Utility of the SENIORS elderly heart failure risk model applied to the RICA registry of acute heart failure

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ABSTRACT

Background: Heart failure (HF) is predominantly a disease of the elderly. Reliable risk stratification would help in the management of this population, but no model has been well evaluated in elderly HF patients in both acute and chronic settings and not being restricted by ejection fraction. To evaluate the utility of the SENIORS risk model, developed from a clinical trial of elderly patients with chronic HF, in an independent cohort (National Spanish Registry: RICA) of elderly acute HF patients.
Methods: We applied the SENIORS risk model to 926 patients in RICA to estimate risk at one year of a) composite outcome of all-cause mortality or cardiovascular hospital admission and b) all-cause mortality.
Results: In the RICA registry mean age was 78 years, mean ejection fraction 51% and 87% were in NYHA II and III. At one year death/CV hospitalization occurred in 31.9% and all-cause mortality in 19.5%. The risk model provided good separation of Kaplan Meier curves stratified by tertile for death/CV hospitalization and all-cause mortality. The observed versus expected rates of death/CV hospitalization in the lowest, middle and highest risk tertiles were (%) 34/24, 45/41 and 57/67, and for death 13/16, 32/38 and 44/70 respectively. C-statistic for all-cause mortality or CV hospitalization was 0.60 and for all-cause mortality 0.66.
Conclusion: The SENIORS risk model was a reliable tool for relative risk stratification among acute heart failure patients in a "real world" registry, but predicted versus observed risk showed some variability. The model provides a useful basis for clinical risk prediction.

1. Introduction

Heart failure (HF) is a growing healthcare problem, particularly in elderly patients. Despite of modern treatments, many patients require frequent readmissions [1–3], which itself is a marker of poor prognosis. Several HF risk models have been developed and validated using data from observational studies and clinical trials, but these have mostly included patients younger than 70 years and mainly with systolic dysfunction [4–12]. Since HF is a syndrome predominantly of the elderly, it is important to have reliable risk stratification tools specifically for this population. We previously developed a risk model from the SENIORS dataset, based on widely available clinical and laboratory variables, to predict prognosis in HF outpatients > 70 years [13]. As patients from clinical trials might not represent those from the "real world" with numerous co-morbidities we applied the SENIORS risk model to RICA (Registro Nacional de Insuficiencia Cardiaca) a prospective multi-centre observational registry of elderly acute HF admissions. We explored the utility of the model to stratify patients and to predict risk.

2. Methods

The RICA registry is a multi-centre, prospective, cohort study, coordinated by the Working Group of Heart Failure of the Spanish Society of Internal Medicine [14,15]. This registry includes data from public and private hospitals in Spain, and was approved by

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the Ethics Committee of the Hospital University Reina Sofia in Cordoba. From March 2008 to January 2013, 1368 patients were enrolled in RICA from 52 centres. All patients consecutively admitted to the Internal Medicine units with acute decompensated HF, and cared for by physicians participating in the registry (and with at least one year follow-up), were included in this study. In addition to giving their informed consent, patients were recruited if they were 50 years old with HF diagnosed according to the criteria of the European Society of Cardiology [16]. Data were collected through a secure web site. The registry recorded demographic data, blood pressure, heart rate, body weight and height, ejection fraction, co-morbidities, functional status, routine laboratory data, complications during admission and prescriptions at discharge. Follow-up consisted of two visits scheduled at 3 months and at 1 year, where new hospitalizations or deaths were recorded.

The SENIORS trial randomized elderly, stable HF patients to the beta-1 selective beta blocker nebivolol or placebo and enrolled 2128 patients 70 years with HF (ejection fraction 35%, or having had a recent HF admission) [17]. Using the SENIORS dataset we have published a model for the prediction of the composite of all-cause mortality or CV hospitalization, and all-cause mortality alone [13].

2.1. Statistical analysis

In the SENIORS risk model five factors (NYHA class, prior myocardial infarction, left atrial dimension, uric acid, and body mass index) were associated with prediction of the composite of all-cause mortality or CV hospitalization, and all-cause mortality alone [13]. In addition to these five variables, peripheral arterial disease, time since diagnosis of HF, right bundle branch block, diabetes mellitus, and orthopnea featured in the composite outcome model, while creatinine, 6-min walk test, coronary artery disease CAD, and age featured in the mortality model. Using the RICA dataset we identified the same baseline variables used in the SENIORS risk model, except the 6 min walk test which was not collected in RICA. Atrial dimension and uric acid were not collected in all RICA patients and as these were important factors in the SENIORS model, patients without these variables were excluded from the analysis. Other missing data were imputed using the mean value for all continuous variables, except for years with HF for which values of zero were used. Missing categorical variables were imputed with the value corresponding to the lowest risk category.

Development of the SENIORS risk model has been described elsewhere [13] but as RICA included an acute HF population and SENIORS an ambulatory chronic HF population the overall risk in RICA was higher. We therefore adjusted the survival function, based on observed annual mortality rate in the original model, for the elevated risk in RICA. Patients included in the RICA dataset were subjected to 200 bootstrap re-sampling procedures as in the original SENIORS model. For each sample the hazard ratio (HR) for all-cause mortality or cardiovascular hospital admission (primary outcome) and all-cause mortality (secondary outcome) for the RICA data was compared to a bootstrap sample of the SENIORS training dataset. The discriminatory properties of the model were tested by estimating the Kaplan–Meier survival curves for tertiles of risk score. The log-rank test was then used to see if the three curves were different from one another. For each tertile of baseline risk, estimates of observed and predicted outcome event rates were made. Utility of the model was also assessed using the c statistic [18]. All analysis was performed using STATA (StataCorp, TX, USA), and a p-value of 0.05 was considered statistically significant.

3. Results

We included 926 patients from RICA out of a possible 1368 who had clean one year follow-up data as of January 30th 2013. Four hundred and forty two patients were excluded due to missing information on atrial dimension and uric acid but baseline characteristics of patients who lacked these variables were similar to those patients who did not. Mean age in RICA was 78 years compared to 76 years in SENIORS, but RICA included a higher proportion of women, diabetes, chronic obstructive pulmonary disease, atrial fibrillation (AF) and peripheral arterial disease. Mean baseline EF was higher in RICA compared to SENIORS (51% versus 36% respectively). Table 1 shows baseline characteristics of RICA and SENIORS patients.

3.1. Follow-up

During one year follow-up 295 patients (31.9%) had a death or cardiovascular hospital admission and 181 patients (19.5%) died in RICA compared to 21.9 and 9.3% in SENIORS respectively (p < 0.001) for comparison of both outcomes between RICA and SENIORS. Distributions of risk for the primary outcome and all-cause mortality are shown in Fig. 1A and B.

The risk model provided good discrimination for the primary outcome and all-cause mortality for tertiles of baseline risk as shown by Kaplan Meier curves in Fig. 2A and B.

Table 1
Baseline characteristics of RICA and SENIORS patients included in the analysis.

Variable	RICA (N 926)	SENIORS (N 1400)	p value
Demographic			
Age (years ± SD)	77.7 ± 9.0	76.1 ± 4.7	<0.001
Gender (Female) %	52.5	37.1	<0.001
Medical history (%)			
Hypertension	85.7	62.7	<0.001
Diabetes	47.4	26.9	<0.001
Prior myocardial infarction	20..6	43.9	<0.001
Atrial fibrillation	54.3	34.9	<0.001
Hyperlipidaemia	47.3	45.7	0.50
Chronic obstructive pulmonary disease	27.3	7.1	<0.001
Peripheral arterial disease	14.4	5.1	<0.001
Clinical characteristics (%)			
NYHA class			<0.001
I	8.8	2.8	
II	53.7	56.5	
III	34.2	38.6	
IV	3.3	2.1	
Body mass index (kg/m²)	29.2 ± 6.4	26.7 ± 4.0	<0.001
Systolic blood pressure (mm Hg)	141.8 ± 29.3	139.5 ± 20.3	0.025
Diastolic blood pressure (mm Hg)	77.8 ± 17.2	80.7 ± 11.0	<0.001
Heart rate (beats/min)	90.3 ± 24.5	79.4 ± 13.9	<0.001
Laboratory			
Haemoglobin (g/dL)	12.2 ± 2.1	13.8 ± 1.5	<0.001
Creatinine (mol/L)	117.2 ± 59.0	102.1 ± 33.6	<0.001
MDRD (ML/min/1.73 m²)	58.3 ± 26.0	65.0 ± 19.6	<0.001
Sodium (mmol/L)	139.3 ± 4.8	141.6 ± 3.8	<0.001
Uric acid (mol/L)	461.4 ± 139.4	395.7 ± 120.2	<0.001
Echo and ECG data			
Left bundle branch block %	19.9	19.8	0.960
Right bundle branch block %	11.8	9.3	0.053
Left ventricular hypertrophy %	27.0	12.1	<0.001
Ejection fraction (%)	50.9 ± 15.1	35.7 ± 12.0	<0.001
Left atrial dimension (cm)	4.7 ± 0.9	4.4 ± 0.8	<0.001
Medications (%)			
Beta Blocker	64.1	48.6	<0.001
ACE inhibitors	55.3	83.4	<0.001
Angiotensin receptors blockers	32.1	7.9	<0.001
Diuretics	89.2	83.4	<0.001
Spironolactone	32.5	27.6	0.011
Digoxin	26.2	41.4	<0.001
Calcium channel-blocker	21.8	13.4	<0.001
Statin	44.4	22.5	<0.001
Vitamin K antagonists	55.2	23.4	<0.001
Anti-arrhythmics	8.2	16.5	<0.001
End points at 1-year (%)			
Mortality or cardiovascular hospitalization	31.9	22.5	<0.001
Mortality	19.5	9.9	<0.001

The observed versus predicted rates for the primary and secondary outcomes are shown in Fig. 3A and B. Both observed and predicted rates show a reliable gradient of risk. For the primary outcome of death/CV hospital admission at one year observed/predicted rates (%) were 34/24, 45/41 and 57/67 from lowest to highest tertile. Thus there was an apparent underestimation of risk in the lower tertile, good agreement in the middle tertile and some overestimation in the upper tertile.

The c statistic for this outcome was 0.60. For all-cause mortality observed/predicted rates (%) were 13/16, 32/38 and 44/70 from lowest to highest tertile respectively. There appeared to be good agreement for the lower and middle tertiles but an overestimation of risk in the upper tertile with a c statistic of 0.66.

Similar results were obtained for the primary (death/CV hospital admission) and secondary (all-cause mortality) endpoints in patients with LVEF 50%, and in those without a history of prior hospitalization due to heart failure (data not shown).
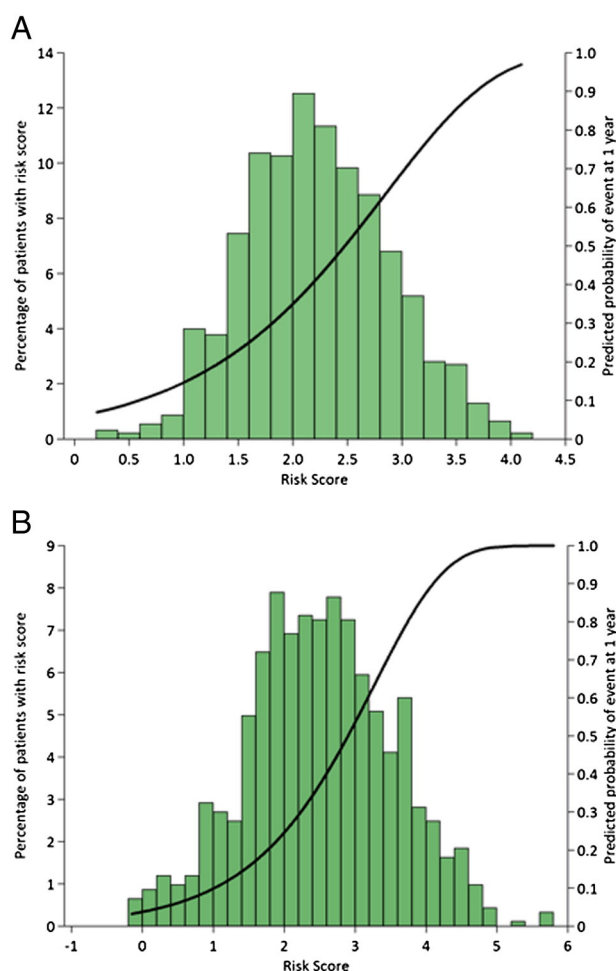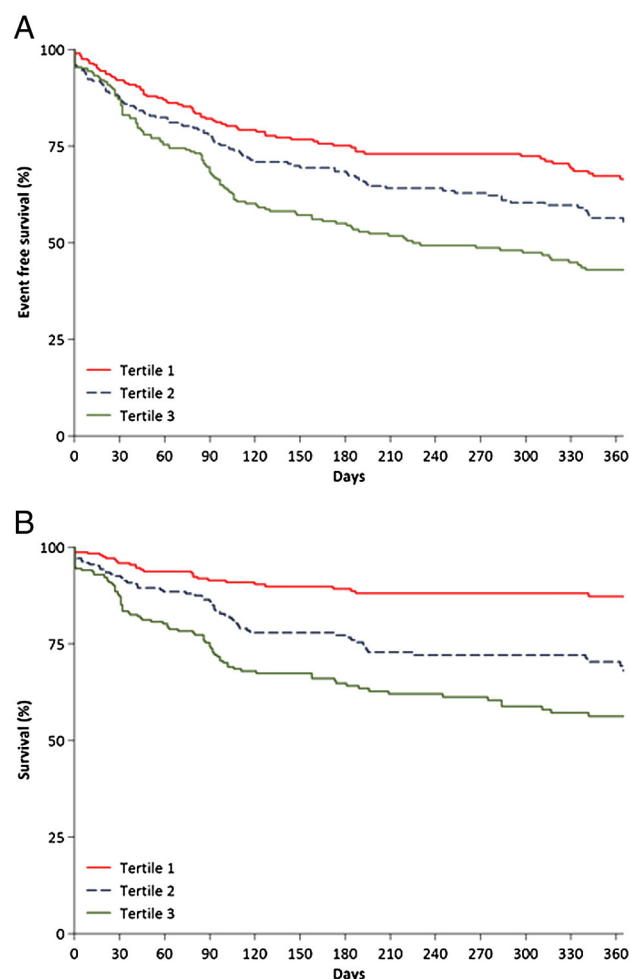
Fig. 1. A and 1B. Distribution of risk scores and association of risk with probability of events. Distribution of risk scores for (A) all-cause mortality or cardiovascular hospital admission (N = 926); Mean (SD) risk score: 2.23 (0.66) and (B) all-cause mortality, and their relation to probabilities of an event occurring over one year years (N = 925); Mean (SD) risk score: 2.51 (1.03). Histograms represent percentage of patients with a particular risk score, and the solid line represents probability of an event over one year follow-up period for a particular risk score.

Fig. 2. A. Kaplan–Meier curves of event rates stratified by tertiles of risk Kaplan–Meier plots for the composite of all-cause mortality or cardiovascular hospital admission; tertile 1, lower risk; tertile 2, intermediate risk; and tertile 3, higher risk. p < 0.001, test long rank. B. Kaplan–Meier curves of event rates stratified by tertiles of risk Kaplan–Meier plots for all-cause mortality; tertile 1, lower risk; tertile 2, intermediate risk; and tertile 3, higher risk. p < 0.001, test long rank.

4. Discussion

Our analysis has applied a risk model derived from a clinical trial of elderly HF patients to a "real world" observational registry of acute HF admissions, in both cases without restriction by left ventricular ejection fraction. We found that the model was a reliable tool for risk stratification (determining if patients were at lower or higher risk) but there was variability in estimating absolute risk. There was moderate correlation for predicting death/CV hospital admission (c statistic = 0.60) but this appeared to be better for all-cause mortality (c = 0.66). Our model is one of the few to focus on elderly HF patients including those with preserved ejection fraction. When restricting the analysis to those with ejection fraction 50% and no evidence of prior HF we found a similar utility to the whole cohort supporting the wide applicability of this risk model. There are several explanations for differences between predicted and observed rates including

- variables that could be relevant to acute heart failure which have not been included in the original SENIORS model
- potential that a single model cannot be applied to acute and chronic HF populations

- inherent weaknesses in the model that limit its applicability across widely different populations as it was derived from a selected clinical trial population.

Our study simplifies the SENIORS risk model in elderly patients using only 8 variables (NYHA class, prior MI, LA dimension, uric acid, and BMI, peripheral arterial disease, right bundle branch block and diabetes mellitus) in the death/CV hospital admission model, and 7 variables (NYHA class, prior MI, LA dimension, uric acid, and BMI, creatinine and age) in the mortality model. These variables are commonly measured in the clinical practice in elderly HF patients which could make the model more applicable in routine clinical care.

Risk models are helpful to determine prognosis in patients with complex conditions. One of the main strategies with elderly HF patients is to maintain a good quality of life and avoid hospital admissions and our risk model could identify those who require more intense treatment and follow-up or in some cases those that require supportive or palliative care. However clinical risk prediction in these patients can be challenging due to the presence of co-morbidities and therefore a specific risk model can provide additional useful information on top of clinical assessment.

A

B
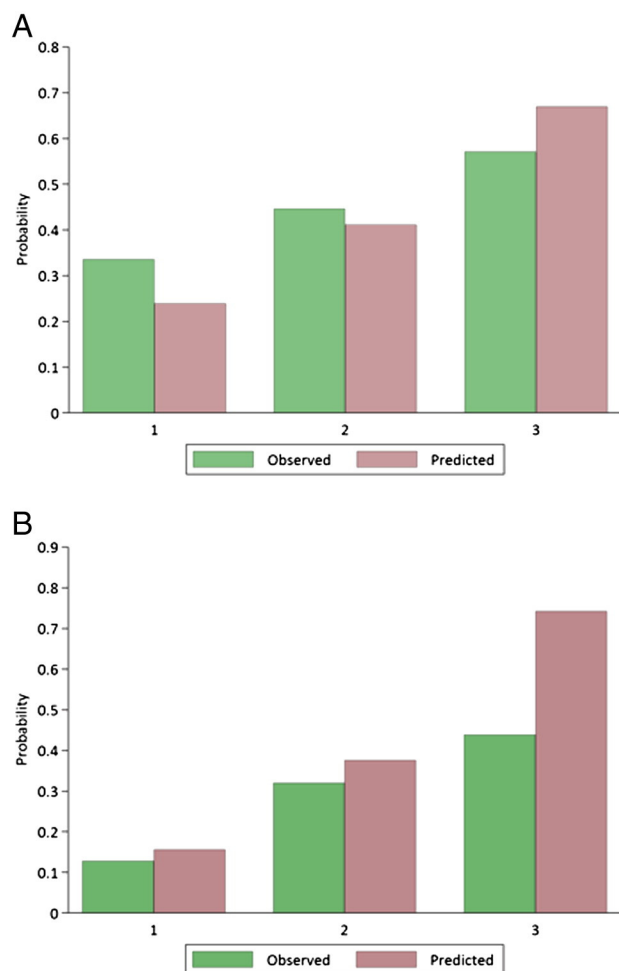
Fig. 3. A. Probability of a primary outcome event (death or cardiovascular hospitalization) observed/expected at 1 year in each tertile of baseline risk. B. Probability of all cause mortality observed/expected at 1 year in each tertile of baseline risk.

Our findings have similarities to other studies for example validation of the SEATTLE risk model, but this did not focus on elderly patients [11]. There is a need to validate risk models in a wide range of HF patients including the elderly and those with diabetes [19–21]. A further validation study applying the SEATTLE risk model to HF patients >80 years showed a large underestimation of risk and the authors concluded that further work was needed to validate risk models in elderly HF patients [21].

Pocock and colleagues [22] have reported a meta-analysis of individual patient level data on 39,372 patients with HF enrolled into 30 cohort studies. The authors identified 13 individual predictors of mortality (age, lower EF, NYHA class, serum creatinine, diabetes, not prescribed beta-blocker, lower systolic blood pressure, lower body mass, time since diagnosis, current smoker, chronic obstructive pulmonary disease, male gender, and not prescribed ACE-inhibitor or angiotensin-receptor blockers). Age appeared to be more predictive of mortality in HF with preserved ejection fraction. The mean age of survivors in the meta-analysis was 64 years (and 72 years for those that died) indicating that most patients in these studies were younger than those included in our analysis. Age did not feature as a predictor in our final model probably because we included an elderly population.

A systematic review of predictive models for patients with HF provides important insights into strengths and weaknesses of those heart failure risk models that have undergone external validation analyses [23]. Their conclusions are that "these models showed inconsistent performance including the Heart Failure Survival Score [24] and Seattle

Heart Failure Model which demonstrated modest discrimination and questionable calibration. A new model derived from contemporary patient cohorts may be required for improved prognostic performance". One key problem is that many models are derived from clinical trials or populations with limited generalizability which is a criticism that can be applied to our analysis. A risk model has also been developed in 4128 patients in the I-PRESERVE trial (preserved EF, mean age 72 years). NT-ProBNP, age, diabetes, previous hospitalization and left ventricular EF were the strongest independent prognostic factors [25]. This study has younger patients than our analysis, was restricted to patients with preserved EF and has not been externally validated yet. Eapen et al. report a 30 day risk stratification model in 33,000 patients with mean age 80 years hospitalized with both impaired and preserved ejection fraction using routinely available data [26]. The 30-day mortality model demonstrated good discrimination with a c-index of 0.75 while the mortality/rehospitalization model demonstrated more modest discrimination with a c-index of 0.62 which is similar to our results even though their model is an "internal" validation in contrast to ours which is an external validation.

There are some limitations to our study. The risk model shows variability in estimates of observed versus predicted risk and although some of this would be expected the upper tertile of all-cause mortality shows a clear discrepancy. However there does not appear to be an accepted standard for discrepancies between observed and predicted risks and this could be a subject for future discussion in professional societies. Also our model cannot be readily applied to the clinical situation as the calculation is complex but this limitation is common to most risk models in HF. One area for further investigation is why the different HF risk models include different variables. This may be in part be due to inclusion of different variables in the study database for example some models include NT-proBNP but this variable is not routinely collected in many studies. In our model we believe that uric acid and left atrial dimension are two key components to improve the approach to the prognosis of elderly HF patients.

5. Conclusion

Our findings show that the SENIORS risk model was a reliable tool for risk stratification of elderly HF patients in a "real world" registry, but predicted versus observed risk showed some variability. This model provides a useful basis for clinical risk prediction but further work is needed to develop a reliable risk tool for elderly patients with acute heart failure.

Acknowledgements

Appendix A

RICA registry members: Anarte L, Aramburu O, Arévalo JC, Bas F, Bettencourt P, Carrera M, Cerqueiro JM, Conde A, Dávila MF, Díez J, Epelde F, Formiga F, González A, Guisado ME, Lebrón JM, Llacer P, Manzano L, Martínez A, Montero M, Muela A, Murado I, Oropesa R, Pérez JI, Quesada MA, Quirós R, Roca B, Ruiz R, Ruiz-Laiglesia F, Salamanca P, Sánchez M, Satué JA, Serrado A, Suárez I, Trullàs JC, and Urrutia A.

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