Arrhythmogenic mechanisms in inherited and acquired cardiac diseases

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SEX- AND AGE SPECIFIC ASSOCIATION OF NEW-ONSET ATRIAL FIBRILLATION WITH IN-HOSPITAL MORTALITY IN HOSPITALISED COVID-19 PATIENTS

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ABSTRACT

Background

Coronavirus disease 2019 (COVID-19) is a systemic disease with cardiovascular involvement, including cardiac arrhythmias. Notably, new-onset atrial fibrillation (AF) and atrial flutter (AFL) during hospitalisation in COVID-19 patients has been associated with increased mortality. However, how this risk is impacted by age and sex is still poorly understood.

Methods

For this multicentre cohort study, we extracted demographics, medical history, occurrence of electrical disorders and in-hospital mortality from the large international patient registry CAPACITY-COVID. For each electrical disorder, prevalence during hospitalisation was calculated. Subsequently, we analysed the incremental prognostic effect of developing AF/AFL on in-hospital mortality, using multivariable logistic regression analyses, stratified for sex and age.

Results

In total, 5782 patients (64% male; median age 67) were included. Of all patients 11.0% (95% CI 10.2–11.8) experienced AF and 1.6% (95% CI 1.3–1.9) experienced AFL during hospitalisation. Ventricular arrhythmias were rare (<0.8% (95% CI 0.6–1.0)) and a conduction disorder was observed in 6.3% (95% CI 5.7–7.0). An event of AF/AFL appeared to occur more often in patients with pre-existing heart failure. After multivariable adjustment for age and sex, new-onset AF/AFL was significantly associated with a poorer prognosis, exemplified by a two- to three-fold increased risk of in-hospital mortality in males aged 60–72 years, whereas this effect was largely attenuated in older male patients and not observed in female patients.

Conclusion

In this large COVID-19 cohort, new-onset AF/AFL was associated with increased in-hospital mortality, yet this increased risk was restricted to males aged 60–72 years.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has infected more than 400 million people worldwide, including more than 160 million Europeans, with almost 5.8 million deaths attributed globally to the virus as of February 11th, 2022.[1] With multiple vaccines available as well as the recent increase in immunisation from the omicron variant, which is possibly associated with an overall lower risk of clinical deterioration, some are optimistic that the end of the coronavirus disease 2019 (COVID-19) pandemic is in sight and that SARS-CoV-2 will become a yearly recurring more endemic virus. However, subsequent waves of new infections with new variants are to be expected in the upcoming years, given the 1) low global vaccination rate of 36%,[2] and global shortage of vaccines, 2) high threshold needed for herd immunity,[3] 3) uncertainties regarding the duration of the immunological effect of the vaccines,[4] 4) high number of intermediate hosts for SARS-CoV-2,[5] and in part due to this, 5) the continuous threat of (more contagious) variants reducing vaccine efficacy.[6] Therefore, research into COVID-19 remains crucial.

Since the start of the pandemic, cardiovascular complications have been increasingly recognised in patients suffering from COVID-19, ranging from vascular damage and cardiac injury to arrhythmias.[7] Arrhythmias in COVID-19 patients may impact significantly on disease progression and outcome. As such, various population-based studies have reported a positive association between atrial fibrillation (AF)/atrial flutter (AFL) and mortality.[8, 9, 10] However, these studies did not look at sex-specific influences, nor at the incremental effect of age (on a continuous scale), despite the fact that these parameters are known to influence AF/AFL outcomes in the general population.[11, 12]

Therefore, in the large international CAPACITY-COVID dataset (NCT04325412) of 5782 hospitalised COVID-19 patients, using the latest methodology, we explored the relation of AF and AFL to in-hospital mortality, with specific attention for sex- and age-related differences.

METHODS

Study design and study population

For the current multicentre cohort study, pseudo-anonymous data generated during routine clinical care retrieved from the international patient registry CAPACITY-COVID (www.capacity-covid.eu) were used.[13] The data within CAPACITY-COVID have been collected by 72 hospitals in 8 European (Belgium, France, Italy, the Netherlands, Spain, Switzerland, Portugal, United Kingdom) and 5 non-European (Egypt, Iran, Israel, Russia, Saudi-Arabia) countries. For this study, patients aged 18 years or older, admitted to any of the participating hospital centres before October 25th, 2020, with a laboratory confirmed SARS-CoV-2 infection during hospitalisation, were included. Readmission(s) from a single patient were evaluated as a single continuous presentation. Due to only few exclusion criteria, the database gives a reliable reflection of hospitalised COVID-19 patients during the first months of the pandemic, thus before availability of vaccine-induced immunity, and our analyses should therefore be interpreted as generalisable to patients with (largely) naïve immunity against SARS-CoV-2. Local ethics approval was obtained in all participating hospitals. Assessment of informed consent was site specific, depending on national regulations, and has been

described previously.[13] Any researcher can request the data by submitting a proposal as outlined on https://capacity-covid.eu/for-professionals.

Data extraction

For this study the following variables were extracted: sex, age, medical history (including history of cardiac electrical disorders), body mass index (BMI), medication, physical examination findings, biomarkers, and follow-up data on the development of electrical disorders, cerebrovascular accident (CVA), pulmonary embolism, and mortality during hospitalisation. Electrical disorders were detected either through continuous rhythm monitoring or with (an) electrocardiogram(s) and were diagnosed according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2006 key data elements and definitions for electrophysiological studies and procedures.[14] Types of electrical disorders included AF, AFL, atrial tachycardia, atrioventricular (AV) nodal re-entry tachycardia, non-sustained ventricular tachycardia (nsVT), sustained ventricular tachycardia (sVT), ventricular fibrillation (VF), first degree AV block, second degree AV block, third degree AV block, complete left bundle branch block (LBBB), and complete right bundle branch block (RBBB).

Statistical analyses

Baseline characteristics of patients with COVID-19 disease are reported for the date of hospital admission. Categorical variables are presented as counts and percentages and numerical variables as means with standard deviations or medians with interquartile ranges (IQR), depending on the distribution.

The prevalence of the development of each arrhythmic and conduction disorder during hospitalisation was calculated for the entire follow-up time (i.e. the time from hospital admission to discharge, death or loss to follow-up) and divided into patients without and with a history of that specific arrhythmic or conduction disorder (i.e. new-onset and recurrent, respectively). Only for patients with AF and for patients with AFL, new-onset versus recurrent AF and new-onset versus recurrent AFL were defined as having no history of both AF and AFL versus a history of AF and/or AFL.

To explore the association between all predefined patient characteristics and the development of the most prevalent new-onset arrhythmic disorder (i.e. AF and/or AFL), univariable logistic regression analyses were performed to estimate crude odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Next, the association between development of new-onset AF and/or AFL during hospitalisation and in-hospital mortality in COVID-19 patients was first examined using univariable logistic regression analysis. Second, multivariable logistic regression analysis was performed with sex, a cubic spline function for age, the development of new-onset AF and/or AFL during hospitalisation, and the interaction between the latter two variables. The results of this analysis were depicted in plots for males and females separately. To explore whether other concomitant comorbidities and/or other known risk factors may have contributed to the observed results, we performed a sensitivity analysis where we additionally adjusted for CHA_2DS_2-VASc score.

For all analyses, the different AF subtypes (paroxysmal, persistent, and permanent) were merged. All statistical analyses were performed using R version 4.0.2 with the bias reduction in binomial-response generalised linear models (brglm) function in the package 'brglm' version 0.7.1, which implements Firth correction reducing finite sample bias in the regression coefficients compared to default maximum likelihood regression.[15] Non-linear relations are graphically displayed using the package 'rms' version 6.6.1 and the package 'ggplot2' version 3.3.2. In all univariable analyses with age and in all multivariable analyses, a cubic spline function for age (and in the univariable analyses for the association between BMI and new-onset AF and/or AFL also a cubic spline function for BMI) with four knots on recommended locations (on the percentiles 0.05, 0.35, 0.65, and 0.95) was used.[16] Missing data for each variable were reported as percentages in the text or as counts in the corresponding tables. Since missing data was overall limited (e.g. maximum n = 24 in mortality analyses), we proceeded with analyses of complete cases. Associations with two-sided p-values < 0.05 were considered statistically significant.

RESULTS

A total of 5782 patients were included in this study. The majority of them were hospitalised in European countries (89.9%). The median duration of hospital admission was 8 (IQR 4–17) days, and 28.8% (n = 1664) of all subjects were admitted to the intensive care unit (ICU). Of the total study population, 63.8% was male and the median age was 67 (IQR 56–76) years. 12.5% (n = 725) had been diagnosed with an arrhythmic event in the past, of which 93.2% (n = 676) consisted of at least one episode of supraventricular arrhythmia and 7.7% (n = 56) at least one episode of ventricular arrhythmia. Of all patients, 1.7% (n = 96) had been diagnosed with at least one conduction disorder in the past. The most prevalent comorbidity registered was hypertension (47.6%), followed by diabetes mellitus (26.1%), chronic obstructive pulmonary disease (11.1%), renal impairment (10.7%), and prior myocardial infarction (9.2%). A complete list of all baseline characteristics, stratified by new-onset AF/AFL during hospitalisation and history of AF/AFL is presented in **Table 1**. Baseline characteristics stratified by other arrhythmias and conduction disorders are presented in **Supplemental Table S1**. All variables had <3% missing, except for peripheral arterial disease (21.6%), BMI (24.7%), temperature (17.8%), C-reactive protein (12.2%), and white blood cell count (11.4%).

Prevalence of AF/AFL

The prevalence of AF and/or AFL in comparison to other arrhythmias and conduction disorders (recurrent and new-onset) during hospitalisation is summarised in **Fig. 1**. Of all patients, 12.8% (95% CI 11.9–13.6) (n = 737) experienced an arrhythmic event during hospitalisation, the vast majority being supraventricular (95.9%). AF and AFL were most common, occurring in 12.0% (95% CI 11.2–12.8) (n = 692) of all patients, of which 86.7% (95% CI 84.0–89.1) (n = 600) experienced only AF, 8.5% (95% CI 6.6–10.8) (n = 59) experienced only AFL, and 4.8% (95% CI 3.4–6.6) (n = 33) experienced both AF and AFL. In 60.7% (95% CI 57.0–64.3) (n = 420) of patients the development of AF and/or AFL was new-onset, whereas in the remaining 39.3% (95% CI 35.7–43.0) (n = 272) AF and/or AFL had been present before hospital admission. Ventricular arrhythmias were rare (0.8% (95% CI 0.6–1.0)) and

Table 1 – Baseline characteristics of hospitalised COVID-19 patients stratified by new-onset and recurrent atrial fibrillation/atrial flutter.

	Total n = 5782	No AF/AFL n = 4712	New-onset or recurrent AF/AFL n = 692	New-onset AF/AFL n = 420	Recurrent AF/AFL n = 271
Demographics					
Male sex n (%)	3686 (63.8)	2955 (62.7)	482 (69.7)	294 (70.0)	188 (69.4)
Age in years median (IQR)	67 (56-76)	64 (54-74)	74 (69-81)	73 (66-79)	78 (73-83)
History of supraventricular tachycardia					
AF n (%)	616 (10.7)	0 (0.0)	257 (37.2)	0 (0.0)	257 (94.8)
AFL n (%)	52 (0.9)	0 (0.0)	23 (3.3)	0 (0.0)	23 (8.5)
Atrial tachycardia n (%)	21 (0.4)	12 (0.3)	3 (0.4)	3 (0.7)	0 (0.0)
AV nodal re-entry tachycardia n (%)	22 (0.4)	15 (0.3)	4 (0.6)	1 (0.2)	3 (1.1)
History of ventricular tachycardia					
Non-sustained ventricular tachycardia n (%)	21 (0.4)	12 (0.3)	7 (1.0)	4 (1.0)	3 (1.1)
Sustained ventricular tachycardia n (%)	15 (0.3)	14 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular fibrillation n (%)	24 (0.4)	17 (0.4)	6 (0.9)	6 (1.4)	0 (0.0)
History of conduction disorders					
1st AV block n (%)	19 (0.3)	13 (0.3)	2 (0.3)	1 (0.2)	1 (0.4)
2nd AV block n (%)	13 (0.2)	8 (0.2)	2 (0.3)	1 (0.2)	1 (0.4)
3rd AV block n (%)	26 (0.4)	16 (0.3)	2 (0.3)	1 (0.2)	1 (0.4)
Left bundle branch block n (%)	24 (0.4)	14 (0.3)	5 (0.7)	4 (1.0)	1 (0.4)
Right bundle branch block n (%)	18 (0.3)	12 (0.3)	4 (0.6)	2 (0.5)	2 (0.7)
Other medical history					
Heart failure n (%)	315 (5.5)	156 (3.3)	88 (12.7)	23 (5.5)	64 (23.6)
Hypertension n (%)	2692 (47.6)	2031 (44.0)	407 (60.2)	227 (55.4)	179 (67.5)
Diabetes mellitus (type I or II) n (%)	1494 (26.1)	1195 (25.6)	188 (27.6)	100 (24.2)	87 (32.6)
Peripheral arterial disease n (%)	271 (6.0)	181 (4.9)	54 (9.8)	26 (8.0)	28 (12.6)
Myocardial infarction† n (%)	523 (9.2)	374 (8.0)	81 (11.9)	47 (11.3)	34 (12.8)
Renal impairment n (%)	620 (10.7)	414 (8.8)	123 (17.9)	58 (13.9)	65 (24.4)
COPD n (%)	643 (11.1)	487 (10.3)	97 (14.1)	53 (12.7)	44 (16.3)

Table 1 – continued.

	Total n = 5782	No AF/AFL n = 4712	New-onset or recurrent AF/AFL n = 692	New-onset AF/AFL n = 420	Recurrent AF/AFL n = 271
Risk factors					
BMI in kg/m² median (IQR)	27.5 (24.6-30.9)	27.5 (24.6-30.9)	27.2 (24.5-30.5)	27.2 (24.7-30.5)	26.9 (24.1-30.4)
Medication					
Digoxin n (%)	112 (1.9)	19 (0.4)	58 (8.4)	12 (2.9)	46 (17.0)
Anti-arrhythmic drugs - class I n (%)	28 (0.5)	6 (0.1)	12 (1.7)	0 (0.0)	12 (4.4)
Anti-arrhythmic drugs - class III n (%)	110 (1.9)	41 (0.9)	24 (3.5)	5 (1.2)	19 (7.0)
Anti-arrhythmic drugs - class IV n (%)	64 (1.1)	39 (0.8)	15 (2.2)	5 (1.2)	10 (3.7)
Beta blockers n (%)	1562 (27.0)	1028 (21.8)	308 (44.5)	136 (32.4)	172 (63.5)
Antihypertensive drugs[‡] n (%)	2575 (44.6)	1913 (40.6)	397 (57.4)	204 (48.6)	192 (70.8)
Platelet inhibitors n (%)	1270 (22.0)	1100 (23.4)	139 (20.1)	111 (26.4)	28 (10.3)
Anticoagulants n (%)	779 (13.5)	219 (4.7)	284 (41.0)	59 (14.0)	224 (82.7)
Antidiabetic drugs n (%)	1105 (19.1)	894 (19.0)	141 (20.4)	73 (17.4)	67 (24.7)
Physical examination and biomarkers (at the start of hospital admission)					
Temperature in °C median (IQR)	37.8 (37.0-38.5)	37.8 (37.0-38.6)	37.7 (37.0-38.5)	37.7 (37.0-38.5)	37.7 (36.9-38.4)
C-reactive protein in mg/L median (IQR)	76.0 (31.0-144.0)	74.0 (29.0-141.0)	95.0 (45.0-170.0)	110.0 (56.0-180.0)	76.0 (31.0-135.5)
White blood cell count x10⁹/L median (IQR)	6.8 (5.0-9.3)	6.8 (5.0-9.2)	6.8 (5.0-9.9)	7.1 (5.0-10.5)	6.3 (4.9-8.8)

AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; n, number.

† ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.

‡ Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.

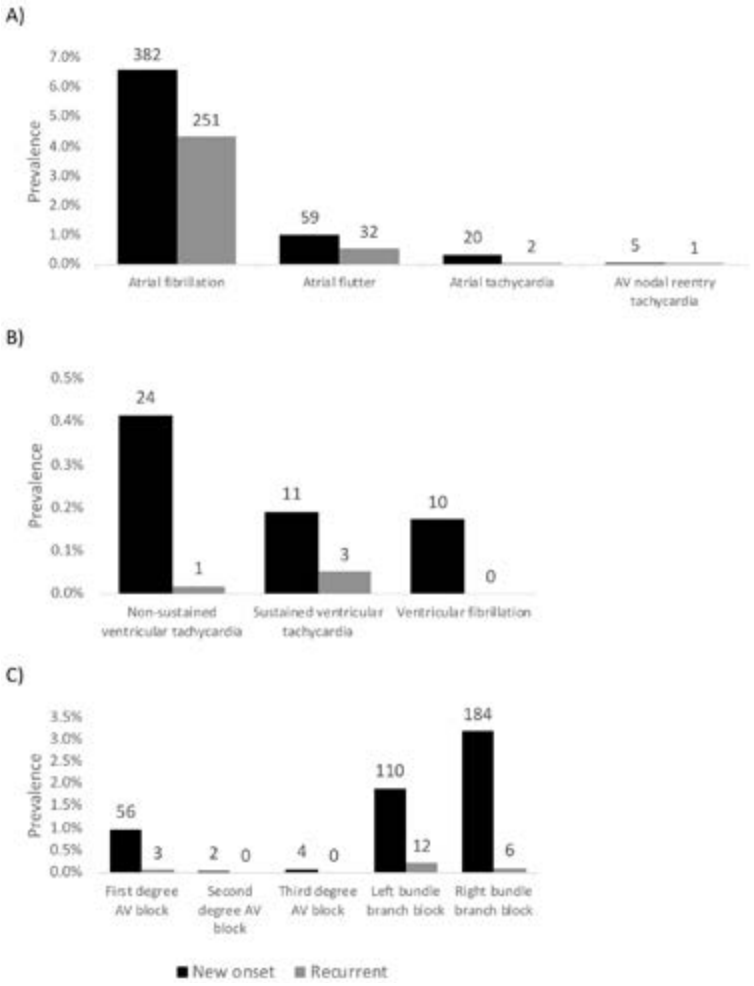

Figure 1 – Prevalence of electrical disorders in hospitalised COVID-19 patients. A). Supraventricular tachycardias. **B)** Ventricular tachycardias. **C)** Conduction disorders. Recurrent is defined as a history of that specific electrical disorder. Only for patients with atrial fibrillation (AF) and for patients with atrial flutter (AFL) new-onset versus recurrent AF and new-onset versus recurrent AFL were defined as having no history of both AF and AFL versus a history of AF and/or AFL. The number of patients per group is presented on top of the specific bar.

50% of them were sVT or VF (n = 23). A conduction disorder during hospitalisation was observed in 6.3% (95% CI 5.7–7.0) (n = 365) of all patients.

Association between patient characteristics and development of new-onset AF and/or AFL

In univariable logistic regression analyses, sex, age, heart failure, hypertension, peripheral arterial disease, prior myocardial infarction, renal impairment, certain drugs, white blood cell count,

duration of hospitalisation, and development of pulmonary embolism, showed an increased statistically significant association with the development of AF and/or AFL. Of medical history, heart failure seemed to be most strongly associated with a higher likelihood of developing AF and/or AFL compared to patients without heart failure: OR 1.72 (95% CI 1.05–2.64) (**Supplemental Table S2**).

Prognostic impact of new-onset AF and/or AFL on in-hospital mortality

In absolute terms, there were only few patients aged < 50 years and > 90 years in our dataset who developed new-onset AF and/or AFL (n = 7 and n = 10, respectively). Because these small numbers could affect the reliability and precision of the point estimates of the outcomes to a high extent, only patients aged ≥ 50 and ≤ 90 years for new-onset AF and/or AFL were included in the mortality analyses.

In univariable logistic regression analyses, we observed that the development of new-onset AF and/or AFL during hospitalisation was associated with increased in-hospital mortality with an unadjusted OR of 1.90 (95% CI 1.52–2.36) (**Supplemental Table S3**). However, in a multivariable model with sex, age, and new-onset AF and/or AFL as covariates to predict in-hospital mortality, there was only an increased significant association between new-onset AF and/or AFL and in-hospital mortality in males aged between 60 and 72 years (**Fig. 2**). When extending this model with the CHA_2DS_2-VASc score in the 24.3% of patients in whom this score could be calculated (n = 1033), the impact of the development of new-onset AF and/or AFL during hospitalisation appeared to be more strongly associated with increased in-hospital mortality: adjusted OR of 3.80 (95% CI 0.03–84.86) instead of 2.16 (95% CI 0.16–14.11) (**Supplemental Table S4**).

In the new-onset AF and/or AFL group, 51.7% (n = 217) was admitted to the ICU. In 24.0% (n = 23) of the patients for which ICU admission date and AF and/or AFL onset date were available (n = 96), AF

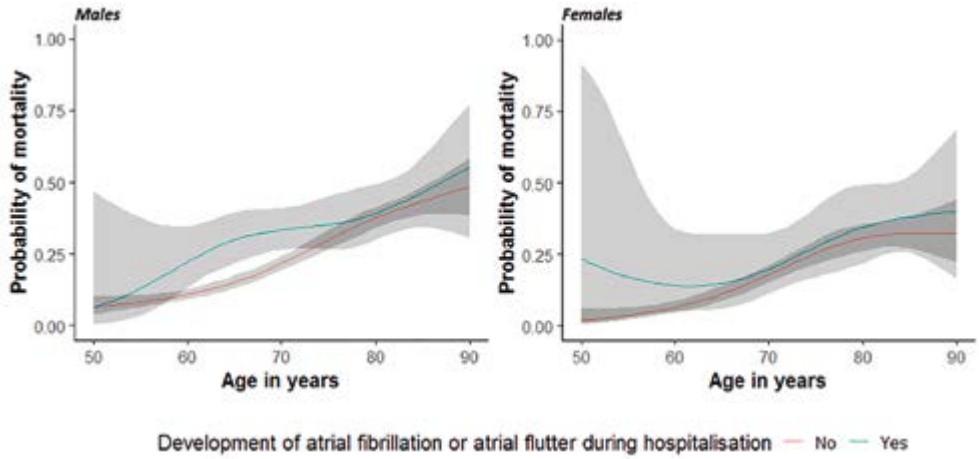

Figure 2 – Risk of in-hospital mortality in COVID-19 patients by sex, age and the development of new-onset atrial fibrillation or atrial flutter during hospitalisation. The plots in **Fig. 2** are developed with the interaction between a cubic spline function for age with four knots (on the percentiles 0.05, 0.035, 0.65, and 0.95) and the development of new-onset AF and/or AFL during hospitalisation.

and/or AFL occurred at least 1 day before ICU admission. In the total cohort, 1.0% (n = 60) of patients developed a CVA, whereas in patients with new-onset AF and/or AFL this occurred in 1.7% (n = 7).

DISCUSSION

In this multicentre cohort study, we extracted data of 5782 hospitalised COVID-19 patients from the large international CAPACITY-COVID registry. Of all electrical disorders, AF and/or AFL was observed in 1 in every 8–9 in-hospital COVID-19 patients. Occurrence of AF and/or AFL during hospitalisation for COVID-19 was associated with a poorer prognosis exemplified by an increased in-hospital mortality in males aged 60–72 years, while this effect was not observed in female patients and largely attenuated in older male patients.

Arrhythmogenesis in COVID-19 and the effect of AF on mortality

Several mechanisms may contribute to arrhythmogenesis in the setting of COVID-19. Pre-existing cardiovascular pathologies, such as heart failure and coronary artery disease, may increase the likelihood of myocardial ischaemia in the setting of hypoxemia. Indeed, in our cohort, heart failure, hypertension, and prior myocardial infarction were frequently present and apparently associated with an increased likelihood of developing AF and/or AFL. In addition, SARS-CoV-2 has been linked to a pro-thrombotic and hypercoagulability state in patients, which by itself may promote the development and propagation of AF and/or AFL.[17] Furthermore, the virus may also directly affect the cardiomyocytes through expression of angiotensin-converting enzyme 2, inducing arrhythmogenic conditions such as intracellular ionic dysregulation, apoptosis, and possibly myocarditis.[18] Additionally, potentially pro-arrhythmic therapeutics (including vasopressors and (hydroxy)chloroquine) and electrolyte disturbances in COVID-19 patients can all contribute to arrhythmogenesis.[19] Irrespective of the underlying mechanism, our findings indicate that development of AF and/or AFL might be prognostically unfavourable in COVID-19 patients.

Sex - and age-dependent effect on AF on mortality

Our study confirms previous (smaller) studies which reported AF/AFL as the most prevalent arrhythmia in COVID-19 patients, in addition to its association with increased mortality. With respect to AF/AFL occurrence, Peltzer et al. and Mountantonakis et al. observed a slightly higher prevalence of AF/AFL compared to our study (16% and 18% compared to 12% respectively), whereas Musikantow et al. found a similar prevalence of 10%.[8, 9, 20] Conversely, Bhatla et al. reported a much lower prevalence of new-onset AF (3.5%), yet in a much smaller dataset of 700 patients.[10]

Similar to our study, Peltzer et al. and Mountantonakis et al. found AF and/or AFL, as well as new-onset AF and/or AFL, to be associated with increased in-hospital mortality.[8, 9] Bhatla et al. did not find such an association between new-onset AF and/or AFL and in-hospital mortality, yet (again) this study included a relatively small dataset with only 25 incident AF cases reported.[10]

Importantly, using the latest prediction methodology (allowing age to remain continuous in all analyses using cubic spline functions), we were – for the first time – able to pinpoint the effect of AF/AFL occurrence on in-hospital mortality to male hospitalised COVID-19 patients aged 60–72 years.

In fact, we ruled out an effect of AF/AFL occurrence on mortality in female patients with COVID-19, while in the general population females with AF/AFL have a worse outcome compared to males.[12] As an example, in a male hospitalised COVID-19 patient of 65 years, the occurrence of AF/AFL would increase his risk of mortality from ~15% to ~35%, whereas in a female patient of 65 years this risk remains well below ~15–20%, regardless of AF/AFL development. More importantly, the correlation between age and its interaction with AF and/or AFL follows a non-linear pattern, which is even different for males and females, thus underlining the importance of our statistical approach. As such, our analyses provide a much more granular assessment of the effect of new-onset AF and/or AFL during hospital admission for COVID-19 by better identifying subgroups of patients where the prognostic impact on mortality is most relevant.

Strengths and limitations

Major strengths of our work include the inclusion of a large international dataset of nearly 6000 hospitalised COVID-19 patients, allowing to perform sophisticated analyses on the incremental impact of AF/AFL occurrence on in-hospital mortality beyond the effects of age and sex. However, our findings might not be restricted to or typical for COVID-19 patients. For example, a recent study by Musikantow et al. shows a similar increase in mortality in hospitalised influenza patients with AF/AFL.[20] This seems to indicate that the found association might be related to a general viral-induced systemic illness rather than specifically COVID-19, suggesting that the findings in this study might be generalised to other patients with viral induced respiratory tract infections (e.g. influenza). Nevertheless, for full appreciation the following topics deserve attention.

First, while our findings show that AF and/or AFL appears *prognostically* unfavourable, particularly in males, this does not imply a *causal* relationship. In fact, it could be argued that the development of AF/AFL and its impact on mortality is merely a more general signal of progression of disease severity and accumulation of comorbidities (e.g. exemplified by higher CHA_2DS_2-VASc scores), and thus could be considered as an 'innocent bystander' in patients experiencing clinical deterioration. To explore the impact of the development of new-onset AF and/or AFL during hospitalisation on in-hospital mortality when adjusting for concomitant comorbidities and risk factors, we performed a sensitivity analysis with additional adjustment for CHA_2DS_2-VASc score. Although this analysis is inherently impacted by a lower degree of statistical robustness due to missing information on the CHA_2DS_2-VASc score in 75.7% of patients (n = 2779), it did yielded similar inferences (**Supplemental Table S3 and S4**). Moreover, in our study the majority of AF and/or AFL cases (60.7%) were detected in patients either before ICU admission or in patients never admitted to the ICU (i.e. before widespread increase in disease severity occurred). Although it is possible that the threshold for ICU referral was higher due to limited capacity during the peak of the pandemic, this suggests that (new-onset) AF and/or AFL, would at least be an early marker for disease progression. Based on our findings this appears to be prognostically unfavourable, particularly in males aged between 60 and 72 years. Second, although diagnoses were centrally defined, with multicentre studies there is always a risk of heterogeneity due to differences in interpretation among centres. Given that the strategy for rhythm monitoring was defined by the attending physicians, and as a consequence

was different per centre, it could well be that electrical disorders may have been underdiagnosed in patients on general wards where continuous rhythm monitoring is not performed. Moreover, grouping the different AF subtypes (paroxysmal, persistent, and permanent) may have resulted in missing subtle disease progression within the AF group. Finally, since only in-hospital death could be recorded, mortality outcome data are limited, and comparison with other studies is hampered by differential follow up due to differences in length of hospital stay.

CONCLUSIONS

Using a large international database, this study confirms that AF and/or AFL is the most prevalent electrical disorder in hospitalised COVID-19 patients, and that new-onset AF and/or AFL is associated with a poorer prognosis exemplified by an increased in-hospital mortality. However, this increased mortality risk appears to be restricted to male patients aged between 60 and 72 years, and was not observed in female patients.

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Supplemental Table S1 – Baseline characteristics of hospitalised COVID-19 patients stratified by the occurrence of different subtypes of cardiac electrical events.

	Total n=5782	No arrhythmic event n=4800	AF/AFL n=692	Ventricular arrhythmia n=46	Conduction disorder n=365
Demographics					
Male sex n (%)	3686 (63.8)	2990 (62.3)	482 (69.7)	38 (82.6)	269 (73.7)
Age in years median (IQR)	67 (56-76)	65 (54-75)	74 (69-81)	71.5 (61.3-76.8)	76 (70-83)
History of supraventricular tachycardia					
AF n (%)	616 (10.7)	326 (6.8)	257 (37.2)	5 (10.9)	77 (21.2)
AFL n (%)	52 (0.9)	21 (0.4)	23 (3.3)	1 (2.2)	13 (3.6)
Atrial tachycardia n (%)	21 (0.4)	17 (0.4)	3 (0.4)	0 (0.0)	1 (0.3)
AV nodal re-entry tachycardia n (%)	22 (0.4)	18 (0.4)	4 (0.6)	0 (0.0)	1 (0.3)
History of ventricular tachycardia					
Non-sustained ventricular tachycardia n (%)	21 (0.4)	13 (0.3)	7 (1.0)	1 (2.2)	4 (1.1)
Sustained ventricular tachycardia n (%)	15 (0.3)	10 (0.2)	0 (0.0)	3 (6.5)	3 (0.8)
Ventricular fibrillation n (%)	24 (0.4)	16 (0.3)	6 (0.9)	1 (2.2)	2 (0.5)
History of conduction disorders					
1st AV block n (%)	19 (0.3)	12 (0.3)	2 (0.3)	0 (0.0)	7 (1.9)
2nd AV block n (%)	13 (0.2)	9 (0.2)	2 (0.3)	0 (0.0)	3 (0.8)
3rd AV block n (%)	26 (0.4)	20 (0.4)	2 (0.3)	0 (0.0)	5 (1.4)
Left bundle branch block n (%)	24 (0.4)	11 (0.2)	5 (0.7)	0 (0.0)	12 (3.3)
Right bundle branch block n (%)	18 (0.3)	10 (0.2)	4 (0.6)	0 (0.0)	7 (1.9)
Other medical history					
Heart failure n (%)	315 (5.5)	190 (4.0)	88 (12.7)	4 (8.7)	58 (15.9)
Hypertension n (%)	2692 (47.6)	2114 (45.0)	407 (60.2)	23 (53.5)	228 (63.9)
Diabetes mellitus (type I or II) n (%)	1494 (26.1)	1211 (25.5)	188 (27.6)	9 (20.0)	130 (36.3)
Peripheral arterial disease n (%)	271 (6.0)	199 (5.3)	54 (9.8)	6 (15.0)	22 (7.6)
Myocardial infarction† n (%)	523 (9.2)	397 (8.4)	81 (11.9)	6 (14.0)	57 (16.1)
Renal impairment n (%)	620 (10.7)	447 (9.3)	123 (17.9)	4 (8.7)	73 (20.1)
COPD n (%)	643 (11.1)	504 (10.5)	97 (14.1)	2 (4.3)	61 (16.8)

Supplemental Table S1 – continued.

	Total n=5782	No arrhythmic event n=4800	AF/AFL n=692	Ventricular arrhythmia n=46	Conduction disorder n=365
Risk factors					
BMI in kg/m² median (IQR)	27.5 (24.6-30.9)	27.5 (24.6-31.0)	27.2 (24.5-30.5)	25.2 (23.7-28.3)	27.6 (24.6-30.8)
Medication					
Digoxin n (%)	112 (1.9)	52 (1.1)	58 (8.4)	1 (2.2)	10 (2.7)
Anti-arrhythmic drugs - class I n (%)	28 (0.5)	14 (0.3)	12 (1.7)	0 (0.0)	2 (0.5)
Anti-arrhythmic drugs - class III n (%)	110 (1.9)	68 (1.4)	24 (3.5)	4 (8.7)	17 (4.7)
Anti-arrhythmic drugs - class IV n (%)	64 (1.1)	46 (1.0)	15 (2.2)	0 (0.0)	4 (1.1)
Beta blockers n (%)	1562 (27.0)	1143 (23.8)	308 (44.5)	21 (45.7)	159 (43.7)
Antihypertensive drugs[‡] n (%)	2575 (44.6)	1994 (41.6)	397 (57.4)	30 (65.2)	244 (67.0)
Platelet inhibitors n (%)	1270 (22.0)	1024 (21.3)	139 (20.1)	14 (30.4)	122 (33.5)
Anticoagulants n (%)	779 (13.5)	444 (9.3)	284 (41.0)	10 (21.7)	101 (27.7)
Antidiabetic drugs n (%)	1105 (19.1)	898 (18.7)	141 (20.4)	6 (13.0)	95 (26.1)
Physical examination and biomarkers (at the start of hospital admission)					
Temperature in °C median (IQR)	37.8 (37.0-38.5)	37.8 (37.0-38.5)	37.7 (37.0-38.5)	37.7 (37.1-37.9)	37.8 (36.9-38.6)
C-reactive protein in mg/L median (IQR)	76.0 (31.0-144.0)	72.0 (28.0-140.0)	95.0 (45.0-170.0)	130.5 (43.8-271.3)	83.0 (39.0-139.0)
White blood cell count x10⁹/L median (IQR)	6.8 (5.0-9.3)	6.7 (5.0-9.2)	6.8 (5.0-9.9)	7.9 (6.1-10.9)	6.6 (5.0-9.6)

AF: atrial fibrillation; AFL: atrial flutter; AV: atrioventricular; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; n: number.

† ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.

‡ Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.

Supplemental Table S2 – Characteristics of COVID-19 patients and their relation to the development of new-onset atrial fibrillation or atrial flutter during hospitalisation (univariable analyses).

		No AF/AFL† n=4712	AF/AFL† n=420	Unadjusted odds ratio (95% CI)
Demographics, risk factors, medical history, and medication (before hospital admission)				
Male sex n (%)		2955 (62.7)	294 (70.0)	1.38 (1.12-1.73)
Sex NA n (%)		1 (0.0)	0 (0.0)	
Age in years				1.15 (1.07-1.28)
Age in years'	median (IQR)‡	64 (54-74)	73 (66-79)	0.92 (0.80-1.04)
Age in years''				1.05 (0.67-1.80)
Age in years NA n (%)		0 (0.0)	0 (0.0)	
BMI in kg/m²				1.06 (0.96-1.18)
BMI in kg/m²'	median (IQR)‡	27.47 (24.62-30.93)	27.19 (24.69-30.46)	0.83 (0.53-1.26)
BMI in kg/m²''				1.47 (0.42-5.27)
BMI in kg/m² NA n (%)		1252 (26.6)	62 (14.8)	
Heart failure n (%)		156 (3.3)	23 (5.5)	1.72 (1.05-2.64)
Heart failure NA n (%)		10 (0.2)	1 (0.2)	
Hypertension n (%)		2031 (44.0)	227 (55.4)	1.57 (1.29-1.93)
Hypertension NA n (%)		101 (2.1)	10 (2.4)	
Diabetes mellitus (type I or II) n (%)		1195 (25.6)	100 (24.2)	0.93 (0.73-1.17)
Diabetes mellitus (type I or II) NA n (%)		51 (1.1)	7 (1.7)	
Peripheral arterial disease n (%)		181 (4.9)	26 (8.0)	1.70 (1.07-2.55)
Peripheral arterial disease NA n (%)		1033 (21.9)	94 (22.4)	
Myocardial infarction§ n (%)		374 (8.0)	47 (11.3)	1.47 (1.04-2.00)
Myocardial infarction§ NA n (%)		56 (1.2)	3 (0.7)	
Renal impairment n (%)		414 (8.8)	58 (13.9)	1.69 (1.24-2.24)
Renal impairment NA n (%)		6 (0.1)	3 (0.7)	
Digoxin n (%)		19 (0.4)	12 (2.9)	7.36 (3.40-14.91)
Digoxin NA n (%)		4 (0.1)	0 (0.0)	

Supplemental Table S2 – continued.

	No AF/AFL† n=4712	AF/AFL† n=420	Unadjusted odds ratio (95% CI)
Anti-arrhythmic drugs (class I, III and/or IV) n (%)	85 (1.8)	9 (2.1)	1.25 (0.56-2.34)
Anti-arrhythmic drugs (class I, III and/or IV) NA n (%)	1 (0.0)	1 (0.2)	
Beta blockers n (%)	1028 (21.8)	136 (32.4)	1.72 (1.38-2.13)
Beta blockers NA n (%)	4 (0.1)	0 (0.0)	
Antihypertensive drugs¶ n (%)	1913 (40.6)	204 (48.6)	1.38 (1.13-1.69)
Antihypertensive drugs¶ NA n (%)	4 (0.1)	0 (0.0)	
Antithrombotics# n (%)	1296 (27.5)	161 (38.3)	1.64 (1.33-2.01)
Antithrombotics# NA n (%)	4 (0.1)	0 (0.0)	
Physical examination and biomarkers (at the start of hospital admission)			
Temperature in °C median (IQR)	37.8 (37.0-38.6)	37.7 (37.0-38.5)	0.99 (0.89-1.10)
Temperature in °C NA median (IQR)	808 (17.1)	106 (25.2)	
C-reactive protein in mg/L median (IQR)	83.00 (40.75-150.00)	112.00 (61.75-182.10)	1.00 (1.00-1.00)
C-reactive protein in mg/L NA median (IQR)	566 (12.0)	64 (15.2)	
White blood cell count x10^9/L median (IQR)	6.80 (5.00-9.20)	7.10 (5.00-10.50)	1.03 (1.01-1.05)
White blood cell count x10^9/L NA median (IQR)	505 (10.7)	62 (14.8)	
Characteristics (during hospitalisation)			
Duration of hospitalisation in days median (IQR)	8 (4-16)	15 (6-30)	1.02 (1.02-1.03)
Duration of hospitalisation in days NA median (IQR)	135 (2.9)	13 (3.1)	
Development of pulmonary embolism n (%)	317 (6.7)	54 (12.9)	2.06 (1.49-2.78)
Development of pulmonary embolism NA n (%)	0 (0.0)	0 (0.0)	

AF: atrial fibrillation; AFL: atrial flutter; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NA: not available.

† There were no missing values for the outcome variable.

ǂ Age and BMI were divided into three subgroups (depicted by [X], [X'], and [X'']) using cubic spline functions, because these variables follow a non-linear pattern with the outcome variable, as visualised in the two graphs below the table.

§ ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.

¶ Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.

Platelet inhibitors, anticoagulants.

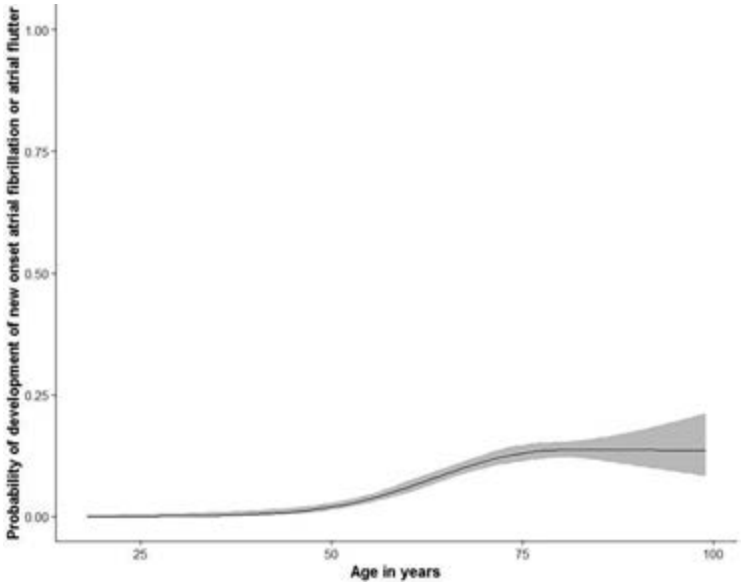

Figure S1 – Risk of development of new-onset atrial fibrillation or atrial flutter in COVID-19 patients by age.

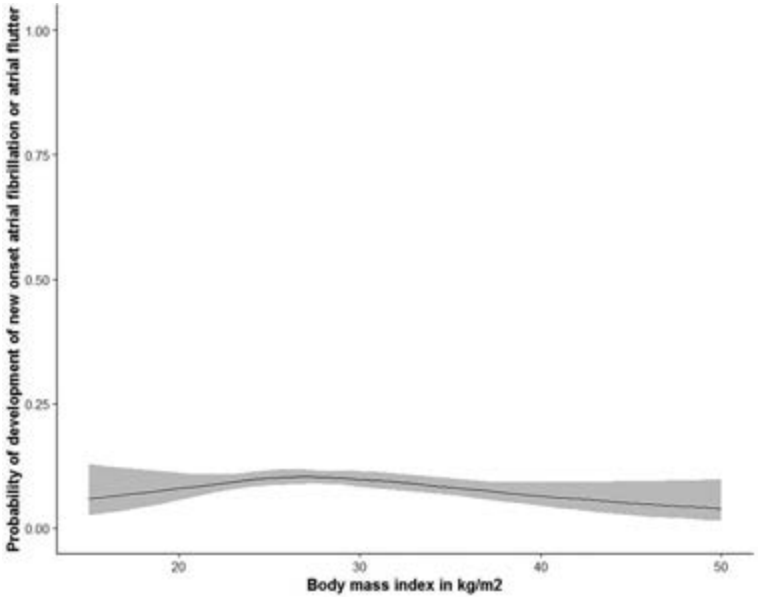

Figure S2 – Risk of development of new-onset atrial fibrillation or atrial flutter in COVID-19 patients by body mass index.

Supplemental Table S3 – Characteristics of COVID-19 patients and their relation to in-hospital mortality in patients with new-onset atrial fibrillation or atrial flutter.

		Univariable analyses†			
		Alive n=3317	**Death** n=938	**Outcome NA** n=24	**Unadjusted odds ratio (95% CI)**
Male sex n (%)		2081 (62.8)	656 (69.9)	15 (62.5)	1.38 (1.18-1.62)
Sex NA n (%)		1 (0.0)	0 (0.0)	0 (0.0)	
Age in years					7.85 (5.60-11.20)
Age in years'	median (IQR)‡	66 (59-74)	75 (68-80)	67 (60.75-73)	26.22 (9.96-75.80)
Age in years''					7.96 (5.77-11.09)
Age in years NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
AF/AFL during admission n (%)		268 (8.1)	134 (14.3)	1 (4.2)	1.90 (1.52-2.36)
AF/AFL during admission NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	

	Multivariable analyses (with spline for age and the interaction between age and AF/AFL)†
	Adjusted odds ratio (95% CI)
Male sex	1.50 (1.28-1.78)
Age in years ‡	8.29 (5.79-12.09)
Age in years' ‡	23.36 (8.59-70.14)
Age in years'' ‡	8.65 (6.12-12.36)
AF/AFL during admission	2.16 (0.16-14.11)
Interaction age and AF/AFL ‡	0.35 (0.10-1.58)
Interaction age and AF/AFL' ‡	0.77 (0.01-169.24)
Interaction age and AF/AFL'' ‡	0.52 (0.18-1.89)

AF: atrial fibrillation; AFL: atrial flutter; CI: confidence interval; IQR: interquartile range; n: number; NA: not available.

† In all above analyses only patients with an age of 50-90 years were included, because the number of patients developing new-onset AF and/or AFL during admission was too low in patients <50 years and >90 years in order to obtain reliable results.

‡ Age was divided into three subgroups (depicted by [X], [X'], and [X'']) using a cubic spline function, because it follows a non-linear pattern with the outcome variable, as visualised in the graph below the table.

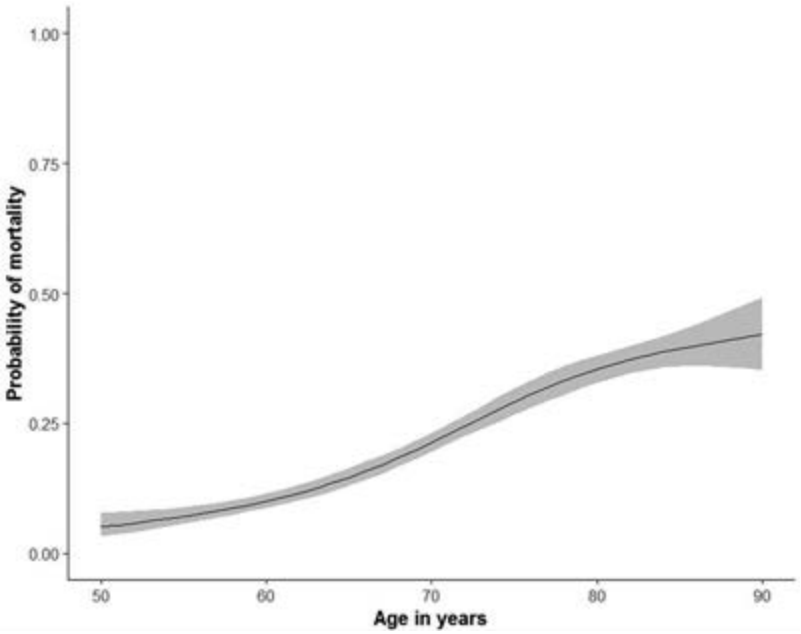

Figure S3 – Risk of in-hospital mortality in COVID-19 patients with new-onset atrial fibrillation or atrial flutter by age.

Supplemental Table S4 – Characteristics of COVID-19 patients, including CHA_2DS_2-VASc-score, and their relation to in-hospital mortality in patients with new-onset atrial fibrillation or atrial flutter.

		Univariable analyses†			
		Alive n=3317	**Death n=938**	**Outcome NA n=24**	**Unadjusted odds ratio (95% CI)**
Male sex n (%)		2081 (62.8)	656 (69.9)	15 (62.5)	1.38 (1.18-1.62)
Sex NA n (%)		1 (0.0)	0 (0.0)	0 (0.0)	
Age in years					7.85 (5.60-11.20)
Age in years'	median (IQR)‡	66 (59-74)	75 (68-80)	67 (60.75-73)	26.22 (9.96-75.80)
Age in years''					7.96 (5.77-11.09)
Age in years NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
CHA_2DS_2-VASc score ≥2 n (%)		718 (21.6)	315 (33.6)	0 (0.0)	4.26 (3.05-6.17)
CHA_2DS_2-VASc score ≥2 NA n (%)		2197 (66.2)	582 (62.0)	22 (91.7)	
AF/AFL during admission n (%)		268 (8.1)	134 (14.3)	1 (4.2)	1.90 (1.52-2.36)
AF/AFL during admission NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	

	Multivariable analyses (with spline for age and the interaction between age and AF/AFL)†
	Adjusted odds ratio (95% CI)
Male sex	1.60 (1.22-2.13)
Age in years ‡	8.66 (4.27-19.14)
Age in years' ‡	17.45 (2.47-185.93)
Age in years'' ‡	6.13 (3.23-12.21)
CHA_2DS_2-VASc score ≥2	2.02 (1.32-3.17)
AF/AFL during admission	3.80 (0.03-84.86)
Interaction age and AF/AFL ‡	0.25 (0.04-4.16)
Interaction age and AF/AFL' ‡	0.21 (0.00-5981.88)
Interaction age and AF/AFL'' ‡	0.13 (0.02-1.33)

AF: atrial fibrillation; AFL: atrial flutter; CI: confidence interval; IQR: interquartile range; n: number; NA: not available.

† In all above analyses only patients with an age of 50-90 years were included, because the number of patients developing new-onset AF and/or AFL during admission was too low in patients <50 years and >90 years in order to obtain reliable results.

‡ Age was divided into three subgroups (depicted by [X], [X'], and [X'']) using a cubic spline function, because it follows a non-linear pattern with the outcome variable, as visualised in the graph below the table.