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# Does atrial fibrillation affect prognosis in hospitalised COVID-19 patients? A multicentre historical cohort study in the Netherlands

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## ABSTRACT

**Objectives** The aim of this multicentre COVID-PREDICT study (a nationwide observational cohort study that aims to better understand clinical course of COVID-19 and to predict which COVID-19 patients should receive which treatment and which type of care) was to determine the association between atrial fibrillation (AF) and mortality, intensive care unit (ICU) admission, complications and discharge destination in hospitalised COVID-19 patients.

**Setting** Data from a historical cohort study in eight hospitals (both academic and non-academic) in the Netherlands between January 2020 and July 2021 were used in this study.

**Participants** 3064 hospitalised COVID-19 patients >18 years old.

**Primary and secondary outcome measures** The primary outcome was the incidence of new-onset AF during hospitalisation. Secondary outcomes were the association between new-onset AF (vs prevalent or non-AF) and mortality, ICU admissions, complications and discharge destination, performed by univariable and multivariable logistic regression analyses.

**Results** Of the 3064 included patients (60.6% men, median age: 65 years, IQR 55–75 years), 72 (2.3%) patients had prevalent AF and 164 (5.4%) patients developed new-onset AF during hospitalisation. Compared with patients without AF, patients with new-onset AF had a higher incidence of death (adjusted OR (aOR) 1.71, 95% CI 1.17 to 2.59) an ICU admission (aOR 5.45, 95% CI 3.90 to 7.61). Mortality was non-significantly different between patients with prevalent AF and those with new-onset AF (aOR 0.97, 95% CI 0.53 to 1.76). However, new-onset AF was associated with a higher incidence of ICU admission and complications compared with prevalent AF (OR 6.34, 95% CI 2.95 to 13.63, OR 3.04, 95% CI 1.67 to 5.55, respectively).

**Conclusion** New-onset AF was associated with an increased incidence of death, ICU admission, complications and a lower chance to be discharged home. These effects were far less pronounced in patients with prevalent AF. Therefore, new-onset AF seems to represent a marker of disease severity, rather than a cause of adverse outcomes.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A major strength of this study is the large national dataset of more than 3000 hospitalised COVID-19 patients from eight different hospitals.
⇒ Due to incomplete data, 458 patients (13%) had to be excluded.
⇒ It is not known whether every patient with newly diagnosed atrial fibrillation (AF) was treated with anticoagulants.
⇒ The timing of the onset of AF and outcomes is not known. It is possible a complication occurred earlier in the admission than the new-onset AF.
⇒ Our data comprise the first COVID-19 waves and may not be fully extrapolated to later waves and different variants of the SARS-CoV-2 virus. It cannot be excluded that new variants cause different arrhythmias and less severe complications. Also, the data reported here were collected before the vaccination campaigns started, and the effect of vaccination against COVID-19 on the risk of AF and associated outcomes as reported here may be different in the postvaccination era cohorts.

## INTRODUCTION

Infection with SARS-CoV-2 is predominantly associated with respiratory symptoms leading to the global COVID-19. In addition to respiratory symptoms, COVID-19 is frequently associated with cardiovascular comorbidities.[1] Incident cardiac arrhythmias, including atrial fibrillation (AF) and atrial flutter, are common in COVID-19 patients and are associated with mortality.[2–7] Offerhaus *et al* recently reported in a large multicentre cohort study that new-onset AF and/or atrial flutter were

associated with increased mortality in men but not in women in hospitalised COVID-19 patients.[8] Musikantow *et al* showed no difference in mortality between hospitalised influenza patients and hospitalised COVID-19 patients with new-onset AF.[9] Patients with severe sepsis and acute respiratory distress syndrome (ARDS) have a higher incidence of AF during hospitalisation. Ten percent of critically ill patients develop new-onset AF, irrespective of the origin of the infectious disease.[10] These results suggest that AF is related to systemic illness rather than COVID-19 infection itself. Contrary to mortality data, data on complications such as physical and cognitive decline in COVID-19 patients with AF are limited, as well as data on discharge destination.

We performed a substudy of a large multicentre historical cohort study on patients from the first, second and third COVID-19 wave in the Netherlands. The first objective of this study was to determine the prevalence of AF at the time of admission and incidence of AF during hospitalisation in hospitalised COVID-19 patients. The second objective was to determine the association between new-onset AF (vs prevalent or no AF) and incident complications, physical and cognitive decline, and discharge destinations. Third, we investigated if AF in itself causes the worse prognosis or if the emergence of new-onset AF constitutes a risk for detrimental outcomes.

## METHODS

In this substudy of a nationwide multicentre historical cohort study, we aimed to include all admitted patients with COVID-19 in eight hospitals (both academic and non-academic) in the Netherlands between March 2020 and July 2021. Data were collected from a larger COVID-Predict registry and included patients of 18 years and older. Given the exceptional circumstances related to the COVID-19 crisis, and in accordance with national guidelines and European privacy law, the need for informed consent was waived. Patients were notified of their enrolment and were given the opportunity to opt-out of participation.

COVID-19 infection was confirmed by pharyngeal swab (PCR tes or antigen detection of SARS-CoV-2 RNA), typical abnormalities on chest CT scan[11] or both. Patient characteristics, vital parameters, laboratory results, outcome measures and discharge destination were collected from electronic patient records. AF was diagnosed with a standard 12-lead ECG. ECGs were performed when clinically indicated (irregular pulse when measuring vital functions, palpitations mentioned by the patient or arrhythmias registered by continuous heart monitoring at the intensive care unit (ICU)). Patients with new-onset AF had no prior history of AF. Patients with prevalent AF were diagnosed with AF prior to the hospital admission for COVID-19 (paroxysmal, persistent, permanent and atrial flutter combined).

The complications were diagnosed by the patient's attending physician, or when needed, by a consulting specialist. Arrhythmias, mortality, ICU admissions and complications were evaluated at 12 weeks after hospital admission. The primary outcome was the incidence of new-onset AF during hospitalisation. Secondary outcomes were all-cause mortality, ICU admission, discharge destination and complications such as stroke, congestive heart failure, endo/myocarditis, physical and cognitive decline, venous thromboembolism.

Patients were occasionally transferred to other hospitals, due to a fair share policy for distribution of COVID-19 patients throughout the Netherlands. When patients were transferred to another participating hospital, the admitting hospital used the same study number as the referring hospital. Sometimes a second study number was already generated. Data of these numbers were merged into one study number. The researchers of the admitting hospital checked with the researchers in the referring hospital if a patient was already included in the study. Patients were excluded from analysis when medical history was missing in the database.

### Patient and public involvement

Patients were not involved in design or analysis of this substudy of a nationwide multicentre historical cohort.

### Comparison of secondary outcomes in patients with and without AF

AF was classified according to the current guidelines on the diagnosis and treatment of AF of the European Society of Cardiology[12]; we defined paroxysmal AF as self-terminating within 7 days, persistent AF as lasting longer than 7 days and permanent AF as accepted AF (also in the case of new-onset AF) where no attempts to restore sinus rhythm were undertaken. We assessed the differences in clinical characteristics and outcome between patients with new-onset AF during hospital admission vs those without AF, and between patients with prevalent AF versus those without prevalent or new-onset AF.

### Statistics

Patient characteristics were compared using standard descriptive statistics. Continuous variables were summarised as median (IQR) and categorical data as frequency (percentages). A $p<0.05$ was considered significant. We performed a univariable logistic regression analysis to assess the influence of AF on prognosis by assessing mortality risk, ICU admissions, complications and discharge destination. In a multivariable logistic regression analysis, these outcomes were adjusted for age, sex, hypertension and diabetes.

To adjust for unforeseen confounders and assess the influence of AF on prognosis, a propensity score matching was performed. Patients with newly diagnosed AF during admission were 1:2 matched to patients without AF, using the propensity score nearest-neighbour matching approach. This score was calculated using 16 potentially confounding variables (age, sex, hypertension, diabetes mellitus (with or without complications), obesity, chronic

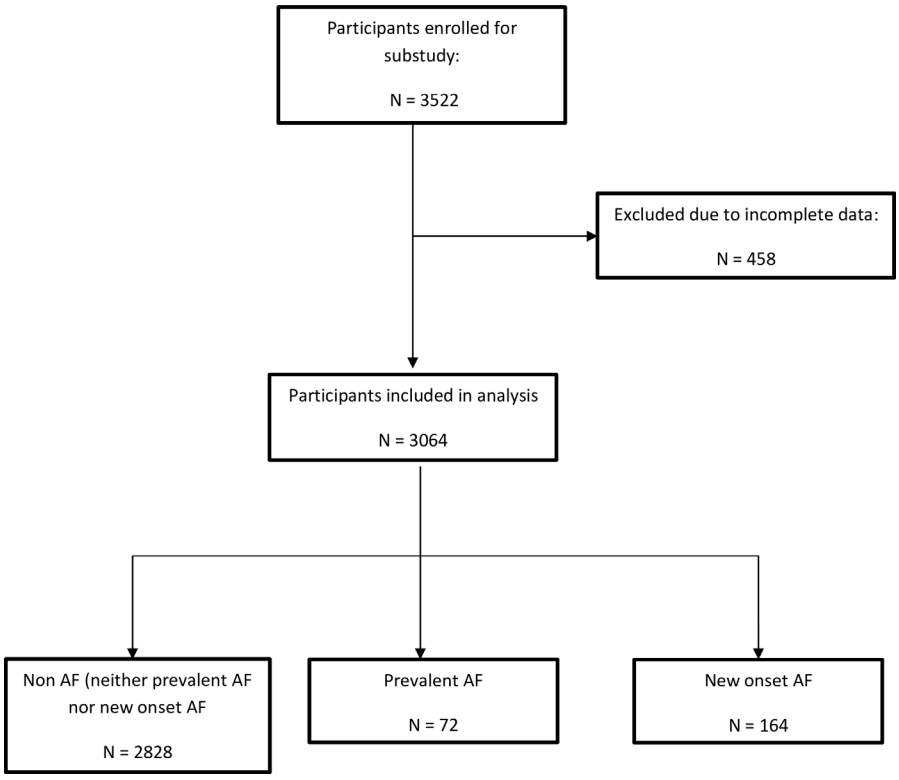


**Figure 1** Flow chart of included participants. AF, atrial fibrillation.

kidney disease, dementia, admission in first, second or third COVID-19 wave, smoking status, alcohol abuse, autoimmune disease, chronic obstructive pulmonary disease, chronic liver disease, malignancy and history of organ transplantation).

A second cohort was created by including patients with both prevalent AF and patients with new-onset AF and were then matched 1:2 to patients without AF, using the same propensity score and the same potential confounders as above. In these matched cohorts, logistic regression analysis was used as well.

All analyses were performed in IBM SPSS Statistics V.28.0.0. A forest plot, to visualise ORs and 95% CIs, was performed in R.

## RESULTS

### Overall outcomes of COVID-19 admission

In this study, 3522 consecutive patients were enrolled. For the current analysis, 458 patients (13%) were excluded because of incomplete data (see figure 1 for flow chart). The clinical characteristics of the remaining 3064 patients are summarised in table 1. Median age (IQR) was 65.0 (55–75) years and 1856 patients (60.6%) were men. Seventy-two patients (2.3%) had prevalent AF. Hypertension was the most prevalent comorbidity (42.9%), followed by obesity (27.7%) and diabetes mellitus without complications (21.6%).

Median (IQR) length of stay in the hospital, including ICU admission, was 7.0 (4.0–15.0) days. During hospitalisation, 509 patients (17.4%) died. Almost 25% (n=763) of the patients were admitted to the ICU at any time during their hospital stay. In these patients, median length of ICU stay (IQR) was 9.0 (5.0–18.0) days. Almost 60% of all patients were discharged home after hospitalisation, 13.7% of patients were discharged to a rehabilitation centre, and 4.8% of patients were admitted to a nursing home. The remainder of the patients either died during hospitalisation or were lost to follow-up after a transfer to another hospital. Complications occurred in 43.6% of the patients. Physical decline was reported most frequently (28.6%), followed by ARDS (15.5%) and delirium (13.1%).

### New-onset AF

During hospitalisation, 164 patients were diagnosed with new-onset AF (5.4% of the studied patients), of whom 46.3% (n=76) developed permanent AF, 7.9% (n=13) persistent AF, 32.9% (n=54) paroxysmal AF, 9.1% (n=15) atrial flutter and 2.4% (n=4) developed atrial tachycardia.

Patients with new-onset AF were older than patients without AF (71.6 (IQR 64–78) years vs 65.0 (54 to 74) years, p<0.001), had higher inflammation parameters (white cell count (WCC) 8.8 (IQR 6–11)×$10^9$/L vs 6.8 (IQR 5–9)×$10^9$/L, p=0.002, C reactive protein (CRP) 119 (IQR 50–211) mg/L vs 85.0 (IQR 43–145 mg/L, p<0.001)) and a higher creatinine (90.0 (IQR 71–119) µmol/L vs 83.0 (IQR 66–109)) at admission (table 1).

The length of stay in the hospital was almost 1-week longer for patients with new-onset AF compared with patients without AF (median length of stay 14.5 (IQR 6–23) days vs 9.0 (IQR 4–17) days p<0.001). A prolonged

Table 1 Patient characteristics, baseline vital functions and laboratory testing stratified by new-onset AF

| | Overall N=3064 | No new-onset AF* N=2828 | New-onset AF N=164 | P value |
|---|---|---|---|---|
| Sex | | | | |
| Men (%) | 1856 (60.6) | 1744 (60.1) | 112 (68.3) | 0.113 |
| Women (%) | 1208 (39.4) | 1156 (39.9) | 52 (31.7) | |
| Age (median, IQR) | 65.0 (55–75) | 65.0 (54–74) | 71.6 (64–78) | <0.001 |
| Comorbidities | | | | |
| Hypertension (%) | 1314 (43.2) | 1231 (42.7) | 83 (51.2) | 0.063 |
| COPD (%) | 509 (16.7) | 481 (16.6) | 28 (17.1) | 0.767 |
| Chronic kidney disease (%) | 345 (11.3) | 325 (11.3) | 20 (12.2) | 0.611 |
| Obesity (%) | 848 (31.5) | 804 (31.6) | 44 (29.3) | 0.291 |
| DM with complications (%) | 211 (6.9) | 192 (6.6) | 19 (11.6) | 0.041 |
| DM without complications (%) | 662 (21.7) | 629 (21.8) | 33 (20.1) | 0.069 |
| Dementia (%) | 81 (2.7) | 76 (2.6) | 5 (3.1) | 0.868 |
| Smoking status | | | | |
| Yes (%) | 169 (7.7) | 161 (7.7) | 8 (7.0) | 0.836 |
| No (%) | 1113 (50.8) | 1058 (50.9) | 55 (48.2) | |
| Former smoker (%) | 911 (41.5) | 860 (41.4) | 51 (44.7) | |
| Vital functions at admission | | | | |
| Temperature, °C (median, IQR) | 37.6 (36–39) | 37.6 (36–39) | 37.5 (36–38) | 0.314 |
| Heart rate in bpm (median, IQR) | 90.0 (79-103) | 90.0 (80.0–102.0) | 94.0 (78-110) | 0.058 |
| Laboratory testing at admission | | | | |
| WCC in $\times 10^9$/L (median, IQR) | 6.9 (5–10) | 6.8 (5–9) | 8.8 (6–11) | 0.002 |
| Creatinine µmol/L (median, IQR) | 84.0 (66–110) | 83.0 (66–109) | 90.0 (71–119) | 0.045 |
| CRP mg/L (median, IQR) | 86.0 (43.0–147.4) | 85.0 (43–145) | 119.0 (50–211) | <0.001 |

*Including patients with prevalent AF.
AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CRP, C reactive protei; DM, diabetes mellitus; WCC, white cell count.

stay at the ICU was also observed in new-onset AF patients (median length of stay 15.0 (IQR 9–27) days vs 7.0 (IQR 3–17) days without AF, p<0.001). Complications were reported in 72% (n=118) of patients with new-onset AF, especially ARDS, physical decline, delirium and coagulation disorders such as pulmonary embolism and deep venous thrombosis (table 2).

Univariate and multivariate logistic regression to assess the association between AF and mortality, length of stay, discharge destination and adverse events were plotted (figures 2 and 3). Patients with new-onset AF had a higher mortality risk (OR 2.39, 95% CI 1.68 to 3.41) compared with patients without AF, which remained significant after adjusting for age, sex, hypertension and diabetes mellitus (adjusted OR 1.71, 95% CI 1.17 to 2.59). New-onset AF was also associated with an increased risk for ICU admission (adjusted OR 5.45, 95% CI 3.90 to 7.61) and complications (adjusted OR 2.92, 95% CI 2.05 to 4.16) during the course of hospital admission. A negative association was observed between AF and discharge to home (OR 0.36, 95% CI 0.25 to 0.52), favouring discharge to nursing homes and rehabilitation facilities.

## Prevalent AF

Patients with prevalent AF (n=72, 34.7% women) were older than patients without AF (median age 76.0 (IQR 73–81) years old vs 65.0 (IQR 54–4) years, p<0.001) and more frequently had hypertension than patients without AF at admission. Vital functions and laboratory testing at admission were similar between patients with prevalent and patients without AF. Median length of stay in the hospital (IQR) was 5.5 (3–15) days, which was not significantly longer than patients without AF (median 9.0 (IQR 4–17, p=0.591). Similarly, length of stay at the ICU admitted patients was the same (median 8 (IQR 5–12) days vs 7 (IQR 3–14) days, p=0.841).

Patients with prevalent AF were older than patients with new-onset AF (median age 76.0 (IQR 73–81) years old vs 71.5 (IQR 64–78) years old, p<0.001), but had a similar risk of dying (OR 0.97, 95% CI 0.53 to 1.76; adjusted OR 0.82, 95% CI 0.44 to 1.53). Patients with new-onset AF had a higher risk of ICU admission (adjusted OR 6.34, 95% CI 2.95 to 13.63) and complications (adjusted OR 3.04, 95% CI 1.67 to 5.55) than patients with prevalent AF. New-onset AF was more often associated with physical

Table 2 Secondary outcomes, stratified by new-onset AF and prevalent AF

| | New-onset AF n=164 | Non AF n=2828 | P value* | Prevalent AF n=72 | P value* |
|---|---|---|---|---|---|
| All-cause mortality (%) | 49 (31.6) | 437 (16.2) | <0.001 | 23 (32.4) | <0.001 |
| Length of stay hospital in days (median, IQR) | 14.5 (6–23) | 9 (4–17) | <0.001 | 5.5 (3–15) | 0.256 |
| ICU and/or MCU admission (%) | 97 (59.1) | 666 (23.0) | <0.001 | 13.0 (18.1) | 0.394 |
| Length of stay ICU in days (median, IQR) | 15.0 (9–27) | 7.0 (3–14) | <0.001 | 8.0 (5–12) | 0.016 |
| Discharge destination | | | | | |
| Home (%) | 49 (29.9) | 1745 (61.7) | <0.001 | 29 (40.3) | <0.001 |
| Nursing home (%) | 8 (4.9) | 129 (4.6) | 0.847 | 9 (12.5) | 0.006 |
| Rehabilitation centre (%) | 26 (15.9) | 374 (13.2) | 0.345 | 11 (15.3) | 0.597 |
| Complications | | | | | |
| Total (%) | 118 (72.0) | 1187 (42.0) | <0.001 | 32 (44.4) | 0.717 |
| ARDS (%) | 65 (39.9) | 373 (13.6) | <0.001 | 6 (8.3) | 0.224 |
| Stroke/CVA (%) | 6 (3.7) | 51 (1.9) | 0.130 | 2 (2.8) | 0.388 |
| CHF (%) | 14 (8.6) | 77 (2.8) | <0.001 | 4 (5.6) | 0.150 |
| Endocarditis/myocarditis (%) | 2 (1.2) | 18 (0.7) | 0.306 | 1 (1.4) | 0.380 |
| Coagulation disorder (%) | 36 (22.1) | 203 (7.4) | <0.001 | 4 (5.6) | 0.817 |
| DVT (%) | 22 (13.4) | 69 (2.4) | <0.001 | 0 (0.0) | 0.417 |
| PE (%) | 24 (14.6) | 133 (4.7) | <0.001 | 4 (5.6) | 0.775 |
| Rhabdomyolysis (%) | 8 (4.9) | 53 (1.9) | 0.019 | 1 (1.4) | 1.000 |
| Physical decline (%) | 77 (49.7) | 740 (27.6) | <0.001 | 15 (20.8) | 0.230 |
| Cognitive decline (%) | 20 (13.7) | 201 (7.6) | 0.011 | 11 (15.5) | 0.022 |
| Delirium (%) | 38 (23.8) | 338 (12.4) | <0.001 | 13 (18.3) | 0.145 |

*Compared with non-AF.
AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ICU, intensive care unit; MCU, medium care unit; PE, pulmonary embolism.

decline (OR 3.95, 95% CI 2.01 to 7.77), coagulation disorders (OR 4.14, 95% CI 1.38 to 12.45) and ARDS (OR 6.94, 95% CI 2.74 to 17.61) compared with prevalent AF. Discharge destination was similar in these groups (discharged to home OR 1.84, 95% CI 0.99 to 3.40, discharged to nursing home OR 2.20, 95% CI 0.75 to 6.51 and discharged to rehabilitation centre OR 1.02, 95% CI 0.46 to 2.27)

### Propensity matched analysis

In this analysis, 164 patients with new-onset AF were matched to 328 patients without AF, so that age, comorbidities and admission in first, second or third COVID-19 wave was similar in both groups (online supplemental table 1). Patients with new-onset AF during hospitalisation, had a higher WCC (median 7.0 (IQR 5–10)×$10^9$/L vs 7.5 (IQR 5.8–10.8)×$10^9$/L compared with the matched patients without AF. All other vital signs and laboratory testing ad admission was not significantly different. Median length of stay in the hospital was 6.5 days longer in patients with new-onset AF compared with the matched controls (14.5 (IQR 6–23) days vs 8.0 (IQR 4–16) days, p<0.001). Patients with new-onset AF had a higher risk for ICU admission (OR 4.64, 95% CI 3.10 to 6.94) and were less likely to be discharged to home (OR 0.44, 95% CI 0.29 to 0.65). New-onset AF was associated with more complications (OR 2.47, 95% CI 1.65 to 3.70), including coagulation disorders (OR 3.37, 95% CI 1.94 to 5.84), ARDS (OR 3.27, 95% CI 2.13 to 5.02), physical decline (OR 2.39, 95% CI 1.60 to 3.56) and delirium (OR 2.03, 95% CI 1.24 to 3.30). After propensity matching, the association between new-onset AF and mortality was numerically increased but no longer significant (OR 1.47, 95% CI 0.96 to 2.25) (table 3).

Next, we matched the combined group of patients with new-onset AF and patients with prevalent AF (n=236) 1:2 with 472 patients without AF (online supplemental table 2). AF (new-onset and prevalent combined) was associated with an increased mortality risk (OR 1.66, 95% CI 1.15 to 2.38). Also, ICU admission (OR 5.23, 95% CI 3.60 to 7.58) and complications (OR 1.79, 95% CI 1.17 to 2.73) occurred more frequently in patients with AF than in patients without, although to a lesser extent than in the comparison between new-onset AF and no AF (online supplemental table 3).

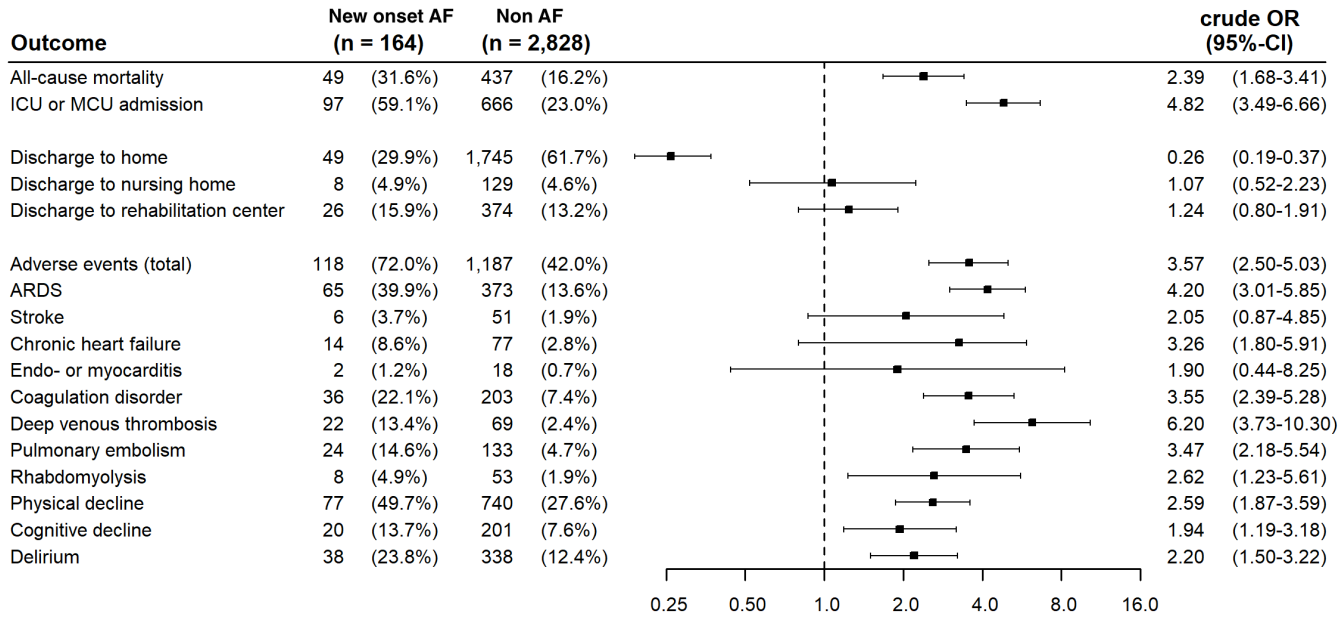


**Figure 2** Associations of new-onset atrial fibrillation (AF) and secondary outcomes in univariate regression analysis. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MCU, medium care unit.

## DISCUSSION

In this large multicentre cohort study of more than 3000 hospitalised patients with COVID-19, the occurrence of new-onset AF was associated with a poorer prognosis, increased risk of ICU admission and complications such as physical decline, delirium, coagulation disorders and fewer discharges to home.

A total of 2.7% of patients had prevalent AF in our study, similar to the prevalence in the general population aged between 55 and 74 years in the Netherlands, which is reported to be 3.5%.[13] Therefore, prevalent AF does not seem to increase the risk for hospitalisation in COVID-19-infected patients.

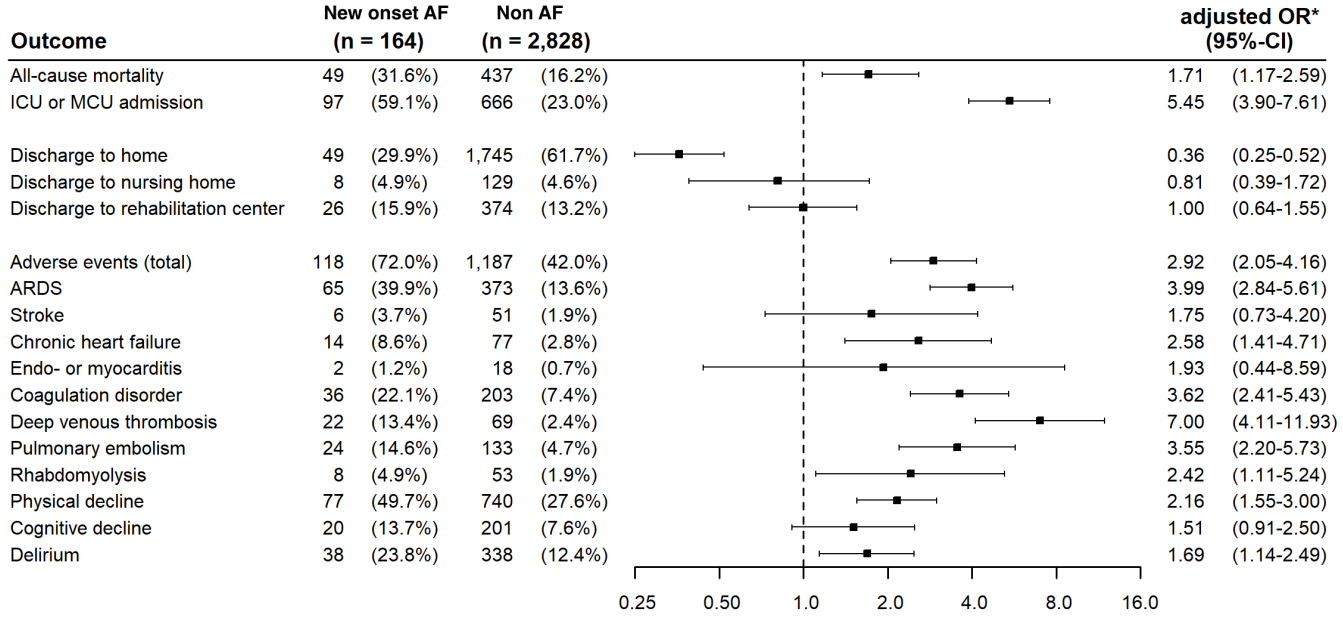


**Figure 3** Associations of new-onset atrial fibrillation (AF) and secondary outcomes in multivariate logistic regression analysis. *Adjusted for age, sex, hypertension and diabetes mellitus. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MCU, medium care unit.

Table 3 Secondary outcomes in matched cohort: new-onset AF versus non-AF (1:2)

| | New-onset AF N=164 | Non-AF N=328 | P value | OR (95% CI) |
|---|---|---|---|---|
| All-cause mortality (%) | 68 (41.5) | 85 (25.9) | <0.001 | 2.03 (1.36 to 3.01) |
| Length of stay hospital in days (median, IQR) | 14.5 (6–23) | 8.0 (4–16) | <0.001 | |
| ICU and/or MCU admission (%) | 97 (59.1) | 78 (20.3) | <0.001 | 4.64 (3.10 to 6.94) |
| Length of stay ICU in days (median, IQR) | 15.0 (9–27) | 9.0 (6–20) | 0.005 | |
| Discharge destination | | | | |
| Home (%) | 49 (29.9) | 162 (49.4) | <0.001 | 0.44 (0.29 to 0.65) |
| Nursing home (%) | 8 (4.9) | 12 (3.7) | 0.629 | 1.35 (0.54 to 3.37) |
| Rehabilitation centre (%) | 26 (15.9) | 57 (17.4) | 0.704 | 0.90 (0.54 to 1.49) |
| Complications | | | | |
| Total (%) | 118 (72.0) | 167 (50.9) | <0.001 | 2.47 (1.65 to 3.70) |
| ARDS (%) | 65 (39.9) | 54 (16.9) | <0.001 | 3.27 (2.13 to 5.02) |
| Stroke/CVA (%) | 6 (3.7) | 7 (2.2) | 0.374 | 1.74 (0.58 to 5.27) |
| Congestive heart failure (%) | 14 (8.6) | 18 (5.6) | 0.245 | 1.59 (0.77 to 3.28) |
| Endocarditis/myocarditis (%) | 2 (1.2) | 3 (0.9) | 1.000 | 1.33 (0.22 to 8.06) |
| Coagulation disorder (%) | 36 (22.1) | 25 (7.8) | <0.001 | 3.37 (1.94 to 5.84) |
| Deep venous thrombosis (%) | 22 (13.4) | 8 (2.4) | <0.001 | 6.20 (2.69 to 14.25) |
| Pulmonary embolism (%) | 24 (14.6) | 18 (5.5) | 0.001 | 2.95 (1.55 to 5.62) |
| Rhabdomyolysis (%) | 8 (4.9) | 7 (2.2) | 0.162 | 2.31 (0.82 to 6.48) |
| Physical decline (%) | 20 (13.7) | 29 (9.3) | 0.194 | 2.39 (1.60 to 3.56) |
| Cognitive decline (%) | 77 (47.0) | 91 (29.3) | <0.001 | 1.54 (0.84 to 2.83) |
| Delirium (%) | 38 (23.8) | 42 (13.3) | 0.006 | 2.03 (1.24 to 3.30) |

AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ICU, intensive care unit; MCU, medium care unit; PE, pulmonary embolism.

The prevalence of new-onset AF was lower in our cohort compared with previous reports (9.6% and 12.5% vs 5.4%).[2 8 14] During the peak of COVID-19 admissions in the first two waves, the clinical frailty scale was used by Dutch general practitioners and nursing home physicians to define very frail patients who were likely to die during hospitalisation. Most of these patients were not admitted to the hospital, but best supportive care was offered at home or in their nursing homes. There is a possibility that the oldest and frailest patients were, therefore, under-represented in our study. Since AF is most prevalent in this group of patients,[15] it is possible this explains the difference in the prevalence of AF compared with other studies.

Our study showed that new-onset AF in patients admitted with COVID-19 is not only associated with mortality, but also a remarkable increase in ICU admission, lower chance of discharged home and complications. In the propensity-matched cohort, the association of new onset and mortality was no longer significant. The propensity matching was executed to reduce confounding. However, our study is a describing study, and causality cannot be established.

The most common complications include venous thromboembolisms, ARDS physical and cognitive decline. It can be postulated that these patients also experience a more disturbed rehabilitation, but unfortunately, long-term follow-up data were not available. Therefore, further studies on the clinical course of post-COVID-19 are needed to assess if AF patients will recover to the same extent as patients without AF.

A notable finding is that patients with prevalent AF were less often admitted to the ICU than patients with new-onset AF. Potentially, the more advanced age of these patients may have been associated with a more restricted policy regarding ICU admission. However, no sufficient data on such restrictions or on policies not to resuscitate patients were available. Alternatively, patients with prevalent AF may have a lower risk of developing adverse events, due to the fact that oral anticoagulation may have had a protective effect on ICU admission through the prevention of thromboembolic events. Nevertheless, this hypothesis was not confirmed in a study by van Haaps *et al* in a cohort of patients that used oral anticoagulation for various indications.[16]

Another recent study showed that a prior history of AF is associated with all-cause death, stroke, heart failure and myocardial infarction in COVID-19 patients, independent of whether acute AF was present or not.[17] In our analysis, the most detrimental outcomes, such as length

of stay, ICU admissions and complications, were encountered in patients with new-onset AF. Mortality in both new-onset and prevalent AF was similar, although the mean age of patients with prevalent AF was 5 years older. In the analysis comparing the combined group of new-onset AF and patients with prevalent AF, the associations were still significant, but the odds rates were numerically lower. Both new-onset AF and prevalent AF were associated with an increased risk of mortality. However, associations with discharge destination and adverse events were only observed in the new-onset AF cohort. Thus, it appears that AF itself is not causing the poorer prognosis. Conversely, new-onset AF is probably more a general marker of disease severity.

The pathophysiology of AF in COVID-19 infection is not completely understood. It is assumed that reduced ACE2 receptor availability, sialic acid-spike protein interaction, inflammatory cytokine storm, viral endothelial damage, imbalances in electrolytes and acid-base abnormalities could be involved in the pathogenesis of AF in these patients.[18] In older patients who are already susceptible to AF, systemic infection and increased sympathetic nervous system activity could add to the higher incidence as well.[19] In our study, patients with new-onset AF had a higher CRP at admission. Potentially, these patients had a higher inflammation burden, which may have contributed to the development of AF and poorer prognose. However, even when adjusting for CRP, patients with AF de novo still have worse outcomes than patients with sinus rhythm or prevalent AF. Another possible explanation for worse prognosis might be haemodynamic instability caused by initiated or altered medication which was started for rhythm/rate control.

## Strengths and limitations

A major strength of this study is the large national dataset of more than 3000 hospitalised COVID-19 patients from eight different hospitals. There are, however, also some limitations. Due to incomplete data, 458 patients (13%) had to be excluded. Second, it is not known whether every patient with newly diagnosed AF was treated with anticoagulants. Third, the timing of the onset of AF and outcomes is not known. It is possible a complication occurred earlier in the admission than the new-onset AF. Furthermore, our data comprise the first COVID-19 waves and may not be fully extrapolated to later waves and different variants of the SARS-COV-2 virus. It cannot be excluded that new variants cause different arrhythmias and less severe complications. Also, the data reported here were collected before the vaccination campaigns started, and the effect of vaccination against COVID-19 on the risk of AF and associated outcomes as reported here may be different in the postvaccination era cohorts.

In conclusion, new-onset AF is associated with an increased risk of mortality, ICU admission, ARDS, coagulation disorders, delirium, and physical and cognitive decline. As these effects were far less pronounced in patients with prevalent AF, new-onset AF seems to represent a marker of disease severity, rather than a cause of adverse outcomes.

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