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Prognostic value of discharge heart rate in acute heart failure patients: More relevant in atrial fibrillation?

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ABSTRACT

Aims: The prognostic impact of heart rate (HR) in acute heart failure (AHF) patients is not well known especially in atrial fibrillation (AF) patients. The aim of the study was to evaluate the impact of admission HR, discharge HR, HR difference (admission-discharge) in AHF patients with sinus rhythm (SR) or AF on long- term outcomes.

Methods: We included 1398 patients consecutively admitted with AHF between October 2013 and December 2014 from a national multicentre, prospective registry. Logistic regression models were used to estimate the association between admission HR, discharge HR and HR difference and one- year all-cause mortality and HF readmission.

Results: The mean age of the study population was 72 ± 12 years. Of these, 594 (42.4%) were female, 655 (77.8%) were hypertensive and 655 (46.8%) had diabetes. Among all included patients, 745 (53.2%) had sinus rhythm and 653 (46.7%) had atrial fibrillation. Only discharge HR was associated with one year all-cause mortality (Relative risk (RR) = 1.182, confidence interval (CI) 95% 1.024–1.366, p = 0.022) in SR. In AF patients discharge HR was associated with one year all cause mortality (RR = 1.276, CI 95% 1.115–1.459, $p \leq 0.001$). We did not observe a prognostic effect of admission HR or HRD on long-term outcomes in both groups. This relationship is not dependent on left ventricular ejection fraction.

Conclusions: In AHF patients lower discharge HR, neither the admission nor the difference, is associated with better long-term outcomes especially in AF patients.

1. Introduction

Acute heart failure (AHF) refers to the rapid onset or worsening of symptoms and/or signs of HF [1]. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission [1]. Despite improvements in the treatment and outcome of chronic heart failure (HF), those for AHF have remained relatively unchanged for the last 30 years [2,3]. Much of this lack of progress can be attributed to imperfect characterization and understanding of the physiopathology of AHF [4,5].

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Elevated resting heart rate (HR) has been associated with increased mortality in the general population [6] as well as in those with coronary artery disease [7,8]. Similar findings have been reported in patients with HF, although most of these studies examined patients with chronic HF [9,10].

The prognostic impact of HR in AHF is less well studied and also few studies have included AHF patients with atrial fibrillation (AF) or had sufficient power to evaluate potential time-dependent differences in the relationship between HR and outcomes [11].

A recent large retrospective study suggested that higher HR was independently associated with higher in-hospital mortality in AHF patients [12]. Higher HR in AHF patients presenting to the emergency department also predicted higher 7-day mortality [13]. These observations lead to the inclusion of admission HR in risk scores for the assessment of short-term prognosis in AHF [14,15].

Despite the importance of HR as a predictor of clinical outcomes for patients with sinus rhythm [16], limited information about the relationship of HR (or the change in HR) to post-discharge outcomes is known in patients with AF and AHF [15].

Also whether early HR reduction improves outcomes in patients hospitalized with AHF is not clear because a recent study suggested the change in HR during hospitalization was a stronger predictor of the risk of future cardiac events in patients with AHF compared with other markers, in patients receiving beta-blockers [17].

The aim of our study was to evaluate the prognostic value of HR at admission, HR at discharge and heart rate difference (HRD) in AHF patients with sinus rhythm (SR) and AF on long-term outcomes.

2. Material and methods

2.1. Study population

We included patients from a national multicentre, prospective registry (REDINSCORII), which includes input from as many as 20 Spanish hospitals of varying complexity. The registry was compiled consecutively between October 2013 and December 2014 and included a total of 1831 patients admitted with acute HF. The REDINSCORII registry did not include any participants from the previous REDINSCOR I study, which examined patients with chronic HF recruited during cardiology consultations [18]. The study complies with the Declaration of Helsinki, ethics committees at the participating hospitals approved the study, and all patients gave written informed consent.

Patients in the registry were older than 18 years and were hospitalized in the cardiology unit for at least 24 h; the main reason for admission was the presentation of symptoms compatible with AHF, both de novo and decompensated, and a chest X-ray indicating pulmonary congestion.

Exclusion criteria included ST-elevation acute coronary syndrome, an end-stage disease with a life expectancy <1 year, and any condition likely to preclude follow-up. Patients with missing baseline electrocardiograms or in paced rhythm were excluded. HF diagnostic was made according to the 2012 European Society of Cardiology HF guidelines [1]. The population was divided according to the rhythm in two groups: sinus rhythm or atrial fibrillation. The flowchart of the patients of the study is shown in Supplementary Figure 1.

2.2. Study variables

Data collected for each AHF patient include demographics, medical/surgical history including any history of AF, admission medications, admission and discharge vital signs, physical examination, the rhythm at the time of admission, serum laboratory tests, pharmacological and no pharmacologic interventions, in-hospital outcomes, and discharge information. In addition, blood samples were obtained for local laboratory analysis and left ventricular ejection fraction (LVEF) was estimated using Simpson's method according to current international recommendations [19]. HF was defined as being ischemic in aetiology if any of the following criteria were satisfied: prior admission because of an acute coronary event (acute myocardial infarction or unstable angina), prior surgical or percutaneous myocardial revascularization, the presence of myocardial infarction on electrocardiogram or echocardiogram, or significant coronary disease detected by angiography.

Heart rhythm was electrocardiographically determined. HR was determined in conformance with the local protocol for obtaining vital signs. In all patients, heart rate was electrocardiographically or telemetrically determined. Heart rate difference (HRD) was defined as the difference between admission HR less discharge HR.

2.3. Follow-up

In addition to clinical follow-up adjusted to the patient's needs, vital status and events were gathered by telephone interview at 1, 3, and 6 months, and at 1 year, if there was no in-person visit at those time points. Patients who died during the hospitalization index were excluded (Supplementary Fig. 1). The outcomes for this analysis were all-cause mortality and HF readmission one-year after discharge.

2.4. Statistical analysis

Quantitative variables are expressed as mean ± SD and qualitative variables are expressed as frequency (percentage). Qualitative variables were compared using the chi-square test or the Fisher exact test, and quantitative variables were compared by the Student *t*-test.

Logistic regression models were used to evaluate the relationship between the outcomes (one-year mortality and one-year heart failure readmission) with HR (at admission, post-discharge or difference). We fit unadjusted and adjusted models separately in SR and AF patients. Adjusted models included age, gender, previous HF, NT-proBNP levels, LVEF, history of diabetes, betablockers at discharge, ischemic HF, creatinine levels at admission, sodium levels at admission, haemoglobin levels at admission, body mass index (BMI) and systolic blood pressure at admission. We studied the possible nonlinear effect of each predictor on the outcome, by means of Generalized Additive Regression models (GAM) using penalized regression splines [20]. Crude and adjusted relative risks (RR) and 95% confidence intervals (CI) for a 10-unit increment in HR were calculated. Interactions were also assessed to study the relationship between post-discharge-HR and mortality (and HF readmission) according to LVEF groups (lower or higher than 40%).

Single-variable Cox models were used to evaluate association in both groups (SR and AF) between the all-time risk of death and of heart failure readmission and post-discharge HR. Taking data censoring into account, the log hazard ratios of the unadjusted Cox models were used as criterion variables X to construct time-dependent Receiver Operating Curves (ROCs) [21] via the corresponding sensitivity and specificity functions: for given time t and criterion threshold c, sensitivity $(c, t) = P(X > c|T \le t)$; specificity$(c,t) = P(X \le c|T > t)$, where T is survival time. For each time t, the area under the time-dependent ROC [AUC(t)] was calculated.

To deal with missing values, we performed a missing data analysis [22]. After assuming that these values were missing at random, multiple imputations by chained equations were used. The main reasons for missing data were the lack of NT-proBNP levels

(459 patients, 30.2%), LVEF (333, 21.9%), BMI (253, 16.6%), ischemic HF (193, 12.7%), and betablockers at discharge (43, 2.8%), or for other information (<1%).

Statistical analyses and graphics were carried out in R using the packages "mgcv", "mice", "survival", "survivalRoc", "voxel" and "ggplot2". These packages are freely available at http://cran.r-project.org. Differences were considered statistically significant at $P < 0.05$

3. Results

3.1. Baseline characteristics

The final cohort of the population included 1398 patients and their characteristics are summarized in supplementary Table 1. The mean age of the analyzed study population was 72 ± 12 years. Of these, 591 (42.4%) were female. The most frequent risk factor was hypertension, affecting 1081 patients (77.6%); 652 patients (46.8%) had diabetes. More than half the patients (776; 55.7%) had a previous HF diagnosis and the mean LVEF was 45 ± 17%. Among all included patients, 742 (53.3%) had sinus rhythm and 651 (46,7%) had atrial fibrillation.

The two groups differed significantly in sex, diabetes mellitus, ischemic aetiology, LVEF, body mass index and in admission HR, discharge HR and HRD. Overall patients with SR were more frequently prescribed angiotensin-converting enzyme inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs), and statins; patients with AF received more frequently digoxin and calcium channel blockers.

3.2. Sinus rhythm group

There were 745 patients in the SR group. The mean discharge HR was 72 ± 13 beats per minute (range 40–127 bpm) and the patients were classified into four groups according to the discharge HR (Q_1 = 40–63 bpm, Q_2 = 63–70 bpm, Q_3 = 70–80 bpm, Q_4 = 80–127 bpm). Patients with lower HR at discharge (Q1, Q2) had higher LVEF, higher doses of amiodarone prescription and lower doses of diuretics compared with patients with higher HR at discharge (Q3, Q4). Also, patients with lower HR at discharge had lower HR at admission (78 ± 22 vs 92 ± 18 bpm, $p < 0.001$) and higher HR difference (21 ± 22 vs 1 ± 20 bpm, $p < 0.001$). We did not find differences in the betablockers or digoxin prescription (Supplementary Table 2).

3.3. Atrial fibrillation group

There were 653 patients in the AF group. The mean discharge HR was 74 ± 15 bpm (range 38–140 bpm). The patients were divided into four groups according to the discharge HR (Q_1 = 38–64 bpm, Q_2 = 64–73 bpm, Q_3 = 73–84 bpm, Q_4 = 84–140 bpm). The main differences between were found in terms QRS duration (Q_1 = 117 ± 33 vs. Q4 = 102 ± 26 ms, $p < 0.001$) and HRD difference (Q_1 = 37 ± 32 vs Q4 = 9 ± 24 bpm, $p < 0.001$). Patients in Q4 were prescribed more frequently on digoxin and calcium channel blockers and less on ACEIs. These results are shown in Supplemenatary Table 3.

3.4. Long-term follow up

The one-year all cause mortality was 17.2% (153 patients) in the SR group and 22.20% (145 patients) in the AF group ($p = 0.285$). The one-year HF readmission was 32.1% (229 patients) in the SR group and 31.8% (199 patients) in the AF group ($p = 0.910$). The baseline characteristics are described in supplementary Table 4.

4. Prognostic effect of admission HR, discharge HR and HRD on one year outcomes in SR patients.

Crude and adjusted models observed that according to regression analysis only discharge HR was associated with all cause one- year mortality (RR = 1.182, CI: 1.024–1.366, $p = 0.022$) (Table 1). However it did not have impact on HF readmission (RR = 1.027, CI: 0.914–1.155, p = ns). It was also found that age, systolic blood pressure at admission; creatinine, sodium, and NT-proBNP levels were predictors of one year all cause mortality (Supplementary Table 5).

A prognostic effect of admission HR or HRD on HF readmission was not found (Table 1). Previous HF was associated with one-year HF readmission (Supplementary Table 5).

5. Prognostic effect of admission HR, discharge HR and HRD on one year outcomes in AF patients

In the same analysis we found that in AF patients discharge HR was associated with all cause one-year mortality (RR = 1.276, CI 1.115–1.459, $p \leq 0.001$) (Table 2) with no effect on HF readmission (RR = 0.938, CI 95%, 0.835–1.053, p = ns) (Table 2). In this group of patients also diabetes mellitus, age, betablockers prescribed at discharge (OR = 0.51, CI 95% 0.320–0.800), creatinine, hemoglobine and NT-proBNP levels were associated with one year all cause mortality (Supplementary Table 6).

As in SR patients a prognostic effect of admission HR or HRD on one year all cause mortality or HF readmission (Table 2) was not found. However, age, haemoglobin and creatinine, levels were predictors of one year HF readmission in this group of patients (Supplementary Table 6).

6. Relationship with left ventricular ejection fraction

A significant linear relationship was found between discharge-HR and mortality in both LVEF groups (LVEF < 40%, LVEF > 40%) The prognostic value is not dependent on LVEF having the highest predictive value in AF patients (Figure 1). Discharge HR was not found to be associated with one-year HF readmission neither in SR nor AF patients.

6.1. Time-dependent prognostic value

We also performed time- dependent AUC (area under curve) to determine the effect of discharge HR during the 12 months after discharge. In both rhythms, the highest AUC is observed during the first month postdischarge (Figure 2). However during the follow up discharge HR has higher predictive value in AF compared with SR.

7. Discussion

In this analysis of patients with AHF enrolled in the REDINSCORII multicentre Registry, we observed that only discharge HR is associated with one-year mortality in SR and AF patients but not admission HR or HR difference. The magnitude of the association is greater in AF patients, especially in the first months post discharge. This relationship is not dependent on LVEF. We demonstrated that there is a linear relationship between discharge HR and mortality in AHF patients with AF suggesting that the lower discharge HR the better outcomes. Indeed, we did not observe HR effect of one- year HF readmission. Our results suggest that in AHF only discharge HR should be considered as a therapeutic target in this population. Several measures aimed to optimize HR at hospital discharge, including guideline recommended medications that need to be started during hospital stay especially, in AF patients.

Table 1
Prognostic impact of admission HR, discharge HR and HRD on long -term outcomes in sinus rhythm patients.

All cause one year mortality	RR, CI 95%	P	RR, CI 95%	p
HR admission	1.005 (0.928–1.089)	0.896	1.064 (0.971–1.165)	0.182
HR discharge	1.155 (1.020–1.307)	0.022	**1.182 (1.024–1.366)**	**0.022**
HR difference	0.950 (0.860–1.050)	0.212	0.995 (0.911–1.088)	0.917
One year HF readmission	RR, CI 95%	p	RR, CI 95%	p
HR admission	0.927 (0.862–0.997)	0.041	0.970 (0.895–1.050)	0.447
HR discharge	1.028 (0.922–1.146)	0.621	1.027 (0.914–1.155)	0.651
HR difference	0.924 (0.861–0.990)	0.025	0.962 (0.892–1.037)	0.311

CI: confidence interval; HF: heart failure; HR: heart rate; RR: relative risk
*Adjusted by sex, age, ischemic heart failure, previous HF, creatinine levels, haemoglobin levels, sodium levels, body mass index, left ventricular ejection fraction, NT-proBNP levels, betablockers at discharge, diabetes mellitus, systolic blood pressure at admission.

Table 2
Prognostic impact of admission HR, discharge HR and HRD on long-term outcomes in atrial fibrillation patients.

All cause one year mortality	RR, CI 95%	p	RR, CI 95%	p
HR admission	0.909 (0.848–0.973)	0.006	1.003 (0.995–1.012)	0.460
HR discharge	1.214 (1.082–1.362)	<0.001	**1.276 (1.115–1.459)**	**<0.001**
HR difference	0.863 (0.806–0.924)	<0.001	0.946 (0.874–1.024)	0.169
One year HF readmission	RR, CI 95%	p	RR, CI 95%	p
HR admission	0.918 (0.865–0.975)	<0.001	0.953 (0.888–1.024)	0.188
HR discharge	0.931 (0.836–1.036)	0.190	0.938 (0.835–1.053)	0.277
HR difference	0.946 (0.896–1.000)	0.0504	0.980 (0.919–1.046)	0.548

CI: confidence interval; HF: heart failure; HR: heart rate; RR: relative risk.
*Adjusted by sex, age, ischemic heart failure, previous HF, creatinine levels, haemoglobin levels, sodium levels, body mass index, left ventricular ejection fraction, NT-proBNP levels, betablockers at discharge, diabetes mellitus, systolic blood pressure at admission.

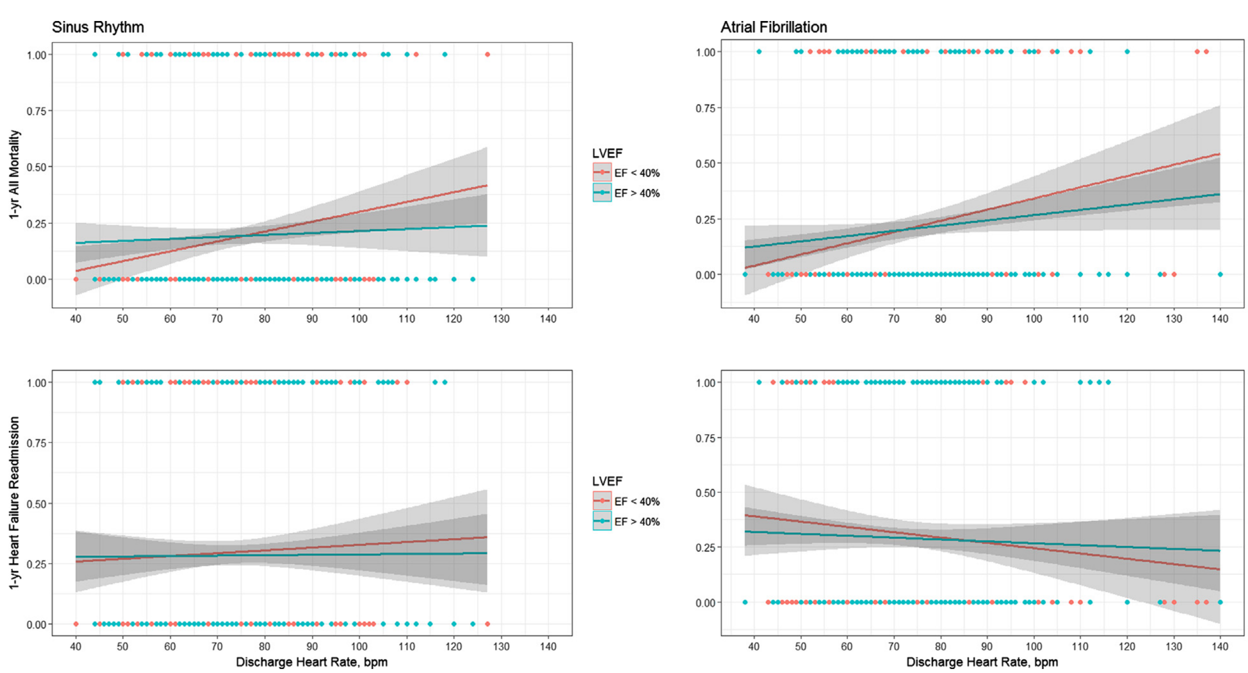

Fig. 1. Effect of post-discharge heart rate on one year all cause mortality, cardiovascular mortality and heart failure readmission in sinus rhythm (A) and atrial fibrillation (B) patients.

The role of HR as a prognostic predictor in chronic and acute worsened HF patients has been evaluated in a number of studies summarized in a recent paper published by Oliva et al. [23]; even though there is a relative paucity of data on the role of HF at discharge after a phase of clinical instability both in patients with SR or AF. The EVEREST trial examined 1947 patients with SR and left ventricular systolic dysfunction who had been admitted for AHF, in the early pre-discharge increases of HR > 70 bpm have been shown to be an independent predictor of mortality during the early follow-up; and a 5 bpm increment in the first week post-discharge was associated with an increase of overall mortality [24]; discharge HR was also associated with higher mortality in the ASCEND-HF trial, where no significant interaction effect was observed between HR at discharge and mortality with beta-blocker therapy at discharge [25].

For the first time we described that in real life patients discharge HR is associated with one year all cause mortality in SR and AF patients. In SR every increase of 10 bpm increases 18%

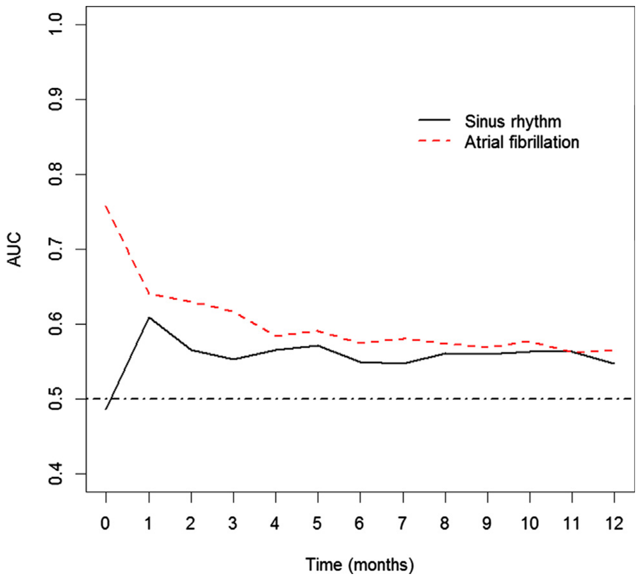

Fig. 2. The area under the time-dependent ROC [AUC(*t*)] of discharge Heart rate in sinus rhythm and atrial fibrillation patients.

the risk of the one-year all cause mortality and in AF every increase of 10 bpm increases 27% the risk of the one year all cause mortality.

Our results are similar to the AHA GWTG-HF prospective registry that has involved 46,000 patients who have been discharged after a phase of clinical deterioration, and had found a correlation between HR at discharge and the likelihood of re-hospitalizations for all-causes [11]. However in this study, only elderly patients (>65 years) were included, our results are applied to the all AHF population regardless of age. Similar findings were described in a study performed in the context of the EFFECT-HF program with a significant correlation between HR and early mortality, particularly in the subgroup of patients with HR comprised between 81 and 90 bpm (hazard ratio: 1.59) and higher than 90 bpm (hazard ratio: 1.56) [26].

Current European Society of Cardiology HF guidelines do not have a clear recommendation for heart rate control in AHF with AF [1] and ventricular rates <70 bpm are associated with a worse outcome [27]. We have demonstrated that the lower discharge HR the better all cause and cardiovascular mortality (Fig. 2) and maybe the recommendation of HR between 60 and 100 bpm should be modified. Our data suggest that post-discharge HR can offer an important contribution in terms of the determination of prognosis; nevertheless, it remains to be clarified whether early HR reduction could have a positive impact on clinical events in AHF patients. Also, we observed that the prognostic value is higher in the first months post-discharge so it is reasonable to believe that post-discharge HR could be an important contribution in the prognostic stratifications of patients with a recent episode of worsening HF.

To our knowledge, only a small single center registry analyzed the prognostic impact of HR changes during hospital admission in patients with AHF. Takahama et al described in this single hospital registry of 421 patients that HR reduction (≥27 bpm during in-hospital stay) was associated with a significantly lower cardiac event rate, isolated HR at discharge was not associated with the prognosis [17]. In our study we did not observe a relationship between HRD and outcomes between SR or AF patients hospitalised for worsening HF; suggesting that only discharge HR should be considered as a therapeutic target in this population.

As previous studies, we found that admission HR did not have predictive value with long-term events [24,28]. Such discrepancy could be explained by the fact that at admission HR represents a marker of the severity of temporary hemodynamic conditions and may be therefore a predictor of early, as compared to late, adverse events [23].

We could not observe the effect of HR on one-year HF readmission. The prognostic impact of HR in early HF readmission has been described [26], however, the impact of HR in long term HF readmission is not well known and unfortunately, our results could not clarify this question.

We also found a beneficial effect of betablockers in SR and AF patients. The role of betablockers in SR patients has been well established [1], however, Mareev et al. [27] questioned the use of betablockers in AF and HF patients. Our results reinforced the beneficial effect of betablockers in AF patients and they should be prescribed according to guidelines recommendations [1] in order to achieve the lower discharge HR especially in AF patients where the benefices of lowering HR are higher than in SR patients.

Several studies have evaluated the prognostic role of HR in chronic HF with reduced and preserved ejection fraction with and without AF [22,23,29,30]. In our study, we described that the effect of postdischarge HR is not dependent of the LVEF in both SR and AF patients suggesting that lower discharge HR should be acquired in reduced and preserved LVEF patients.

Although some studies [23] suggested a J-shaped for HR in chronic HF patients we studied the possible nonlinear effect of discharge HR on the outcome by using penalized regression splines. However a linear relationship between HR and mortality was found. We must acknowledge some limitations; the REDINSCORII registry includes patients admitted to Spanish cardiology services with decompensated or de novo HF and who were monitored prospectively for 1 year. Our results are therefore limited to this patient category, which is underrepresented in the literature because most registries include outpatients with stable chronic HF or a mix of acute and chronic HF patients. Also given the observational nature, unobserved variables may exert a confounding effect on the results. HR was measured in two time-points: admission and discharge; so time until HR control was not taken into consideration. The evaluated treatments are those prescribed at hospital discharge, and we are therefore also unable to confirm whether the therapeutic strategy was maintained throughout the follow-up period, a factor that could influence prognosis. We did not have information about how many patients who were admitted with atrial fibrillation were cardioverted to sinus rhythm. However our results showed the impact of HR in a real cohort of patients with AHF.

8. Conclusions

In a cohort of AHF patients, only high discharge HR is associated with worse outcomes in SR and AF patients. Our study suggests that HR should be optimized with guideline recommended medications in the transition from hospital to ambulatory care in the community especially in AF patients.

Funding

Nothing to declare.

Declaration of Competing Interest

We declare that we have no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100444.

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