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Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score ☆

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ABSTRACT

Background: Prognostic stratification in heart failure (HF) is crucial to guide clinical management and treatment decision-making. Currently available models to predict HF outcome have multiple limitations. We developed a simple risk stratification model, based on routinely available clinical information including comorbidities, the Cardiac and Comorbid Conditions HF (3C-HF) Score, to predict all-cause 1-year mortality in HF patients.
Methods: We recruited in a cohort study 6274 consecutive HF patients at 24 Cardiology and Internal Medicine Units in Europe. 2016 subjects formed the derivation cohort and 4258 the validation cohort. We entered information on cardiac and comorbid candidate prognostic predictors in a multivariable model to predict 1-year outcome.
Results: Median age was 69 years, 35.8% were female, 20.6% had a normal ejection fraction, and 65% had at least one comorbidity. During 5861 person-years follow-up, 12.1% of the patients met the study end-point of all-cause death (n = 750) or urgent transplantation (n = 9). The variables that contributed to outcome prediction, listed in decreasing discriminating ability, were: New York Heart Association class III–IV, left ventricular ejection fraction <20%, no beta-blocker, no renin–angiotensin system inhibitor, severe valve heart disease, atrial fibrillation, diabetes with micro or macroangiopathy, renal dysfunction, anemia, hypertension and older age. The C statistic for 1-year all-cause mortality was 0.87 for the derivation and 0.82 for the validation cohort.
Conclusions: The 3C-HF score, based on easy-to-obtain cardiac and comorbid conditions and applicable to the 1-year time span, represents a simple and valuable tool to improve the prognostic stratification of HF patients in daily practice.

1. Introduction

Risk assessment in heart failure (HF) is crucial for clinical management, treatment decision-making, counseling of patients and their families, and monitoring the quality of health care. Prognostic stratification is nevertheless a difficult task. Variability in the outcomes of

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HF patients is large, one-year mortality rates range from 5% to 75% in randomized clinical trials [1,2] and from 11% to 42% in community studies [3,4]. No single parameter can be expected to reliably predict prognosis in this markedly heterogeneous population.

The combination of several variables in prognostic models has emerged as the most appropriate approach to capture the complexity of the HF syndrome. However, the still imperfect predictive accuracy of currently available risk stratification models trades off with multiple limitations. Most models are based on retrospective or single-centre assessment, or are derived from small series [5–7]. Selection bias is another issue: many studies included patients from randomized clinical trials or on the heart transplant waiting list, did not consider the entire spectrum of systolic function, or focused on middle-aged patients without comorbidities [8–12]. In some instances the clinical relevance or availability of predictive variables was poor and the statistical approach inadequate. Until now, no model has gained widespread acceptance. In daily clinical practice estimates of patient's prognosis are mainly founded on individual clinician's experience based on some specific prognostic indicators.

We tried to address these limitations in a cohort study, on a large sample of patients, with a wide range of HF severity and comorbidities, who were enrolled in different settings and episodes of care. We aimed to develop a simple risk stratification model, based on routinely available clinical information, in order to predict one-year outcome in daily practice.

2. Methods

2.1. Study population and protocol

We invited 24 Cardiology and Internal Medicine Units to enroll at least 100 HF patients consecutively seen during a 6- to 12-month period between 2002 and 2006. Participating institutions had a minimum yearly volume of >100 HF admissions during the sampling period and had taken part in registries or surveys on HF.

Prospectively enrolled patients from the first 8 institutions that joined the study formed the derivation cohort (n=2016), that was used to build the prognostic model. Subjects recruited at the 16 centres, that accepted to participate later on, constituted the validation cohort (n=4258), that was used to test the prognostic accuracy of the model. These centres also enrolled a subset of patients retrospectively identified among those meeting eligibility criteria.

Inclusion criteria were a diagnosis of HF based on symptoms and signs of congestion and objective evidence of cardiac dysfunction at rest [13]. Left ventricular ejection fraction (LVEF) was measured by echocardiography within 6 months of enrolment. Patients with HF symptoms and a LVEF≥50% had to show lung congestion by chest X-ray.

We excluded patients who died during the index admission. Patients with an indication for any cardiac surgical procedure, other than transplantation, were excluded because of the independent impact of heart surgery on outcome. Patients with metastatic cancer were excluded because of their very poor life expectancy independently of the HF syndrome.

We recruited subjects either at discharge or in the outpatient clinic. For prospectively enrolled subjects, information was gathered at hospital discharge or at the index outpatient visit. For retrospective enrolment, we reviewed hospital records identified through a primary diagnosis of HF (ICD-9-CM code 428.xx), as well as outpatient clinic records of subjects followed-up at different institutions.

We considered clinical, laboratory, and echocardiographic data within the last 6 months prior to enrolment. Existing guidelines were used to define severity of valve heart disease [14] and optimization of medical treatment [13].

Patients were followed-up at each centre after the index discharge or outpatient visit (time 0). One-year survival status (the study endpoint) 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. Urgent heart transplantation, defined as UNOS status 1 [15], 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 centre. Observational studies, where no experimental treatment was evaluated, did not require a formal review board waiver until 2008 in the European countries, where the participating centres were located. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [16].

Data were sent to the Heart Failure Research Centre, Bergamo, Italy for reassessment of completeness and accuracy; periodical queries were issued for missing or inconsistent information.

2.2. Statistical analysis

Routinely available established predictors [17] of HF survival were considered for inclusion in a logistic regression model for the binary indicator of one-year survival since baseline. It was decided a priori that, in case of statistical significance, an analysis via Cox proportional hazards model would be performed for confirmation. Whenever appropriate, before inclusion in model, the predictors were dichotomized on the basis of clinically significant cut-offs. The patients in the prospective derivation cohort were iteratively partitioned into two sets. At each iteration, the former set was used to "train" the model, and the latter to then obtain an unbiased assessment of predictive performance. This allowed us, on the basis exclusively of the derivation cohort, to eliminate redundant predictors, and to assess the resulting model in terms of predictive discrimination via C statistic, i.e., the area under the ROC curve [18] and Brier score [19].

We also checked for possible centres with an unduly large impact on the estimated parameters. The model predictive performance was further, and independently, assessed on the basis of the validation cohort, separately in the following strata of the cohort: retrospectively and prospectively enrolled, discharged patient or outpatient, Cardiology or Internal Medicine patient, normal or reduced LVEF, eligible for cardioverter defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) [20], device carrier/not carrier at baseline.

To create a practical prognostic score system, the Cardiac and Comorbid Conditions Heart Failure (3C-HF) score, we multiplied model regression coefficients, corrected by age effect, by 10 and rounded to the nearest integer [21].

Reliability for abstraction of categorical variables in 204 randomly selected retrospective records (11%) was high. Using crude agreement, the interobserver reliability and the kappa statistic were, respectively, 0.99 and 0.94 (95% CI 0.88–0.99) for chronic obstructive lung disease, 0.97 and 0.89 (95% CI 0.83–0.95) for complicated diabetes, 0.96 and 0.92 (95% CI 0.83–0.99) for hypertension, and 0.98 and 0.97 (95% CI 0.93–1.0) for NYHA class III–IV.

Analysis was based on software we developed under R (Version 2.6.0) and SAS (Version 9.2; SAS Institute Inc, Cary, NC, USA).

3. Results

We recruited overall 6274 patients, both in Internal Medicine (1447, 23%) and Cardiology Units (4827, 77%); 1823 patients (29%) were enrolled retrospectively and 4451 (71%) prospectively. Quantitative assessment of LVEF was available in 6225 patients (99%). At enrolment, 714 patients had a device in place: ICD (n=382, 6%), CRT (n=122, 2%) or both (n=210, 3%). These figures represented 23% and 59% of the patients eligible [20] for ICD (n=2541) or CRT (n=564), respectively; overall 26% of the 2743 subjects (44%) with an indication for devices had been implanted.

During 5861 person-years follow-up, 12% of the patients met the study end-point of all-cause mortality (n=750) or urgent heart transplant (n=9); transplant-free survival is presented in Fig. 1.

The derivation and validation cohorts originally contained 2016 and 4258 patients, respectively. Clinical characteristics of both original cohorts are summarized in Table 1. As many as 213 (3%) subjects

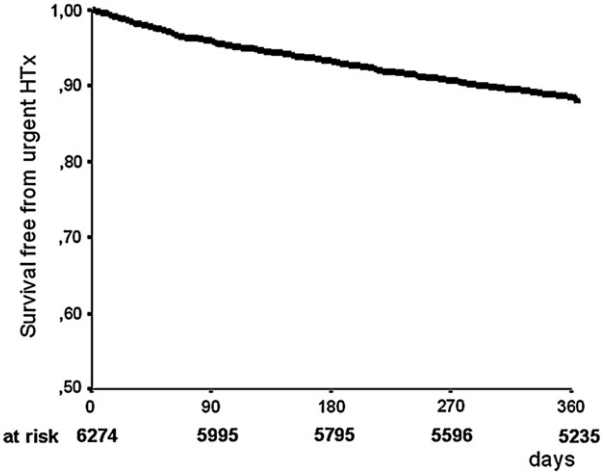

Fig. 1. One-year survival free from urgent heart transplantation in the overall study cohort.

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Table 1
Clinical characteristics of the derivation and validation cohorts.

Study cohorts	Derivation N. 2016	Validation N. 4258
Female gender	603 (29.9)	1647 (38.7)
Age (years)	68 [58–76]	70 [60–77]
≥2 comorbidities	488 (24.2)	1197 (28)
NYHA class III–IV (n = 6247)	677 (33.6)	1420 (33.6)
LVEF% (n = 6225)	35 [27–40]	38 [29–50]
LVEF <20%	92 (4.6)	187 (4.4)
LVEF ≥50%	195 (9.7)	1099 (26.1)
No beta blocker	580 (28.8)	1487 (34.9)
No RAS inhibitors	237 (11.8)	749 (17.6)
Severe valve heart disease	233 (11.6)	631 (14.8)
Atrial fibrillation	550 (27.3)	1166 (27.4)
Diabetes with target organ damage	304 (15.1)	813 (19.1)
Chronic kidney dysfunction (creatinine > 176 μmol/L)[a] (n = 6152)	157 (7.8)	394 (9.5)
Serum creatinine (μmol/L)	106 [88–128]	102 [86–131]
Anemia (hemoglobin < 11 g/dl) (n = 6205)	190 (9.4)	528 (12.6)
Hemoglobin (mg/dL)	13.6 [12.3–14.7]	13.2 [12–14.5]
Hypertension (blood pressure ≥ 140/90 mm Hg)	939 (46.6)	1909 (44.9)
Chronic obstructive lung disease (GOLD guidelines)	302 (15.0)	737 (17.3)
Eligible for device therapy (ICD and/or CRT)	1117 (55.4)	1626 (38.2)
Carrier of device (ICD and/or CRT) (% of eligible subjects)	280 (25.1)	434 (26.7)
Deceased/transplanted at 1-year	225 (11.2)	534 (12.5)
3C-HF score (n = 6061)	10 [3–20]	12 [4–23]

Data are expressed as number (percentage) or median [interquartile range]. CRT, cardiac resynchronization therapy; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin–angiotensin system; target organ damage includes microangiopathy (retinopathy, neuropathy, nephropathy) or macroangiopathy (coronary artery disease, peripheral vessel disease).
[a] Creatinine > 2 mg/dl.

were eliminated from further analysis because of missing values in at least one of the predictors, which left us with 2012 subjects in the derivation and 4049 subjects in the validation cohort, for a total of 6061 subjects retained for outcome analysis. Close examination of the discarded individuals did not raise any suspicion that the missingness could be related to outcome-informative mechanisms, conditionally on the recorded predictors.

Table 2 summarizes the results from the fitting of a logistic regression model for one-year mortality to the derivation cohort data, using the entire set of candidate predictors on their original (possibly continuous) scales. For each predictor, the table reports the estimated regression effect on an odds-ratio scale, together with its corresponding 95% confidence intervals, and the p-value for the null hypothesis of no effect, according to a univariate Wald's test. The C statistic for this model using continuous variables was 0.88 (95% CI 0.86 to 0.90). We detected no evidence of interaction between the predictive variables nor any unduly large impact of the data from a particular centre on the estimated coefficients.

Bootstrap elimination of redundant variables left us with the set of variables listed in Table 3, which we consider our final selected, and recommended, set of predictors. A logistic regression model based on the combined set of selected predictors was fitted to the entire derivation cohort. The results from this fitting are summarized in Table 3, which contains the estimated regression effects, expressed on an odds-ratio scale, together with the corresponding 95% confidence interval and the relative contribution of each variable to the additive 3C-HF score. The predictive performance of additive 3C-HF score was 0.87 (95% CI 0.86 to 0.88) in the derivation cohort.

Both the logistic regression model and the additive score were then applied to the validation cohort, avoiding refitting. When assessed in the validation cohort, the logistic model performance was 0.83 (95% CI 0.82 to 0.84), while the additive 3C-HF score achieved a C statistic of 0.82 (95% CI 0.81 to 0.83), with a Brier score of 0.082. Table 4 summarizes the predictive performance of the additive 3C-HF score across different strata of the validation cohort.

One-year all-cause mortality and urgent heart transplant rates with 95% confidence intervals in patient groups based on deciles of 3C-HF score were separately plotted for the derivation and validation cohorts (Fig. 2).

Kaplan–Meier event-free survival curves by in deciles of 3C-HF score in the overall population (n = 6061) are presented in Fig. 3 (log rank test $P<0.0001$). A Web-based calculator (http://www.3chf.org) has been built up, allowing easy and interactive calculation of individual patient's estimated survival, through the logistic regression model and the additive score.

4. Discussion

In a large, multicentre HF population, enrolled in different clinical settings, we developed a prognostic model, the 3C-HF score, that combines cardiac and comorbid conditions commonly present in patients affected by this syndrome. The score allowed a good separation of 1-year survivors from non-survivors, with a C statistic of 0.82 in the

Table 2
Candidate predictors of one-year mortality or urgent heart transplant by multivariable logistic regression.

Variable	Odds ratio	95% CI	*P* value[a]
Age (per decade increase)	1.13	1.0–1.4	<0.0001
Cardiac variables			
NYHA class III–IV	4.09	3.3–5.4	<0.0001
No RAS inhibitors	2.02	1.6–2.4	<0.0001
Severe valve heart disease	2.01	1.6–2.5	<0.0001
No beta blocker	1.58	1.2–1.8	<0.0001
Atrial fibrillation	1.45	1.2–1.7	0.0003
LVEF (per 5 unit increase)	0.96	0.95–0.98	<0.0001
Comorbid conditions			
Diabetes with target organ damage	1.48	1.20–1.80	<0.0001
Hemoglobin (per 0.5 g/dL increase)	0.89	0.84–0.94	<0.0001
Serum creatinine (per 26 μmol/L increase)	1.03	1.01–1.04	0.0004
Hypertension	0.78	0.6–0.9	0.004
Gender (female)	0.73	0.4–1.2	0.11
Chronic obstructive lung disease	1.20	0.8–1.5	0.09
Device therapy (ICD and/or CRT)	0.78	0.4–1.3	0.21

CI= confidence interval
[a] Wald's test. For abbreviations see Table 1.

Table 3
Dichotomized logistic regression model and corresponding points for the additive version of the 3C-HF score (http://www.3chf.org).

Variable	Odds ratio	95% CI	*P* value[a]	Points (additive score)
Age (per 10 years ≧ 40)	1.03	1.0–1.2	<0.0001	1
Cardiac variables				
NYHA class III–IV vs I–II	4.09	3.3–5.4	<0.0001	13
LVEF <20% vs ≥20%	2.77	1.5–4.1	<0.0001	11
No RAS inhibitors	2.01	1.6–2.5	<0.0001	8
Severe valve heart disease	2.02	1.6–2.4	<0.0001	7
Atrial fibrillation	1.58	1.2–1.8	<0.0001	7
No beta blocker	1.45	1.2–1.7	0.0003	4
Comorbid conditions				
Chronic kidney dysfunction	1.79	1.5–2.1	<0.0001	6
Diabetes with target organ damage	1.62	1.4–1.8	<0.0001	6
Anemia	1.47	1.2–1.8	0.0011	4
Hypertension	0.78	0.6–0.9	0.0040	−4

CI= confidence interval
[a] Wald's test. For abbreviations see Table 1.

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Table 4
Performance of the 3C-HF score in the validation cohort across patient subgroups.

Groups	N	%	*C* statistic (95% CI)	Brier score	*P* value
Retrospectively enrolled	1736	(42.8)	0.83 (0.81–0.85)	0.06	0.64
Prospectively enrolled	2313	(57.2)	0.82 (0.80–0.83)	0.07	0.72
Cardiology units	2618	(64.6)	0.82 (0.80–0.84)	0.08	0.77
Internal Medicine units	1431	(35.4)	0.85 (0.82–0.88)	0.07	0.67
Left ventricular ejection fraction <50%	2969	(73.3)	0.82 (0.81–0.83)	0.06	0.79
Left ventricular ejection fraction ≥50%	1080	(26.6)	0.83 (0.81–0.85)	0.09	0.69
Not eligible for device[a]	2526	(62.3)	0.83 (0.82–0.84)	0.08	0.84
Eligible for device	1523	(37.7)	0.84 (0.82–0.86)	0.08	0.55
Eligible for device, not implanted	1138	(74.7)	0.82 (0.80–0.84)	0.10	0.40
Eligible for device, implanted	385	(25.3)	0.84 (0.81–0.87)	0.07	0.77

CI= confidence interval
[a] Device includes ICD and/or CRT.

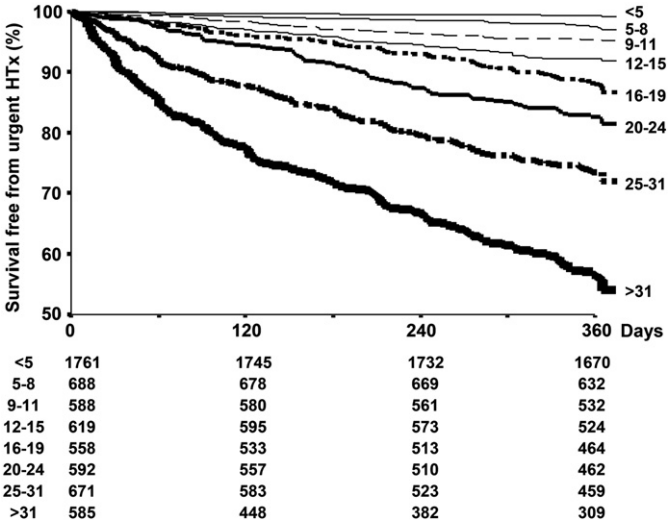

Fig. 3. Kaplan–Meier analysis of survival free from urgent heart transplant according to deciles of 3C-HF score in the overall cohort (n = 6061); the first 3 deciles (score < 5) have been grouped in a single class (log rank $P < 0.001$). Numbers of patients in score classes at each time point are shown below the *x* axis.

validation sample, the highest among those of previously published prognostic models, which ranged from 0.69 to 0.76 [5–12]. The 3C-HF C statistic compares favorably with the most validated cardiovascular risk scoring system, the Framingham Score [22] (0.74 in men and 0.77 in women).

Currently available HF risk stratification models present important limitations [5–12,23–25].

The exclusion of elderly patients and comorbidities from risk assessment is a serious drawback, as most community HF patients have at least one associated disease [26]. In contrast, this multicentre cohort well represents "real world" HF patients, as seen by cardiologists or internists, and quite distinct from typical trial patients [8,9,12]. Subjects were recruited from both Cardiology and Internal Medicine Units, two out of three had one or more comorbidities, one third were older than 75 years, a substantial proportion had a normal LVEF and one-year mortality was comparable to previous HF community studies and registries [27–30].

The 3C-HF score is the first model validated in a large non-trial HF population with a normal LVEF (≥50%, 1080 patients, 26.6% of to the validation cohort to exhibit a good predictive performance (statistic 0.83). Even when a previously reported cut-off (≥40%, 47.9% of the validation cohort) [9,10] was considered, the C statistic was comparably good (0.83). The proportion of subjects with preserved LVEF in our series and their clinical profile are close to prevalence and characteristics of these patients in community studies. Conversely, in the Seattle Heart Failure Model [9], only two of the six study cohorts (9.2% of subjects) included patients with a LVEF > 40%. Moreover, our score largely outperformed the model developed both from the CHARM study [8] and from the SENIORS trial [12] (C statistic 0.74 and 0.69, respectively). Despite well-known differences in the clinical profiles of patients with preserved or reduced LVEF, our score succeeded in balancing the informative value of each cohort's peculiar characteristics, as shown by its accurate prediction across the entire spectrum of ventricular impairment. This result has important implications for the applicability of the score to unselected patients in the community [3,27,28].

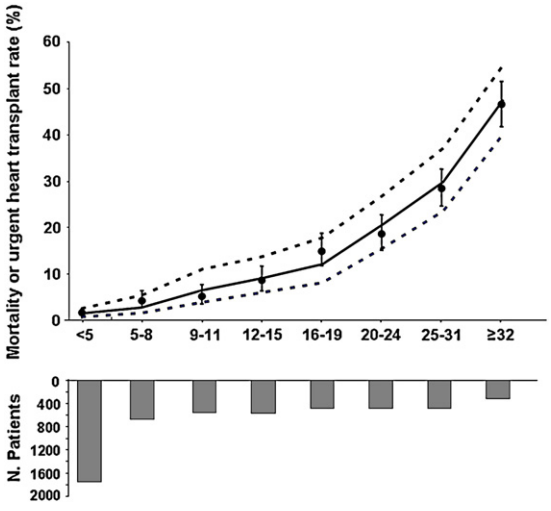

Fig. 2. The graph compares the event rates for the study end-point (all-cause death or urgent heart transplant) in the derivation (n = 2012) and validation (n = 4049) cohorts) by deciles of 3C-HF score. Predicted mortality (central continuous line) with 95% confidence intervals (hatched lines) is plotted against observed mortality (closed squares) with 95% confidence intervals (vertical bars). The first 3 deciles (score <5, death rates all <1%) have been grouped in a single class. Histograms in the lower panel represent the total number of patients (n = 6061) in each score class.

In order to verify whether the model could be used in future retrospective analyses, we also included patients who were retrospectively identified from each centre database. Model performance overlapped in this subset (0.82) and in prospectively enrolled (0.83) subjects.

The variables included in the 3C-HF score were selected for their ready availability and previously reported prognostic significance. In a prognostic model, accurate prediction should be balanced against practicality. In an attempt to maximize predictive performance, some studies have proposed models that require the collection of extensive or costly data, which may make them impractical for routine use. For example, <5% of HF patients undergoes a cardiopulmonary exercise test [27]; thus, although data on maximal oxygen consumption may increase predictive accuracy, their inclusion in the model will hamper its use in clinical routine. By restricting to simple, easy-to-obtain, items, prognostic indices are closer to real practice, have greater practical value, and may be used in primary care and at the bedside.

The incorporation of medications into the score is crucial, as drug therapy may be modified to improve patient survival. Pharmacological treatment was generally optimized in the present series, as suggested by prescription rates of beta-blockers (67%) and renin–angiotensin system inhibitors (84%), which were close to the recommended targets in the absence of contraindications. Patients who are not prescribed, or cannot tolerate these drugs because of advanced disease

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or contraindications, are unsurprisingly at higher risk of death. In this respect, direct comparison with other scores is not possible as, e.g. in the Seattle HF Model, beta-blockers and renin–angiotensin system inhibitors were not directly included in the model and hazard ratio estimates were based on literature data [9].

Device therapy is increasingly practiced in HF and indications have changed since our study cohort was enrolled. Although CRT and/or ICD had been implanted in 59% and 23% of potentially eligible patients, absolute numbers were very low overall and might account for the lack of predictive value for device therapy in the model. On the other hand, these low numbers are consistent with reports from large unselected series, where the proportion of subjects eligible for CRT or ICD ranged from 6.8 to 17% and 47% to 51%, respectively [31]. Potential CRT benefits, such as improvement of ventricular function, reduction of functional mitral regurgitation, and introduction of beta-blockers, were indirectly incorporated into the score. Eventual CRT should prompt a recalculation of the score.

The 3C-HF score stratifies the individual patient risk at one year, a time span that is critical for treatment choices, such as device therapy, but still minimizes the potentially larger impact of comorbidities, rather than cardiac conditions, on outcome. Risk stratification should be repeated after one year, since in an elderly population comorbidities in particular may change.

The clinical implications of our simple predictive tool are relevant. Patients should receive care at the level best suited to their individual needs, to appropriately allocate scarce and costly specialist resources. Low-risk patients could be routinely managed in primary care, once the specialist has prescribed the optimized polypharmacy in a stable patient. Conversely, patients at intermediate risk should receive more intensive specialist follow-up and be referred for invasive interventions, when indicated. In subjects at very high risk (score ≥ 32; 50% one-year mortality) ICD or any surgical treatment may be futile, and a palliative care approach might be considered instead.

5. Limitations

Although large and mainly prospective, our study has several limitations inherent to its observational nature. Selection bias might have resulted from some characteristics: the centres invited to participate were among those with expertise in HF management and each volunteered to participate, and mostly white and Caucasian patients were enrolled.

To enhance the applicability of the score to complex real world patients in whom coronary angiography, mandatory for an accurate ascertainment of the ischemic aetiology of HF, may be difficult to perform, we chose not to consider this variable among candidate predictors.

Both anemia and renal dysfunction, which contribute in a level-dependent fashion to negative outcomes in HF, may be classified in different ways. Our clinically consistent cut-offs for hemoglobin and creatinine did not result in significant loss of predictive ability over continuous values. Although use of estimated glomerular filtration rate over creatinine has been advocated to increase accuracy in the assessment of renal dysfunction, the >176 μmol/L creatinine cut-off underestimated severe renal dysfunction, as determined by glomerular filtration rates <30 mL/min*1.73 m^2 in only 1.8% of our series.

Our model does not include all variables that may significantly and independently contribute to outcome. Natriuretic peptides, potentially useful predictors of outcome, were not yet routinely available in most centres at the time of the study. However, the evidence that these biomarkers have prognostic value across the entire spectrum of the HF population is currently limited [32], in particular among elderly patients and those with renal dysfunction, who were both well-represented in our series. Moreover, the addition of natriuretic peptides to cardiovascular clinical prediction models only modestly improved the C statistic [33]. Further studies are probably needed to evaluate whether adding BNP can be valuable to improve the predictive value of this score.

6. Conclusions

Estimating prognosis is a key element of HF management. The 3C-HF score, based on cardiac and comorbid conditions, is easy to obtain, applicable to the 1-year time span, and minimizes the limitations present in previous models. The score represents a valuable tool for physicians who are confronted daily with decisions on the type of care to offer and on the appropriateness of therapeutic interventions. Although good clinical judgment is still of paramount importance, prognostic models should be included in clinical practice as decisional support tools.

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