickman AM, Spitznagel MB, Narkhede A, Griffith EY, Cohen R, Sweet LH, Josephson R, Hughes J, Gunstad J. Reduced gray matter volume is associated with poorer instrumental activities of daily living performance in heart failure. *J Cardiovasc Nurs* 2016; **31**: 31–41.
33. Woo MA, Ogren JA, Abouzeid CM, Macey PM, Sairafian KG, Saharan PS, Thompson PM, Fonarow GC, Hamilton MA, Harper RM, Kumar R. Regional hippocampal damage in heart failure. *Eur J Heart Fail* 2015; **17**: 494–500.
34. Suzuki H, Matsumoto Y, Ota H, Sugimura K, Takahashi J, Ito K, Miyata S, Furukawa K, Arai H, Fukumoto Y, Taki Y, Shimokawa H. Hippocampal blood flow abnormality associated with depressive symptoms and cognitive impairment in patients with chronic heart failure. *Circ J* 2016; **80**: 1773–1780.
35. Garcia S, Spitznagel MB, Cohen R, Raz N, Sweet L, Colbert L, Josephson R, Hughes J, Rosneck J, Gunstad J. Depression is associated with cognitive dysfunction in older adults with heart failure. *Cardiovasc Psychiatry Neurol* 2011; **2011**: 368324.
36. Sohani ZN, Samaan Z. Does depression impact cognitive impairment in patients with heart failure? *Cardiol Res Pract* 2012; **2012**: 524325.
37. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol* 2010; **56**: 692–699.