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ORIGINAL PAPER

Prognostic significance of atrial fibrillation in acute decompensated heart failure with reduced versus preserved ejection fraction

Alexander Jobs[1,2] · Julia Schwind[1] · Alexander Katalinic[3] · Valentin Babaev[3] · Roland Richard Tilz[1,2] · Stefan Rausch[1] · Holger Thiele[4] · Ingo Eitel[1,2] · Charlotte Eitel[1,2]

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Abstract

Objective The prognostic impact of atrial fibrillation (AF) in patients with acute decompensated heart failure (ADHF) has not been fully elucidated yet. Aim of the present study was thus to investigate the association of AF with all-cause mortality in patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

Methods We performed a retrospective single center study and analyzed data of 1286 patients admitted for ADHF. Patients were grouped according to AF status (i.e., "never AF", "history of AF", or "AF on admission") and type of heart failure. Patient and treatment characteristics were extracted by chart review. The primary outcome of all-cause mortality within 3 years following index hospitalization was determined by death registry linkage.

Results In total, 529 (41.1%), 215 (16.7%), and 542 (42.1%) patients were grouped as "never AF", "history of AF", and "AF on admission", respectively. With regard to type of heart failure, 558 (43.4%) and 728 (56.6%) had HFrEF and HFpEF, respectively. Compared to "never AF", "AF on admission" was associated with increased all-cause mortality in an adjusted Cox regression model [hazard ratio, 1.64 (95% confidence interval 1.32–2.04); $P < 0.001$]. However, this association remained significant only for patients with HFpEF [2.16 (1.58–2.95)], but not for patients with HFrEF [1.18 (0.85–1.63)] in a subgroup analysis (P for effect modification = 0.020).

Conclusions AF is common in the setting of ADHF and is associated with increased all-cause mortality. However, this association remained significant only in patients with HFpEF, but not in patients with HFrEF.

Keywords Acute decompensated heart failure · Atrial fibrillation · Heart failure with reduced ejection fraction · Heart failure with preserved ejection fraction

Abbreviations

ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
CI	Confidence interval
ECG	Electrocardiography
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IQR	Interquartile range
RCT	Randomized controlled trial

Introduction

Heart failure is associated with several comorbidities of which atrial fibrillation (AF) is one of the most frequent. Vice versa, heart failure is also common in AF [1]. Epidemiological data indicate that both conditions may promote

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✉ Alexander Jobs
alexander.jobs@uksh.de

1 Department of Cardiology, Angiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, University Heart Center Lübeck, Medical Clinic II, Ratzeburger Allee 160, 23538 Lübeck, Germany

2 German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany

3 Institute for Cancer Epidemiology e.V., University of Lübeck, Lübeck, Germany

4 Department of Internal Medicine/Cardiology, Heart Center Leipzig, University Hospital, Leipzig, Germany

each other [2]. This is due to a complex relationship with similar risk factors on the one hand [3] and the fact that each condition can trigger the other on the other hand. AF can provoke heart failure through rapid heart rate, loss of atrial transport function, and atrioventricular dyssynchrony [4] whereas heart failure can trigger AF through rise in left atrial filling pressure and/or chronic atrial fibrosis [5]. In acute decompensated heart failure (ADHF), clinical deterioration often requires hospitalization which is associated with a considerably increased mortality risk [6]. Heart failure with preserved ejection fraction (HFpEF) accounts for almost 50% of ADHF admissions and its prevalence is increasing [7]. Of note, the survival is similar for HFpEF compared to heart failure with reduced ejection fraction (HFrEF) [8]. In patients with chronic heart failure, AF is associated with a poor prognosis [9]. Moreover, the prognostic impact of AF in heart failure may differ between patients with HFrEF and HFpEF [10]. However, data in patients hospitalized for ADHF are sparse [11–13]. Therefore, we aimed to investigate the impact of AF on all-cause mortality in a large cohort of patients hospitalized for ADHF and to further explore whether prognosis might differ between HFrEF and HFpEF.

Methods

Study population

Patients with the primary discharge diagnosis of heart failure (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification code I50.*) treated for at least 3 days in our department (Department of Cardiology, University Heart Center, Lübeck, Germany) between April 1st, 2008, and December 31st, 2014 were identified through a hospital information system query. In patients hospitalized more than once, only the first hospitalization (i.e., index hospitalization) was considered. The diagnosis of ADHF was verified based on chart review if two or more of the following symptoms or signs were reported: dyspnea on minimal exertion or at rest/orthopnea (New York Heart Association functional classification ≥ III), jugular venous distention, pulmonary rales, and bilateral edema of the lower extremities. Patients were included in the final analysis if left ventricular ejection fraction was at least semiquantitatively assessed by echocardiography during index hospitalization and heart rhythm on admission was reported. The study was approved by the ethical review committee of the University of Lübeck. Figure 1 depicts the flow of identification of the study population.

Data extraction and definitions

Data were extracted by retrospective chart review. Baseline characteristics including age, gender, date of admission, date of discharge, and laboratory values were extracted directly from the hospital information system. Comorbidities including history of AF and heart rhythm on hospital admission were obtained by reviewing discharge letters. Echocardiography parameters were obtained by reviewing echocardiography reports.

Patients were grouped according to AF status based on the discharge letter: never AF (never AF group), history of AF without AF on admission (history of AF group), and AF on admission (AF on admission group) which was regarded as history of AF per default. In addition, findings of device interrogation were also used in patients with implanted pacemaker or defibrillators.

Patients were considered to have HFrEF when the echocardiography report stated that left ventricular ejection fraction was moderately or severely abnormal. According to the 2005 recommendations for chamber quantification [14] this translates to a left ventricular ejection fraction of < 45% which is close to ≤ 40% stated in the current ACCF/AHA heart failure guidelines for the HFrEF definition [15]. Patients with normal or mildly abnormal ejection fraction (i.e., ≥ 45%) were considered to have HFpEF. Worsening renal function was defined as increase in creatinine concentration of ≥ 1.5-times from baseline or ≥ 26.5 µmol/l within 48 h as recently suggested [16].

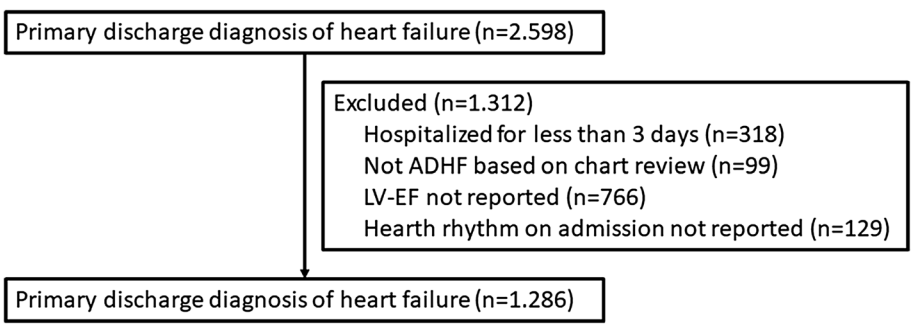

Fig. 1 Flowchart visualizing the identification of the study population. *ADHF* acute decompensated heart failure, *LV-EF* left ventricular ejection fraction

Mortality data

The primary outcome of all-cause mortality was assessed via the death registry of the province of Schleswig–Holstein. For patients who did not die, the end of follow-up was defined as the latest documented contact, i.e., either discharge from index hospitalization, discharge from the last local hospitalization at the University Hospital of Lübeck, or date of the death registry query. Since follow-up was longer than 3 years only for a minority of patients, all patients alive were censored at 3 years after index hospitalization.

Statistical analysis

The final study population consisted of patients meeting the above mentioned criteria. Categorical patient characteristics were summarized as frequencies and compared using Pearson's Chi-square test. Continuous variables were summarized as median with interquartile range (IQR) and compared using Wilcoxon rank-sum test in case of two groups or Kruskal–Wallis test in case of more than two groups. Associations of AF status with all-cause mortality were assessed by means of Cox regression models. Multivariable models were adjusted for patient characteristics available at hospital admission with less than 5% missing values (i.e., age, sex, history of coronary artery disease, history of myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, history of diabetes mellitus, history of chronic obstructive pulmonary disease, history of stroke, history of peripheral artery disease, history of hypertension, symptoms at rest on admission, estimated glomerular filtration rate on admission, hemoglobin level on admission, and presence of hyponatremia on admission). To assess whether the type of heart failure influences the prognostic impact of AF, the overall cohort was stratified in HFrEF and HFpEF. Effect modification was assessed on the multiplicative scale and presented as recommended [17]. Cumulative mortality rates were visualized by means of a Kaplan–Meier plot and compared using log-rank test. All statistical tests were 2-sided and considered significant if $P<0.05$. All statistical analyses were performed with R version 3.1.3 (http://www.r-project.org).

Results

Patient characteristics

Over the study period, 1286 patients met the inclusion criteria with documentation of heart rhythm at hospital admission and were included in the final analysis. Of these, 601 patients (46.7%) had sinus rhythm, 542 (42.1%) had AF, 22 (1.7%) had atrial tachycardia, and 121 (9.4%) had an unspecified rhythm (including pacemaker stimulation). A history of AF was documented in 757 (58.9%) patients. Combining heart rhythm on admission and history of AF, patients were classified as follows: never AF in 529 (41.1%) patients, history of AF in 215 (16.7%) patients, and AF on admission in 542 (42.1%) patients.

According to echocardiography reports, 558 (43.4) and 728 (56.6%) of patients were classified as having HFrEF and HFpEF, respectively. Prevalence of HFrEF was not different between AF groups ($P=0.444$ for Pearson's Chi square test).

In both heart failure groups, patients with AF were older than patients without AF, more often showed tricuspid regurgitation and a greater inferior vena cava diameter. On admission mitral regurgitation and symptoms at rest were present more often in the AF subgroup of HFpEF patients, whereas coronary artery disease was less often present in the AF HFrEF subgroup (Table 1). When comparing heart failure groups irrespective of AF status, both groups showed a typical comorbidity profile in that HFpEF patients were older, more often female, and had less often coronary artery disease (Online Resource).

Clinical outcome

Median follow-up of all patients was 16 (IQR 7–36) months. During this time, 436 (33.9%) patients died. Considering all patients, AF on admission (HR 1.67, 95% CI 1.38–2.01; $P<0.001$) and history of AF (HR 1.66, 95% CI 1.36–2.04; $P<0.001$) but not heart failure type (HR for HFrEF 0.99, 95% CI 0.82–1.20; $P=0.911$) was associated with all-cause mortality in univariable Cox regression models. After covariate adjustment, HFrEF became significantly associated with all-cause mortality (HR for HFrEF 1.28, 95% CI 1.04–1.58; $P=0.019$) and AF on admission (HR 1.58, 95% CI 1.30–1.92; $P<0.001$) as well as history of AF (HR 1.47, 95% CI 1.19–1.81; $P<0.001$) remained significantly associated with all-cause mortality.

Combining data about history of AF and AF on admission to a single AF status (i.e., never AF, history of AF, or AF on admission) revealed that AF is associated with all-cause mortality in the overall population as well as in patients with HFpEF and HFrEF in unadjusted Kaplan–Meier analyses (Fig. 2). However, only patients with AF on admission (HR 1.64, 95% CI 1.32–2.04; $P<0.001$) but not patients with a history of AF (HR 1.13, 95% CI 0.84–1.51; $P=0.429$) were at increased risk for all-cause mortality in adjusted Cox regression models. This association remained significant only in patients with HFpEF but not in patients with HFrEF (Table 2). This effect modifying influence of HFrEF status

Table 1 Patient characteristics according to heart failure type and AF group

	HFpEF				HFrEF			
	Never AF $n=289$	History of AF without AF on admission $n=122$	AF on admission $n=317$	P	Never AF $n=240$	History of AF without AF on admission $n=93$	AF on admission $n=225$	P
Demographics								
Age (years)	78 (72–85)	80 (74–86)	81 (75–87)	< 0.001	73 (63–80)	77 (71–81)	77 (70–83)	< 0.001
Male sex	112/289 (39)	56/122 (46)	120/317 (38)	0.28	159/240 (66)	68/93 (73)	146/225 (65)	0.35
Comorbidities								
History of AF	0/289 (0)	122/122 (100)	317/317 (100)	< 0.001	0/240 (0)	93/93 (100)	225/225 (100)	< 0.001
Coronary artery disease	137/289 (47)	69/122 (57)	134/317 (42)	0.03	178/240 (74)	69/93 (74)	135/224 (60)	0.002
History of myocardial infarction	57/289 (20)	29/122 (24)	41/317 (13)	0.01	78/240 (32)	31/93 (33)	52/225 (23)	0.05
Previous PCI	61/289 (21)	31/122 (25)	50/316 (16)	0.05	88/240 (37)	32/93 (34)	50/224 (22)	0.002
Previous CABG	37/289 (13)	18/122 (15)	31/317 (10)	0.28	40/240 (17)	15/93 (16)	24/225 (11)	0.15
Diabetes mellitus	113/289 (39)	42/122 (34)	104/317 (33)	0.26	84/240 (35)	33/93 (35)	81/225 (36)	0.97
Chronic obstructive pulmonary disease	55/289 (19)	22/122 (18)	22/122 (18)	0.82	40/240 (17)	15/93 (16)	24/225 (11)	0.15
Hypertension	261/289 (90)	109/122 (89)	275/317 (87)	0.37	198/240 (82)	82/92 (89)	190/225 (84)	0.33
Peripheral arterial disease	261/289 (90)	109/122 (89)	275/317 (87)	0.37	33/240 (14)	10/93 (11)	19/222 (9)	0.21
Previous stroke	39/289 (13)	16/122 (13)	45/316 (14)	0.94	23/240 (10)	12/93 (13)	33/225 (15)	0.24
CHA2DS2-VASc	5 (4–6)	5 (5–6)	5 (4–6)	0.79	5 (3–6)	5 (4–6)	5 (4–6)	0.009
Echocardiographic characteristics								
IVCmax	17 (14–22)	20 (15–24)	21 (17–24)	< 0.001	20 (16–24)	21 (17–25)	22 (18–26)	0.04
Mitral regurgitation II°–III°	25/247 (10)	22/107 (21)	74/301 (25)	< 0.001	74/225 (33)	29/86 (34)	71/202 (35)	0.89
Tricuspid regurgitation II°–III°	39/225 (17)	32/106 (30)	137/280 (49)	< 0.001	49/214 (23)	24/81 (30)	72/199 (36)	0.01
Laboratory characteristics								
eGFR according to MDRD at baseline (ml/min/1.73 m^2)	62 (42–77)	55 (39–67)	56 (41–75)	0.13	59 (45–82)	55 (45–66)	53 (38–70)	0.008
Hemoglobin at baseline (g/dl)	120 (107–136)	120 (107–136)	120 (106–134)	0.60	129 (115–142)	134 (116–144)	130 (115–142)	0.85
Hyponatremia	64/289 (22)	29/122 (24)	75/317 (24)	0.89	51/240 (21)	18/93 (19)	45/224 (20)	0.91
In-hospital characteristics								
Symptoms at rest including orthopnea on admission	191/289 (66)	95/122 (78)	257/317 (81)	< 0.001	192/240 (80)	78/93 (84)	195/225 (87)	0.15
Length of stay (days)	7 (5–11)	8 (6–11)	8 (6–13)	0.01	9 (6–14)	9 (7–14)	10 (7–13)	0.72
Worsening renal function	74/289 (26)	28/122 (23)	63/317 (20)	0.24	60/240 (25)	25/93 (27)	49/224 (22)	0.58
Discharged with anticoagulant	27/283 (10)	83/122 (68)	221/309 (72)	< 0.001	41/234 (18)	60/90 (67)	161/219 (74)	< 0.001

Data are median (IQR) or *n*/*N* (%). Data for inferior vena cava diameter, eGFR according to MDRD at baseline, and hemoglobin at baseline is missing in 388 (30.2%), 1 (0.1%), and 1 (0.1%) of patients, respectively. Other continuous variables do not have missing data

CABG coronary artery bypass surgery, *CHA2DS2-VASc* congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65–74 years, sex, *eGFR* estimated glomerular filtration rate, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *MDRD* modification of diet in renal disease study equation, *PCI* percutaneous coronary intervention

was stronger in patients with AF on admission compared to patients with a history of AF (Table 2).

Discussion

This study demonstrates that AF was highly prevalent in a large contemporary population of patients admitted for ADHF. Overall, AF was associated with an increased risk for all-cause mortality during long-term follow-up; however, stratification by left ventricular ejection fraction revealed that this association is confined only to patients with preserved ejection fraction.

History of AF in our cohort was relatively high (58.9%) but within the range of previously reported contemporary ADHF trials (average over treatment groups: CHANCE-HF [18]=58.9%, ATOMIC-AHF [19]=54.5%, RELAX-AHF [20]=51.9%, CARRESS-HF [21] =54.3%, and DOSE [22]=52.6%). In a recent Get With The Guidelines (GWTG)-HF analysis, the reported AF prevalence was considerably lower (31.4%) which is primarily based on the AF definition. In this GWTG-HF analysis, AF was defined as the presence of AF on admission irrespective of history of AF [11]. Closer to this, 42.1% of patients had AF on admission in our cohort. European AF guidelines distinguish five types of AF, of which paroxysmal AF, persistent AF, and permanent AF are the most prominent [23]. Due to the retrospective design of our study, we were unable to classify AF exactly as recommended. However, it may be assumed that patients with a history of AF, but without AF on admission might correspond to patients with paroxysmal AF (either paroxysmal AF or regressed from persistent AF), whereas patients with AF on admission may have first diagnosed AF, persistent AF, or permanent AF. The majority of AF patients probably had long-standing persistent or permanent AF. This is in line with another retrospective analysis, in which permanent AF was the most prevalent type of AF in an ADHF population [12]. Previous ADHF studies did not analyze the prognostic impact of AF type. Considering the total cohort, only patients with AF on admission but not patients with a history of AF without AF on admission were at increased risk for all-cause mortality compared to patients who never had AF (neither a history nor on admission). This suggests that patients with AF on admission may have more advanced disease which is supported by the fact that these patients more often had moderate to severe tricuspid regurgitation and a wider inferior vena cava diameter. These are markers of right-sided heart failure known to be an adverse prognostic marker in both HFrEF and HFpEF [24].

Two meta-analyses conclude that AF is associated with increased all-cause mortality in chronic heart failure [9, 10]. Moreover, it is suggested that in the presence of AF the prognosis may be worse in HFpEF compared to HFrEF [10]. With regard to ADHF, a large registry analysis revealed that AF is independently associated with higher in-hospital mortality and longer hospital stay [11]. The same conclusion was drawn from a small retrospective analysis [12]. An ASCEND-HF post hoc analysis linked AF to higher 30-day mortality, but this association was not significant after model adjustment [13]. The prognostic impact of AF in ADHF stratified by HFrEF and HFpEF was analyzed in a COACH substudy [25]. In this substudy, AF was diagnosed by an ECG at hospital discharge in 336 of 927 patients (36%) and was related to an increased risk for the outcome of death or heart failure-related hospitalization in HFpEF patients, but not in HFrEF patients. No such relation was observed for death alone despite numerically more deaths in AF subgroups. On the contrary, in our study, AF was independently associated with all-cause mortality in the overall population and in the HFpEF subgroup but not in the HFrEF subgroup. Comparing patient characteristics and event rates between the COACH substudy and our study reveals that in our cohort patients had more advanced disease (e.g., symptoms at rest were considerably more frequent) which might have led to a higher event rate (240 versus 436 deaths) resulting in greater power to detect a significant difference. Of note, discharge ECGs were used for AF diagnosis in the COACH substudy whereas history of AF as well as AF on admission was used in our study. Therefore, patients with paroxysmal AF or persistent AF but successful spontaneous/medical/electrical cardioversion during hospital treatment were diagnosed as having sinus rhythm in the COACH substudy. However, our data suggest that even the history of AF in the absence of AF on admission ECG might be of prognostic relevance in patients with HFpEF. Hospitalization for ADHF itself is associated with a worse prognosis [6]. One might, therefore, speculate that the impact of left ventricular ejection fraction on the prognostic effect of AF is offset in this situation. However, our analysis argues against this hypothesis.

Interestingly, HFpEF patients with AF significantly more often reported symptoms at rest on admission whereas this was not observed in HFrEF patients. This suggests that AF may be more important for symptom severity in HFpEF as compared to HFrEF. HFpEF patients frequently have hypertrophy and reduced compliance of the left ventricle, therefore, atrial contraction (i.e., booster pump function) might be more important for diastolic filling in these patients [26] with consecutive symptom deterioration due to loss of atrial contribution.

Catheter ablation of AF is an established treatment option in patients with symptomatic AF [27–30]. Based on the results of several observational and randomized studies using surrogate endpoints, current European AF guidelines state that AF ablation should be considered in symptomatic patients with AF and HFrEF to improve

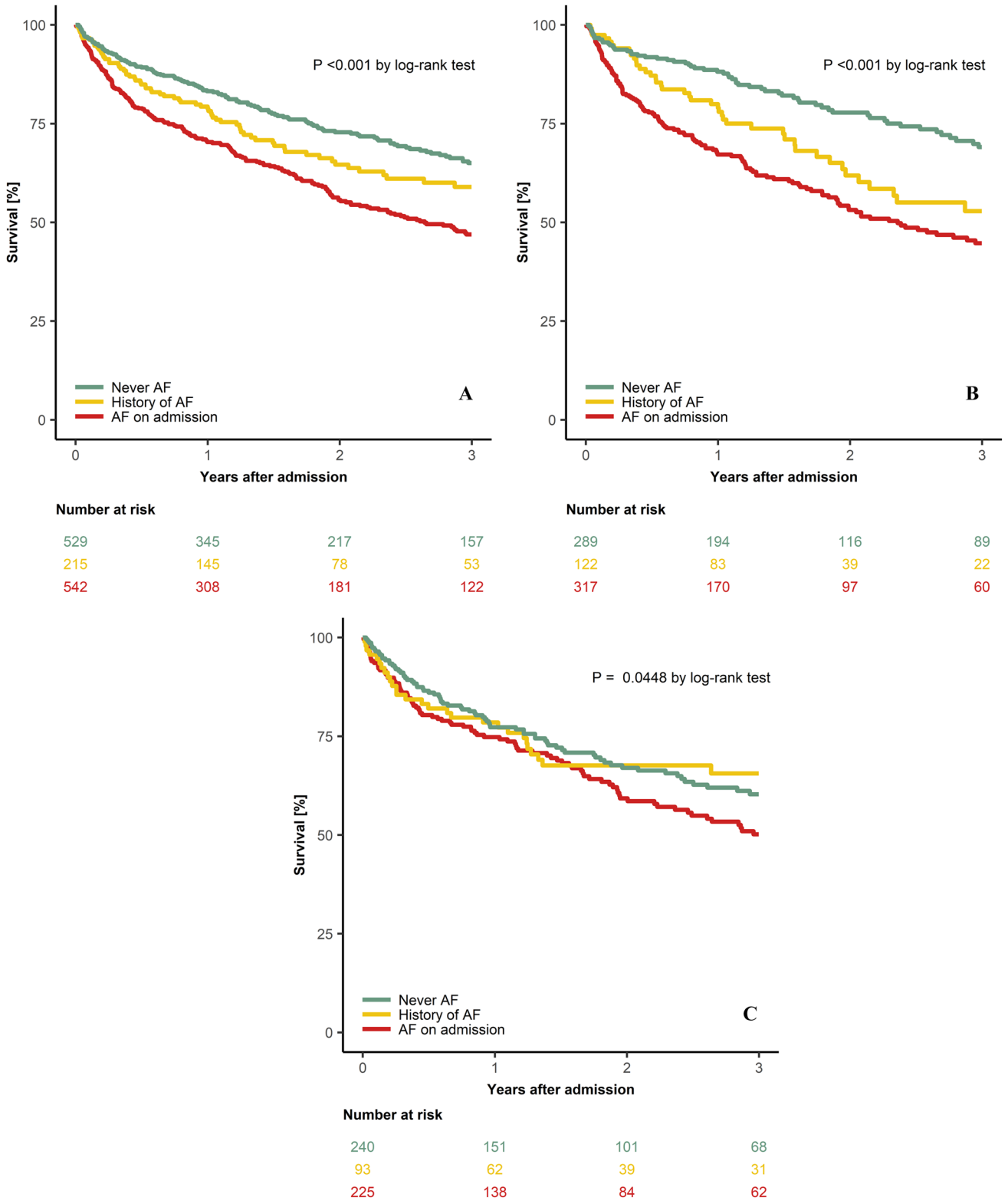

Fig. 2 Kaplan–Meier survival analysis for all-cause mortality stratified by atrial fibrillation (AF) status in **a** all patients, **b** in patients with preserved ejection fraction, and **c** in patients with reduced ejection fraction

Table 2 Hazard ratio with 95% confidence interval for all-cause mortality calculated using multivariable Cox regression models

	HR (95% CI) for each combination of AF status and HFrEF status compared to never AF and HFpEF			HR (95% CI) for History of AF within HF stratum	HR (95% CI) for AF on admission within HF stratum
	Never AF	History of AF	AF on admission		
HFpEF	1 (reference)	1.48 (0.99–2.19) $P=0.054$	2.09 (1.54–2.84) $P<0.001$	1.53 (1.02–2.28) $P=0.038$	2.16 (1.58–2.95) $P<0.001$
HFrEF	1.82 (1.28–2.59) $P=0.001$	1.55 (0.98–2.46) $P=0.061$	2.27 (1.62–3.19) $P<0.001$	0.84 (0.54–1.31) $P=0.441$	1.18 (0.85–1.63) $P=0.329$
Measure of interaction on multiplicative scale: ratio of HRs (95%CI)		0.58 (0.32–1.04); $P=0.066$	0.60 (0.39–0.92); $P=0.020$		

HRs are adjusted for age, sex, history of coronary artery disease, history of myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, history of diabetes mellitus, history of chronic obstructive pulmonary disease, history of stroke, history of peripheral artery disease, history of hypertension, symptoms at rest on admission, estimated glomerular filtration rate on admission, hemoglobin level on admission, and presence of hyponatremia on admission

AF atrial fibrillation, *CI* confidence interval, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HR* hazard ratio

symptoms and cardiac function when tachycardiomyopathy is suspected [23]. This recommendation is strengthened by the results of the recently published CASTLE-AF trial [31]. However, no formal recommendation has been made for HFpEF because data are limited to one small single center observational study [32] and virtually no randomized data exist for this population so far [33]. Moreover, no treatment has been shown to improve prognosis of patients with HFpEF. Interestingly, alteration of left atrial function is different in HFpEF and HFrEF and left atrial dysfunction is associated with mortality in HFpEF but not in HFrEF [34]. AF promotes left atrial remodeling on the electrical and structural level [26] and catheter ablation of AF may beneficially influence LA remodeling [35, 36]. In light of the reported strong association between AF and survival in HFpEF, further research is warranted to investigate whether rhythm control strategies like AF catheter ablation could be beneficial for HFpEF patients.

Limitations

Several limitations are inherent to the retrospective design of our study and should be mentioned. First, we were unable to distinguish AF type according to current guidelines. This will be of potential relevance for our current AF group which will comprise not only patients with persistent AF and permanent AF but also patients with first diagnosed AF. The latter group might have a considerably better prognosis than the two former mentioned types and, therefore, dilute our finding with regard to the prognostic impact. Moreover, some patients with paroxysmal AF might be missed due to insufficient history of AF reporting in extracted discharge letters. Furthermore asymptomatic AF episodes are not adequately registered due to lack of continuous rhythm monitoring. Second, left ventricular ejection fraction was rated semiquantitatively in most cases; therefore, the distinction between HFrEF and HFpEF according to contemporary cutoffs is limited. Third, some patient characteristics could not be reliably retrieved from chart review and therefore could not be considered as covariate in our regression model (e.g., blood pressure, heart rate, urea, NT-proBNP, detailed differentiation of clinical signs/symptoms of heart failure, and heart rhythm at discharge). For these reasons the results of our analysis have to be interpreted as exploratory. However, our data were drawn from a large contemporary ADHF population with long-term follow-up treated according to current guidelines and the findings fit well into existing evidence and may generate hypotheses and stimulate further research.

Conclusions

AF is common in the setting of ADHF and is associated with increased all-cause mortality during long-term follow-up. However, this association remained significant only in patients with HFpEF, but not in patients with HFrEF. AF on admission is associated with a worse prognosis than history of AF without AF on admission suggesting a more advanced disease in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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