



Reasons why patients suffering from chronic heart failure at very high risk for death survive



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ABSTRACT

Background: An accurate prognostic stratification is essential for optimizing the clinical management and treatment decision-making of patients with chronic heart failure (HF). Among the best available models, we used the Cardiac and Comorbid Conditions HF (3C-HF) Score, to predict all-cause mortality in patients with CHF. **Methods:** we selected and characterized the subgroup of patients at very high risk with the worst mid-term prognosis belonging to the highest decile of 3C-HF score with the aim to assess predictors of survival in subjects with an expected probability of 1-year mortality near to 45%.

Methods and results: We recruited 1777 consecutive chronic HF patients at 3 Italian Cardiology Units. Median age was 76 ± 10 years, 43% were female, and 32% had preserved ejection fraction. Subjects belonging to the highest decile of 3C-HF score were 246 (13.8% of total population). During a median follow-up of 21 [12–40] months, 110 of these patients (45%) survived and 136 (55%) died. The variables that contributed to survival prediction emerged by Cox regression multivariate analysis were the lower degree of renal dysfunction and higher body mass index.

Conclusions: The prognostic stratification of chronic HF patients allows in daily practice to select patients at different risk for death and identify prognosticators of survival in outliers at very high risk of death. The reasons why these patients outlive the matching part of subjects who expectedly die are related to the maintenance of a satisfactory renal function and body mass index.

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1. Introduction

An accurate prognostic stratification is essential for optimizing the clinical management and treatment decision-making of patients with chronic heart failure (HF). In daily clinical practice the assessment of risk for adverse outcomes is often limited and based on individual clinician's capabilities. The combined use of specific and sensible variables tested in prognostic models has appeared as the most appropriate methodology to decipher the natural history of HF syndrome in the single individual [1–7]. By this approach, however, it is habitually

possible to identify the macro-phenomena leading to the adverse clinical events, while it is “by definition” not possible to characterize the patients defined as “outliers”, who have atypical behaviors and outcomes far from those expected. To this end, no data are available on the protecting conditions from adverse clinical events in patients with chronic HF and high risk of death.

Accordingly, in this study, among the best available models, we used the Cardiac and Comorbid Conditions HF (3C-HF) Score [8], to predict all-cause mortality in patients with chronic HF. Thus, according to the score, we selected the subgroup of patients with chronic HF at very high risk for all-cause mortality with the aim to characterize and assess the predictors of survival in those subjects who unexpectedly resulted alive at the end of the follow-up.

2. Material and methods

The study patients were enrolled by 3 Italian HF clinical units into a prospective evaluation and their data were collected in the same database. We selected adults' subjects in stable clinical conditions in New York Heart Association (NYHA) functional class II or III

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who had previously experienced at least an episode of HF requiring a hospital admission. At the time of hospitalization, the diagnosis of HF was based on Framingham criteria, on documented new-onset fatigue and dyspnea, confirmed with cardiomegaly, congestion, or pleural effusions on chest X-ray, response to diuretics, echocardiographic parameters and B-type natriuretic peptide [9]. At enrollment, we considered clinical, laboratory, and echocardiographic data within the last 6 months prior to enrollment. Practical guidelines were used to define severity of valve heart disease [10] and optimization of medical treatment [9]. Left ventricular ejection fraction (LVEF) was measured by echocardiography. Patients with HF symptoms and a LVEF $\geq 50\%$ (defined as “patients with preserved LVEF”) had to show lung congestion (clinical or by chest X-ray), abnormal BNP values or high LV filling pressure at echocardiographic evaluation. History of hypertension was defined a condition preceding the first episode of congestive HF as systolic blood pressure of ≥ 140 mm Hg and/or a diastolic blood pressure of ≥ 90 mm Hg and/or pharmacologically treated high blood pressure of unknown etiology. Obesity was diagnosed if patients had body mass index ≥ 30 kg/m². Cut-off point for defining the condition of “underweight” was 18.5 kg/m² [11]. To assess renal function we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation.

Patients were followed-up at each center for a period lasting 1 year at least. Survival status was ascertained locally by follow-up visits or chart review, telephone interview with the patient, or his/her family, or primary care physician, or by examination of death certificates. Cause of death was physician-reported. Urgent heart transplantation, defined as UNOS status one [12], was counted as a death. Patients who underwent elective heart transplantation were censored seven days after the procedure. Patient follow-up was 100% complete. Patients expressed their general written consent to the anonymous use of data for their care and research purposes. Databases for clinical use were authorized at each center. The study complies with the Declaration of Helsinki; the locally appointed ethics committee has approved the research protocol.

For this investigation we initially categorized all the participants according to the classification deriving by the 3C-HF score [8], which considered the following 11 variables: age, NYHA functional class, history of hypertension, atrial fibrillation, diabetes with target organ damage, anemia, chronic kidney dysfunction, LVEF, severe heart valve disease, current treatment with beta-blocker, and current treatment with RAS-inhibitor. Thus, we selected the subgroup of patients belonging to the highest decile of the score (those with >31 points) having a probability of 1-year mortality approximately to 45% [8]. Patients with an ascertained diagnosis of hypertrophic or restrictive cardiomyopathy, those with acute myocarditis or with alcohol-induced myocardial injury were excluded from the study. Those subjects who experienced a myocardial infarction and/or underwent a percutaneous trans-catheter coronary angioplasty or coronary artery bypass graft or any intervention for valvular disease within 3 months before our first evaluation or during the follow up were also rejected. Implanted cardioverter defibrillator and/or cardiac resynchronization therapy were not considered contraindications for enrollment.

2.1. Assessment and follow-up

A careful history was obtained from all patients: this included an evaluation of NYHA functional class and a complete physical and echocardiographic examination, routine blood tests and standard electrocardiography. During the follow-up, patients received diuretics (flexible regimen), low dose of spironolactone and highest tolerated dose of angiotensin-converting enzyme inhibitors, which were replaced on angiotensin type 1 receptor blockers if not tolerated. Carvedilol, metoprolol, bisoprolol or nebivolol were used in combination with angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers at the highest tolerated dose. Anticoagulant treatment was recommended in patients with a valvular prosthesis and atrial fibrillation. However, drug prescriptions and the indications to perform diagnostic/therapeutic procedures were completely left to the decisions of the participating cardiologists. Primary end-point was survival at the end of follow-up and patients were censored for all-cause death.

2.2. Statistical analysis

Categorical variables are presented as percentages, while continuous variables are presented as their means and SD. Categorical variables were compared by the chi-square test and continuous variables by the *t*-test or the Mann–Whitney *U*-test. Log cumulative hazard functions were computed by univariate and multivariate Cox proportional hazards analyses (SPSS version 19.0, SPSS Inc. Chicago, Illinois, USA) to identify the predictors of primary end-point (survival). Variables significantly related to the primary end-point in univariate tests ($p < 0.05$) were included in the multivariate model. Multivariate model included as covariates: age, LVEF, renal function (as GFR), hemoglobin ($<vs \geq 11$ mg/dl), body mass index, and beta-blocker therapy. Gender was forced into the model. The final model was internally validated by means of bootstrap technique (number of samples = 1000, level of confidence interval = 95%). ROC curve analyses were performed to identify the best cut-off points of the variables independently associated to the primary end-point which were identified by Cox regression analysis. A 2-tailed value of $p < 0.05$ was used to reject the null hypothesis.

3. Results

3.1. Study population

During the enrollment period, 1912 patients with chronic HF were included in the database and 1777 (93%) were eligible for this study (Fig. 1); among these 1777 subjects, 246 (13.8%) were selected according to the highest decile of 3C-HF score (>31 points) and formed the final study population. Baseline demographics and clinical characteristics of the 246 patients with the highest risk of death are reported and compared with those of 1531 patients at lower risk in Table 1. As expected, the 246 patients with the highest risk were older, more often suffering from diabetes mellitus, atrial fibrillation, anemia or severe chronic renal disease, had lower body mass index and LVEF than those who had a lower risk. At entry, the former were receiving less frequently beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers than the latter. Considering the total population of 1777 patients, the probability of all-cause mortality at 1-year follow-up estimated by the logistic method was 15%. During a median follow-up of 21 [12–40] months, all-causes mortality rate was 55% and 17% in patients who had the highest risk and in those who had not, respectively ($p < 0.0001$). The incidence of re-hospitalization (occurred during the same period of observation) was 70% in the former and 25% in the latter.

3.2. Picture of the outliers

During the follow-up (median 21 months), among the 246 patients with the highest risk of death, 110 (45%) survived. These patients were younger, had significantly higher body weight, body mass index and LVEF, a better renal function and a lower prevalence of anemia than the 136 counterparts who died (55%). Furthermore, patients who survived were receiving more frequently beta-blockers than those who did not (Table 2). Although patients were selected according to the highest decile of the prognostic 3C-HF score, those who died exhibited still a higher score as compared to those who survived (39.4 ± 6.9 vs 36.8 ± 5.1 points, respectively; $p = 0.001$). Mode of death was cardiovascular cause in 82% of cases (progressive pump failure = 64%; sudden death = 14%; acute myocardial infarction 4%), non-cardiovascular cause in 18% of cases (respiratory disease = 6%; renal failure = 3%; cancer = 3%; stroke = 2%; other causes = 4%).

3.3. Predictors of survival

Multiple regression Cox analysis was performed to characterize patients who survived in spite of the very high risk of death predicted by the prognostic 3C-HF score. Among the covariates age, LVEF, renal function (measured as GFR), hemoglobin ($<vs \geq 11$ mg/dl), body mass index, beta-blocker therapy and gender, which were selected by univariate analysis, those that contributed to survival prediction emerged in decreasing discriminating ability by Cox regression multivariate analysis were the lower degree of renal dysfunction and higher body mass index (Table 3). This model was internally validated by bootstrap technique which confirmed its solidity and constancy: GFR and body mass index, indeed, appeared also by this technique as the two prognosticators of survival (both $p = 0.001$).

The best cut-off points of these two variables independently associated to the primary end-point were identified by ROC curve analyses: they were 40 ml/min/1.73 m² for GFR (AUC 0.56, [CI 0.48–0.64], sensitivity 58%, specificity 50%) and 25.0 kg/m² for body mass index (AUC 0.67 [CI 0.56–0.80], sensitivity 72%, specificity 62%). Based on the results of Cox regression and ROC analyses, four sub-groups of patients were identified according to their GFR and body mass index. As shown in Fig. 2, all-cause mortality rates ranged from 90% in the subgroup of patients with GFR < 40 ml/min/1.73 m² and body mass

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