and gnomAD population databases identified no mutation carriers, indicating a very low allele frequency in control populations. *In silico* studies with the RaptorX program showed that the affected proline residue (Pro1424) participates in hydrogen bonds required for the formation of the calcium binding site in this region (epidermal growth factor [EGF] like domain 24). The substitution of this proline by serine would alter the site and cause protein misfolding and disrupted function (Figure 1B).[3]

A complete familial analysis (Figure 1A) detected the c.4270C >T mutation in 9 family members manifesting variable signs of MS (Table 1). Aortic root dilatation was reported only in the probands and patient V.10, and the most frequent cardiovascular finding was mitral valve prolapse. Myopia > 3 diopters was recorded in 2 patients, and none of the patients had ectopia lentis. Almost all patients had skeletal alterations. Most had scoliosis, flat foot deformity, or above-normal height, whereas wrist or thumb signs were found in only 3 patients. No pathological findings were recorded in noncarrier relatives.

Together, these data indicate familial cosegregation of the mutation with variable clinical manifestations. This behavior has been described previously for pathogenic mutations of this gene,[4] and complete familial analyses should therefore be conducted at referral centers to obtain a better understanding of the phenotypic behavior of these gene variants.[5] All the patients apart from V.4, IV.8, and IV.9 can be categorized as having the MASS phenotype because they do not meet one of the revised Ghent criteria for MS.[1] Most of the carriers are young, which might explain the general absence of cardinal manifestations such as aortic root dilatation and ectopia lentis. Trans-acting mutations in *FBN1* have been proposed to play a modifying role,[4] and a recent study demonstrated that cis-regulatory variants can be present in the same allele as a disease-causing mutation, providing a possible explanation for the variable penetrance and expressivity observed in mutation carriers.[6] Although c.4270C >T mutation carriers showed no signs of dural ectasia, spina bifida occulta was detected in 2 brothers (V.4 and V.5).

Another mutation affecting the same amino acid has been identified in several MS patients. However, the Pro1424Ala (g.48764814G >C) mutation has not been examined by cosegregation analysis, and this variant has been identified in 54 out of 277 166 individuals in gnomAD control populations, raising doubts about its pathogenicity.

In summary, the clinical and genetic study of this family confirms the association of the p.Pro1424Ser genetic variant in FBN1 with the development of the MASS phenotype and MS. Although the phenotypes generated by this genetic variant vary widely and are sometimes mild, it is important to monitor aortic diameter regularly in carriers of this mutation because it can be associated with aneurysm and dissection.

CONFLICTS OF INTEREST

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Palliative Care Needs in Heart Failure. A Multicenter Study Using the NECPAL Questionnaire

Necesidad de cuidados paliativos en insuficiencia cardiaca: estudio multicéntrico utilizando el cuestionario NECPAL

To the Editor,

Palliative care (PC) support has been broadened in the last few years to include patients with advanced-stage disease. Although heart failure (HF) has a poor prognosis, very few patients are actually included in PC programs[1] due to a lack of integration of PC in HF management and its unpredictable clinical trajectory. Currently, prognostic markers in HF are highly focused on heart disease and have major limitations, since they do not include multimorbidity or other parameters such as dependence and frailty. PC involves support of physical, emotional and spiritual needs to both patients and their families and is not limited to end-of-life care. Nowadays, PC in HF is an unresolved challenge and identifying those patients who might require some type of palliative intervention is mandatory. The aim of our study was to evaluate theoretical PC requirements in HF by a simple scale that integrates predictive variables of HF severity with palliative

Table 1

Demographic, Clinical, and Pharmacological Treatment Data of the Study Population

Characteristics	Total N = 922	NECPAL-HF − n = 625	NECPAL-HF + n = 297	P
Age, y	69.3 ± 12.2	66.4 ± 11.8	75.3 ± 10.8	< .001
Women, %	274 (29.7)	164 (26.2)	110 (37)	.001
Etiology, %				.13
Ischemic heart disease	409 (44.4)	279 (44.6)	130 (43.8)	
Dilated cardiomyopathy	156 (16.9)	118 (18.9)	38 (12.8)	
Hypertensive cardiomyopathy	102 (11.1)	62 (9.9)	40 (13.5)	
Alcoholic cardiomyopathy	68 (7.4)	45 (7.2)	23 (7.7)	
Drug-related (medication) cardiomyopathy	89 (9.7)	61 (9.8)	28 (9.4)	
Valvular disease	48 (5.2)	27 (4.3)	21 (7.1)	
Other	50 (5.4)	55 (5.3)	17 (5.7)	
Heart failure duration, mo	44 [14-99]			
LVEF, %	41.4 ± 14	41.4 ± 13	41.6 ± 15.9	.84
NYHA functional class, %				< .001
I	56 (6.1)	49 (7.8)	7 (2.4)	
II	685 (74.3)	521 (83.4)	164 (55.2)	
III	158 (17.1)	47 (7.5)	111 (37.4)	
IV	23 (2.5)	8 (1.3)	15 (5.1)	
Comorbidities, %				
Hypertension	585 (63.4)	365 (58.6)	220 (74.1)	< .001
Diabetes mellitus	351 (38.1)	214 (34.2)	137 (46.1)	.001
Treatments, %				
ACEI/ARB	662 (71.8)	502 (80.3)	160 (53.9)	< .001
Beta-blockers	801 (86.9)	569 (91)	232 (78.1)	< .001
Loop diuretics	703 (76.2)	445 (71.2)	258 (86.9)	< .001
Aldosterone receptor antagonists	460 (49.9)	328 (52.5)	132 (44.4)	.02

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. Data are expressed as mean ± standard deviation, median [P25–P75], or absolute number (percentage).

approach elements according to patient needs; secondarily, we assessed its prognostic value in predicting mortality.

The NECPAL CCOMS-ICO questionnaire[2] is a validated easy-to-use tool that identifies patients with advanced chronic palliative needs due to any cause. It includes 4 blocks: *a)* surprise question (SQ) for clinicians/nurses: "Would you be surprised if this patient died within 12 months?"; *b)* request for PC care by health professionals or the patient/family; *c)* generic clinical markers of health status severity and frailty (nutritional/functional markers, emotional distress, comorbidities); and *d)* disease-specific clinical prognostic markers for oncological, pulmonary, heart, neurological, liver, and renal diseases or dementia. For this study, we used the chronic heart disease-specific markers (from now on, NECPAL-HF). A patient was considered NECPAL-HF + when the SQ response was 'No' and ≥ 1 blocks were positive (at least 1 positive answer in blocks 2 and/or 3, or at least 2 positive answers in block 4).

All consecutive ambulatory patients attended in the HF clinics of 3 university hospitals during a 4-month period were enrolled. The NECPAL-HF questionnaire was applied by a nurse and/or a physician at a scheduled visit. Each patient's vital status was assessed at 1 year via hospital records, other hospital records, or by contacting the patient's relatives. Data were verified using the local health system databases. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 922 patients were included. The patients' demographic, clinical, and treatment data are shown in Table 1. One third of the patients included were NECPAL-HF + (32.1%). NECPAL-HF + pati-

ents were older, predominantly women, mainly in New York Heart Association (NYHA) functional class III, and with higher diuretic treatment. Clinicians and nurses answered 'No' to the SQ in 35.2% of cases. Nevertheless, only 6.1% of patients had at least 1 positive answer in block 2 (4.1% by patients/families and 4.4% by clinician request). This finding may reflect the difficulty and extended avoidance of topics related to PC and/or death in noncancer patients in our environement. By contrast, 70.5% of patients had at least 1 positive answer in block 3 (having ≥ 2 concomitant diseases was the most usual criteria). Regarding block 4 (HF-specific items), only 16.9% had ≥ 2 positive indicators among the 6 evaluated by the questionnaire: "left ventricular ejection fraction (LVEF) < 30% or pulmonary artery pressure > 60 mmHg" in 18.5% of the patients, and "NYHA functional class III/IV or severe valve disease or inoperable coronary disease" in 24.4%.

Although the tool was not designed to predict mortality, we also analyzed the association between NECPAL-HF + and prognosis. Cohort mortality at 1 year was 9.7% and was significantly higher in NECPAL-HF + patients (21.9% vs 3.8% in NECPAL-HF -; *P* < .001). Indeed, 73% of deaths occurred in NECPAL-HF + patients. The area under the ROC curve (AUC) for the NECPAL-HF + questionnaire and SQ + for predicting all-cause 1-year mortality were 0.73 (95% confidence interval [95%CI] 0.68-0.78) and 0.74 (95%CI 0.69-0.79), respectively. Table 2 (top) shows the hazard ratios of NECPAL-HF blocks regarding 1-year mortality in a multivariate binomial regression analysis. Remarkably, block 3, which was the most prevalently positive, showed the lowest prognostic value. The highest prognostic significance was found

Table 2

Multivariate Binomial Regression Analyses for 1-year Mortality

	HR	[95%CI]	P
NECPAL components			
Surprise question +	5.04	[2.77-9.15]	< .001
Block 2 +	2.91	[1.54-5.51]	.001
Block 3 +	1.27	[0.64-2.21]	.49
Block 4 +	1.86	[1.10-3.13]	.02
NECPAL-HF plus covariates			
Age	1.01	[0.99-1.04]	.35
Sex	0.65	[0.37-1.15]	.14
Ischemic etiology	0.84	[0.50-1.39]	.49
NYHA class	2.75	[1.87-4.06]	< .001
LVEF	1.00	[0.98-1.02]	.98
Hypertension	0.87	[0.50-1.50]	.61
Diabetes mellitus	1.77	[1.08-2.80]	.02
NECPAL-HF +	4.20	[2.41-7.32]	< .001

95%CI, 95% confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

for the SQ, followed by request for PC care. Indeed, on multivariate regression analysis with other covariables, NECPAL-HF + remained independently associated with 1-year all-cause death (hazard ratio [HR] 4.20 [95%CI 2.41-7.32], P < .001), together with NYHA functional class and the presence of diabetes mellitus (Table 2, bottom).

No data on the NECPAL-HF questionnaire has been reported previously. The main result of our study was that one third of HF outpatients might require some type of palliative intervention when a tool that includes criteria of severity and extreme frailty is used, even considering that most were stable patients, in NYHA functional class II, had HF with mid-range ejection fraction, and were relatively young. This finding suggests the need for a holistic medical and social approach to the management of these patients. Secondarily, we found a reasonable predictive capacity of the tool for 1-year mortality (AUC 0.73), the predictive negative value being the most robust finding (96.2). Most of our patients were NECPAL-HF + due to block 3 (severe and extreme frailty criteria), far ahead of patients with positive specific severity HF items (block 4) or request for PC request (block 2), although this block 3 showed the lowest prognostic power. The SQ has been previously evaluated in many settings. In a recent meta-analysis that included 17 cohorts with heterogeneous conditions (cancer, renal failure and end-stage heart or lung disease) the SQ was worse at discriminating patients with noncancer illness (AUC 0.77) than patients with cancer (AUC 0.83).[3] This AUC in noncancer patients was similar to that in our study (0.74).

In conclusion, the high prevalence found in our study for the need to receive PC suggests that a palliative approach should be implemented in multidisciplinary HF clinics to improve HF care, and that the evaluation of such patients should include elements such as comorbidity, functional and nutritional markers and frailty, beyond classic prognostic factors in HF. Further studies are needed to define how and when PC interventions in HF programs should be initiated, since the PAL-HF study[4] showed the benefits of a longitudinal PC intervention on quality of life, emotional distress, and spiritual well-being compared with usual care.

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