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Role of biological and non biological factors in congestive heart failure mortality: PREDICE-SCORE: A clinical prediction rule

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Abstract

Background: *Congestive heart failure (HF) is a chronic, frequent and disabling condition but with a modifiable course and a large potential for improving. The aim of this project was to develop a clinical prediction model of biological and non biological factors in patients with first diagnosis of HF that facilitates the risk-stratification and decision-making process at the point of care.*

Methods and Results: *Historical cohort analysis of 600 patients attended at three tertiary hospitals and diagnosed of a first episode of HF according Framingham criteria. There were followed 1 year. We analyzed sociodemographic, clinical and laboratory data with potential prognostic value. The modelling process concluded into a logistic regression multivariable analysis and a predictive rule: PREDICE SCORE. Age, dependency for daily basic activities, creatinine clearance, sodium levels at admission and systolic dysfunction diagnosis (HF with left ventricular ejection fraction < 40%) were the selected variables. The model showed a c-statistic of 0.763. PREDICE Score, has range of 22 points to stratifications of 1-year mortality.*

Conclusions: *The follow-up of 600 patients hospitalized by a first episode of congestive HF, allowed us to obtain a predictive 1 year mortality model from the combination of demographic data, routine biochemistry and easy handling social and functional variables at the point of care. The variables included were non-invasive, undemanding to collect, and widely available. It allows for risk stratification and therapeutical targeting and may help in the clinical decisions process in a sustainable way.* (Cardiol J 2012; 19, 6: 578–585)

Key words: heart failure, systolic dysfunction, prognosis, predictive rules

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Introduction

Heart failure (HF) is a disease known to progress with high morbidity and mortality [1, 2]. Epidemiological studies have shown that HF patients suffer a significant deterioration in their quality of life and progress worse than many types of cancer [3].

The prognosis for patients diagnosed as having HF remains poor. In 2002, risk adjusted 1-year mortality was 27.5% (95% CI 27.1–27.9), more than 3 times higher than for age and sex matched patients [1].

However it is a clinical entity with a modifiable course and with high potential for control and health status improvement. The management of chronic diseases has become a need in health systems so they are already implementing health initiatives and strategies, which are profitable and sustainable and aimed at improving patient care [4, 5].

Related to HF it has been demonstrated that disease management programmes in HF can reduce mortality and readmission, optimizing medication, providing education, coordinating care, and facilitating self-care as recommended in international guidelines [6–9].

For patients with HF it is possible to make a prognostic estimation from parameters that are easy for the clinician to obtain and transforming them in a clinical prediction rule at point of care using exclusively clinical, biochemical, personal and social parameters acquired from anamnesis and patient exploration [10].

Most of the predictive models described for patients with HF are mainly based on constitutional aspects: (age [10–12], gender [12], body mass index [13, 14]), clinical data detected through exploration [15, 16], biochemical markers [10, 17, 18], kidney function impairment parameters [10, 19–21], hyponatremia [17, 22, 23], electrocardiographic alterations (QRS prolongation, QRS low voltage, atrial fibrillation) [24], the findings in the cardiac function test as echocardiogram (left ventricular ejection fraction [LVEF] < 45%) [20, 25, 26], left atrial diameter or right ventricle dysfunction, New York Heart Association functional classification (NYHA) [10, 11, 18, 20, 27], alteration of the 6-minute walk test [28] or associated diseases, such as hypertension, chronic obstructive pulmonary disease, diabetes or kidney disease [10–12, 18, 21, 22, 29–31].

Many of them are complex to undertake at the point of care while ignoring something crucial for the improvement of patient clinical evolution such as, the patient's functioning and social support, as components of prognostic evolution and thus as therapeutic targets. In fact, social aspects are given scant consideration in the trials as possible predictive factors of mortality [32, 33] and rehospitalization [34, 35].

Very few studies have evaluated specifically their impact in cardiovascular mortality [36, 37]. In spite of this, it is plausible to think that personal functioning and social support are prognostic factors, which are usually ignored but which would have a great potential for action in individuals with HF and even being incorporated in clinical prediction rules.

So, the main objective of this study was to develop a practical and user-friendly clinical prediction algorithm of biological and non biological factors in naïve patients admitted to hospital after a first episode of chronic HF, PREDICE-score. In order to facilitate the decision-making process and help in risk stratification for immediate care and design of long-term strategies for secondary prevention. The outcome chosen to test the predictive skills of the involved factors was mortality at 1 year.

Methods [10, 18]

Study design

This observational, historical cohort study was conducted at three tertiary care hospitals with large dependent health districts (over 500.000 inhabitants), the Hospital 12 de Octubre of Madrid (Spain), the Rocio Hospital of Seville (Spain) and the Valme Hospital of Seville (Spain).

The study population consisted of patients at study hospitals that involved emergency admission with HF (following Framingham criteria) and aged over 17 years old, between 2003 and 2006, both years included. Inclusion criteria were: patient treated at the study center between 01/01/2003 and 31/12/2006, with a primary diagnosis of HF, over 18-year-old, residents in the area of reference of the study center. Exclusion criteria: those with HF as a complication after admission. Patients were followed up for 1 year from the time of inclusion. Investigators retrospectively acquired all the clinical information from inpatient medical records and considered 1 year follow-up information through outpatient medical records.

The study was approved by the Ethics Committee of the leader hospital and performed in accordance with Good Clinical Practices criteria.

Protocol study included patient's related information: demographic data; clinical data, previous cardiovascular risk factors, previous cardiovascu-

lar events, previous cardiovascular and non-cardiovascular significant diseases; subtype of ischemic congestive HF, based on Framingham classification; therapy related data after first-ever ischemic congestive HF episode and findings of ultrasonography, scintigraphy and coronagraphy; sociodemographic and psychosocial variables examined: social and family support [32]: home environment was analyzed, that is, if the patient lived alone, with family or at a care home, regardless of the degree of formal support received. Patient's autonomy: the degree of autonomy of the patient was evaluated and also the dependence for basic activities [38] and for instrumental activities [39].

Statistical analysis

Qualitative variables are expressed as absolute frequencies and percentages. Continuous variables are described using mean, median, standard deviation and range. Firstly, significant risk factors for congestive HF mortality were identified using χ^2 test in case of qualitative variable. In other cases, T-Student test or nonparametric Mann-Whitney test were used depending on variable normality. Secondly, a multivariate analysis of significant risk factors of congestive HF identified in the bivariate analysis, as well as other risk factors that we considered clinically relevant, was performed using a logistic regression. Odd ratios (OR) and 95% confidence intervals (CI) were calculated for each risk factor.

For the validity of the model's estimations, Hosmer-Lemeshow test was used and in the same way, the area under the receiver operating characteristic (ROC) curve was calculated to evaluate the performance (predictive ability) of the regression model.

The logistic regression model was converted to a more user-friendly integer score predicting an individual's probability of mortality within 12 months. With each quantitative factor grouped into categories, an individual score increases by an integer amount for each level above the lowest category. Each integer amount is a rounding of the exact coefficient obtained from the logistic regression model. A 0 score should mean that a person is at very low risk and a 22 score should mean that the individual is at very high risk. This risk score was based on increasing categories of probability of death, based on the methodology of risk score function implemented in the Framingham study [40]. All the analyses were considered to be significant at a p-value < 0.05. All statistical analyses were carried out using STATA/SE 10 software.

Results

Descriptive study by 1-year mortality groups

The mean age of the patients was 73.5 ± 12.3 years and 50.8% were female. There were 98 deaths amongst the study population (n = 600), which means an overall mortality rate of 16.3%, with no statistically significant differences by sex (16.27% women, 16.39% male; p = 0.968). Table 1 describes and compares the baseline demographic characteristics; clinical, social, analytical data and pharmacological treatment, depending on the outcome observed annually. Comparison was made between the patients who died and those who did not. Patients who died the year following the HF diagnostic, had a creatinine clearance value which was statistically significantly lower, 57.2 ± 32.16 vs. 76.47 ± ± 39, p = 0.000.

The most frequent diagnosed type of HF was diastolic HF, which affected 74.5% of the study sample. The presentation of systolic HF was statistically significantly higher in the deceased group (36.3%) compared to those who did not die 22.1% (p = 0.000); 16,5% of patients had ischemic cardiopathy, 29.5% had atrial fibrillation and 26.6% had associated valvulopathies. The outcome observed at end of 1 year did not differ significantly regardless associated cardiovascular diseases.

Taking into account the pharmacological treatment used for HF, in the deceased group, were indicated significantly less ACE inhibitors (42.7% vs. 56.94%; p = 0.01), beta-blockers (19.9% vs. 33.53%; p = 0.008) and oral anticoagulants (23.5% vs. 35.9%; p = 0.018). There were no differences between study groups for the rest of the pharmacological groups.

The results obtained from the non-biological variables evaluated are presented in Table 2, where it is shown that mortality is superior in patients who were dependent for instrumental and basic activities without influence of social support.

Predictive 1-year mortality model for heart failure. The results of independent prognostic factors of 1-year mortality for patients with HF identified in the multivariable analysis are included in Table 3. Within the group of biological variables, the following showed to be independent predictors: age, creatinine clearance and sodium levels at admission, systolic dysfunction diagnosis (HF with LVEF < 40%). Amongst the social variables, the most important were functional dependence for basic daily activities. The Figure 1 showed ROC curve of the predictive 1-year mortality model for HF.

Table 1. Basal biological characteristics of overall population study and comparison between outcomes at 1 year after discharge in patients with heart failure (HF).

Biological characteristic	All (n = 600)	Death (n = 98)	Non death (n = 502)	P
Demographics				
Age [years]	73.57 ± 12.32	78.06 ± 9.88	72.69 ± 12.57	0.000
Male	295 (49.17%)	48 (48.97%)	247 (49.20)	0.968
Female	305 (50.79%)	50 (51.02%)	255 (50.79%)	
Comorbidity				
Ischemic cardiopathy	98 (16.33%)	79 (15.74%)	19 (19.39%)	0.371
Atrial fibrillation	177 (29.50%)	27 (27.55%)	150 (29.88%)	0.664
Valvulopathy	160 (26.67%)	32 (32.65%)	128 (25.50%)	0.143
Pathophysiological diagnosis*				
Systolic HF	106 (23.93%)	21 (36.84%)	85 (22.02%)	0.034
Diastolic HF	305 (68.85%)	31 (54.39%)	274 (70.98%)	
Unknown HF	32 (7.22%)	5 (8.77%)	27 (6.99%)	
NYHA scale				
Class I. Without limiting the habitual physical activity	203 (33.83%)	25 (25.50%)	178 (35.50%)	0.144
Class II. Slight limitation of physical activity routine	224 (37.33%)	42 (42.90%)	182 (36.30%)	
Class III. Marked limitation of physical activity. No dyspnea at rest	136 (22.67%)	27 (27.60%)	109 (21.70%)	
Class IV. Dyspnea at rest	37 (6.17%)	4 (4.17%)	33 (6.60%)	
Urgency exploration:				
DBP [mm Hg]	78.53 ± 18.55	73.71 ± 17.52	79.47 ± 18.62	0.005
SBP [mm Hg]	143.08 ± 31.35	136.71 ± 30.58	144.31 ± 31.38	0.029
Glucemy [mg/dL]	158.75 ± 81.66	171.04 ± 98.55	156.35 ± 77.83	0.166
Total cholesterol [mg/dL]	175.56 ± 43.99	168.12 ± 46.16	176.98 ± 43.48	0.097
Sodium [mEq/L]	138.09 ± 4.60	137.20 ± 5.23	138.26 ± 4.46	0.037
Potasium [mEq/L]	4.33 ± 0.69	4.47 ± 0.81	4.30 ± 0.66	0.057
Cretinine clearance rate [mL/min]	73.52 ± 38.62	57.22 ± 32.16	76.70 ± 39	0.000
Hemoglobin [g/dL]	12.84 ± 2.26	12.06 ± 2.43	12.99 ± 2.20	0.000
Total lymphocytes/mm^3	1661.45± 1148.97	1583 ± 1125.79	1676.83 ± 1153.91	0.459
Signs and symptoms:				
Crepitants	430 (71.67%)	79 (80.61%)	351 (69.92%)	0.032
Third heart sound	41 (6.83%)	9 (9.18%)	32 (6.37%)	0.313
Jugular ingurgitation	139 (23.17%)	22 (22.45%)	117 (23.31%)	0.854
Hepathomegalia	76 (12.67%)	14 (14.29%)	62 (12.35%)	0.598
Hepathojugular reflux	29 (4.83%)	5 (5.10%)	24 (4.78%)	0.892
Lower limb oedema	379 (63.16%)	72 (73.47%)	307 (61.16%)	0.021
Drug treatment:				
ACE inhibitors	328 (54.67%)	41 (41.80%)	287 (57.20%)	0.005
Beta-blockers	188 (31.33%)	19 (19.40%)	169 (33.70%)	0.005
ARBs	104 (17.33%)	14 (14.30%)	90 (17.90%)	0.437
Calcium antagonists	951 (5.83%)	16 (16.30%)	79 (15.70%)	0.884
Antiagregants	263 (43.83%)	39 (39.80%)	224 (44.60%)	0.379
Oral anticoagulants	203 (33.83%)	23 (23.50%)	180 (35.90%)	0.018
Digoxine	152 (25.33%)	20 (20.40%)	132 (26.29%)	0.220
Diuretics	439 (73.17%)	69 (70.40%)	370 (73.70%)	0.500
Statins	150 (25.00%)	18 (18.36%)	132 (26.29%)	0.097
Isosorbide mononitrate	70 (11.67%)	14 (14.28%)	56 (11.15%)	0.373

*Echocardiogram available in 443 cases; Creatinine clearance rate estimated by MDRD equation; NYHA — New York Heart Association; DPB — diastolic blood pressure; SBP — systolic blood pressure; ACE — angiotensin-converting enzyme; ARBs — angiotensin receptor blockers

Table 2. Basal non-biological characteristics of overall population study and comparison between outcomes at 1 year after discharge in patients with heart failure.

Social characteristic	All (n = 600)	Death (n = 98)	Non death (n = 502)	P
Independent basic daily activities:				
Yes	537 (89.50%)	72 (73.50%)	465 (92.60%)	0,000
No	63 (10.50%)	26 (26.50%)	37 (7.40%)	
Independent instrumental activities:				
Yes	521 (86.83%)	67 (68.40%)	454 (90.40%)	0,000
No	79 (13.17%)	31 (31.60%)	48 (9.60%)	
Total dependent:				
Yes	50 (8.33%)	21 (21.88%)	29 (5.75%)	0,000
No	550 (91.67%)	77 (78.60%)	473 (94.25%)	
Social and family support:				
Live alone	124 (20.67%)	20 (20.40%)	104 (20.71%)	0,951
Live with family	416 (69.33%)	69 (70.40%)	347 (69.12%)	
Live in care center	60 (10.00%)	9 (9.18%)	51 (10.15%)	

Table 3. Multivariate analysis predictor of mortality at 1 year in patients with heart failure (n = 600).

			95% confidence interval	
	OR	P	Lower	Upper
Age	1.03	0.028	1.003	1.067
Creatinine clearance rate at hospital admission [mL/min]*	0.988	0.043	0.97	0.99
Dependent basic daily activities	2.02	0.039	1.03	3.96
Pathophysiological diagnosis (systolic vs. diastolic)	2.67	0.004	1.36	5.23
Sodium	0.92	0.028	0.86	0.991

*Creatinine clearance estimated by MDRD equation; Statistic C: 0.763; R^2 Negelkerke: 0.157; R^2 Cox and Nell: 0.084; Correctly classified: 87%

Clinical prediction rule table for risk stratification. Table 4 shows an user-friendly table for HF risk of death at 1 year stratification. It is composed of 5 variables with entries for scoring with adjusted weights.

Discussion

Our results confirm the prognostic value for HF outcome of factors described previously such as age, systolic dysfunction, creatinine clearance rate and sodium levels, and provides strong evidence for new prognostic factors as functional autonomy for daily activities.

Age has an influence in the prognosis, thus in patients under 50-year-old, the mortality rate was 4.9%, it was 12.3% for 50–75 years patients and 20.3% for those over 75. The risk of death after 1 year increased 3% for every year lived OR 1.03 (95% CI 1.003–1.067), and agrees with other studies [41]. The overall mortality observed in patients

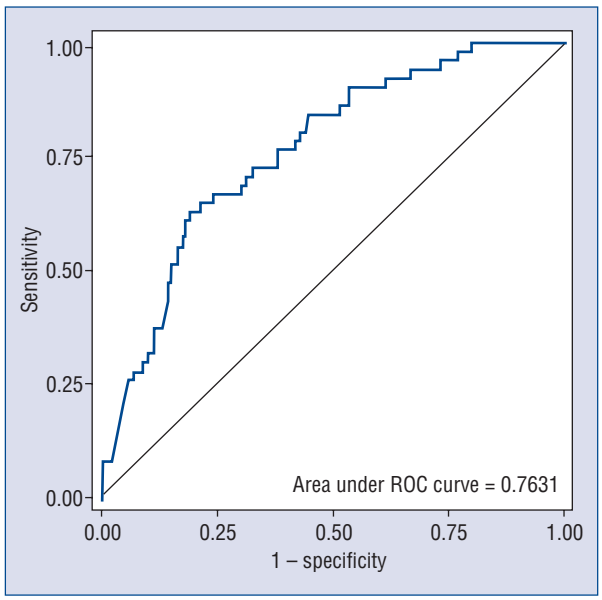

Figure 1. Receiver operating characteristic curve for predictive 1-year mortality model for heart failure.

Table 4. Clinical prediction rule PREDICE-SCORE.

						Score	Probability of death
Age [years]	**< 50**	**50–59**	**60–69**	**70–79**	**≥ 80**	0	< 10%
	0 points	1 points	2 points	3 points	5 points	1–2	10–20%
Serum creatine clearance	**< 77**	**77–100**	**100–150**	**150–200**	**> 200**	3–4	20–30%
(admission hospital)	9 points	7 points	6 points	4 points	0 points	5	30–40%
Dependent basic daily activities	**YES**	**NO**				6–7	40–55%
	2 points	0 points				8–10	55–75%
Physiopathology diagnosis	**Systolic**	**Diastolic**				11–13	75–85%
(systolic vs. diastolic)	3 points	0 points				14–17	85–95%
Sodium	**< 135**	**135–145**	**> 145**			18–22	> 95%
	3 points	0 points	3 points				

with a history of ischemic cardiopathy, atrial fibrillation and valvulopathies was 19.4%, 15.2% and 20%, respectively. No significant differences were found with alive patients group. These entities were not associated with outcome. These findings disagree with the results obtained by other studies [18, 21, 22, 27, 33], but notice that patients could be in a different stage of evolution.

Pathophysiologic diagnosis. It can also be seen that systolic dysfunction is more frequent in the group that dies (36.8% vs. 22.16%), so the probability of dying in the following year after diagnosis is 2.67 times higher for the subjects with systolic dysfunction (LVEF < 40%, OR 2.67, 95% CI 1.36––5.23; p = 0.004). It has been noted that the presence of ventricular dysfunction increases intrahospital mortality [26] both at short term (30 days) [22] and at long term (1 year) [20, 22, 27]. Although some studies show that patients with systolic dysfunction have a worse prognosis [26, 42, 43], others have not found differences in survival between the patients with or without ventricular dysfunction [40, 44, 45]. This discrepancies in the prognostic effect of LVEF could be due again to different selection criteria or disease stage of patients involved [44, 45]. It is known that mortality increases for all causes when LVEF decreases [20].

Kidney function: Creatinine clearance and sodium levels. As in other studies [23, 46, 47], the presence of kidney failure and hyponatremia were associated with a worse prognosis. At 1 year after the diagnosis of HF, those who die had a mean creatinine clearance significantly lower: 57.2 ± 32.16 vs. 76.7 ± 39 mL/min. Additionally, in our study creatinine clearance and sodium levels have been demonstrated to be independent factors of good prognosis, showing that for every unit increase of these parameters the risk of mortality can be reduced by 2% (OR 0.988, 95% CI 0.97–0.99) and by 8% (OR 0.92, 95% CI 0.86–0.991), respectively.

Signs and symptoms at admission. The presence of crepitants and lower limb edemas at the moment of exploration in the first examination, even high 80.6% vs. 73.4%, respectively, did not change the prognosis. Surprisingly no sign or symptom was identified as a negative prognosis factor, such tachypnea, hypotension or tachycardia, seen also in other studies [1, 15, 16], and including NYHA functional class at admission. Although there is controversies among studies [20].

Pharmacologic treatment. ACE inhibitors and beta-blockers, as well as anticoagulants, were proportionally less used in the group that died (42% received ACE inhibitors and 19.7% received beta--blockers), but without prognostic value for outcome.

Independence for daily activities and instrumental activities. The presence of dependence for the basic daily activities was highly associated with mortality (OR 2.02, 95% CI 1.03–3.96), emerging as a potent and not mentioned independent prognostic factor for HF. Worse basal conditions could explain this fact, but in our study, the presence of comorbidity does not correlate to the degree of functional autonomy of patients. The degrees of dependence will mandatory drive the needs for care in these patients.

Social and family support. However the degree of social and familiar support was not associated to the prognosis at 1 year in our study. Very few studies included home living situation, social support, and follow-up visits, among patients with HF as a matter of study. Only it was found associated with readmissions [16, 34]. In acute myocardial infarction, living alone has been described as

a prognostic factor of mortality [33]. Different scales for structural or functional measurement were used in mentioned studies [48, 49]. Probably the interview used in our study was not accurate enough and an standardized approach would be needed for the reliable measurement of these circumstances in the clinical setting. The information provided by functional and social assessment of patients profile has a large potential for use in the planning of chronic patient's care turning traditional and expensive clinical test to a more sustainable grounds.

Limitations of the study

The partial limitation of our study is that it is a retrospective cohort analysis that represents first results of a new predictive model. However, we were able to develop a simple model PREDICE SCORE to evaluate the 1-year risk for all cause mortality from the combination of demographic data, routine biochemistry and easy handling social and functional variables at the point of care that allows for risk stratification and therapeutical targeting. The variables included were non-invasive, undemanding to collect, and widely available, either at emergencies room, hospitalization, discharge or during outpatient visits (at point of care testing). Personal functioning and social support are prognostic factors which are usually ignored but which have a great potential for action in individuals with chronic diseases as HF in a sustainable way.

Clinical perspective

Congestive HF is a frequent and disabling condition but with a modifiable course and a large potential for improving. Many prognostic factors have been described mainly based in clinical data, complex heart, kidney and metabolic biochemical markers in addition to several image techniques.

Non biological factors as personal functioning and social support are prognostic factors usually ignored, but with a great potential for information for clinical action.

This study involved a cohort of 600 patients from the first episode of HF, with the purpose to determinate the predictive variables of 1-year mortality and to develop a practical and user-friendly clinical prediction algorithm (PREDICE-score) of non-biological and biological factors for medical decision about course of action.

In this study, creatinine clearance rate, levels of sodium or presence of systolic dysfunction were biological factors associate with prognosis of patients. We underline that being dependent for daily basic activities was found as a relevant non-biological prognostic factor. These findings are remarkable, because these variables are non-invasive and widely available. PREDICE-score is a predictive tool, that lets and facilitates the risk stratification for immediate care and help in decision-making process, in a sustainable manner, and design of long--term strategies for secondary prevention in congestive HF patients.

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Conflict of interest: none declared

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