MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2025; 31: e946192
DOI: 10.12659/MSM.946192

Received: 2024.08.15
Accepted: 2024.12.08
Available online: 2025.01.29
Published: 2025.03.11

New-Onset, But Not Chronic Atrial Fibrillation, Is a Significant Factor Contributing to Mortality Among Patients with Severe COVID-19

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Jakub Klimkiewicz
ABDE 1 Mateusz Gutowski
ABDE 1 Andrzej Michałowski
ABDE 1 Kamil Paryż
ACDEF 2 Anna Klimkiewicz
ACDEF 3 Arkadiusz Lubas

1 Department of Anesthesiology and Intensive Care, Military Institute of Medicine – National Research Institute, Warsaw, Poland
2 Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland
3 Department of Internal Diseases Nephrology and Dialysis, Military Institute of Medicine – National Research Institute, Warsaw, Poland

Corresponding Author: Jakub Klimkiewicz, e-mail: jklimkiewicz@wim.mil.pl
Financial support: None declared
Conflict of interest: None declared

Background: Atrial fibrillation (AF) is a common arrhythmia in the general population and the most frequently presented arrhythmia in the intensive care unit. We investigated the effects of AF on the outcomes of critical COVID-19 patients, especially focusing on differences between chronic (CAF) and new-onset AF (NOAF) during critical disease.

Material/Methods: In this case-control study, we investigated the association of CAF and NOAF as an exposure, with in-hospital mortality as an outcome. We identified 2 patient groups, NOAF and CAF, which were compared with controls (all other hospitalized patients with critical COVID-19 pneumonia). No specific selection or matching was performed. The chi-square test was used for categorical variables; *t* test and Mann-Whitney U tests were used for continuous variables, depending on distribution. $P<0.05$ was considered significant.

Results: In-hospital mortality was significantly higher in the NOAF group, while in the CAF group, it was similar to that of the control group. The NOAF group had significantly higher markers of inflammation and more severe acute respiratory distress syndrome (ARDS), measured with computed tomography. NOAF was strongly associated with in-hospital death, with OR 6.392 (95% CI, 2.758-14.815), $P<0.000$. In comparison, the CAF group was older and had more cardiovascular comorbidities, with similar markers of inflammation and severity of ARDS as the control group.

Conclusions: NOAF in COVID-19 was linked with significant risk of death, being a sign of extreme cardiac, pulmonary, and metabolic instability. NOAF should be considered as an important marker of instability and predictor of poor outcomes among patients with COVID-19.

Keywords: Atrial Fibrillation • Cardiovascular Diseases • COVID-19 • Mortality

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/946192

4026 6 1 36

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Introduction

Atrial fibrillation (AF) is a common rhythm disorder. The frequency of AF can reach up to 0.51% in the general population, with lifetime risk of 25% [1]. AF places a substantial burden on medical care [1]. One large study found that AF onset in the intensive care unit (ICU) was associated with a substantial treatment cost increase ($41,303 vs $28,298, $P<0.01$), per hospitalization. The difference was even higher when calculations were based among survivors only, with a cost per an ICU hospitalization with AF onset of $81,120, as compared with $59,710 for patients without AF [2]. A study by Fernando et al showed that, in general, the presence of AF onset in the ICU was a significant predictor of total hospital costs (odds ratio [OR] 1.09 [95% CI: 1.02-1.21]) [2]. The higher costs of ICU stays resulted mostly from the length of stay in the ICU and the use of renal replacement therapy, invasive mechanical ventilation, and antiarrhythmic agents [2]. AF influences morbidity and mortality directly or by its complications [3]. Common complications of AF are stroke/embolism, left ventricle dysfunction, heart failure, and cognitive impairment/dementia [3]. AF contributes to emergency department visits, hospitalizations, and lower functional status and quality of life [3], and it is the most common arrhythmia among ICU patients, with a prevalence of 33% [4]. AF observed in the ICU can be present before ICU admission as chronic atrial fibrillation (CAF) or can develop during the ICU stay as new-onset atrial fibrillation (NOAF) [4]. The prevalence of NOAF in the ICU is high, reaching 23% [5]. The high prevalence of AF in the ICU comes also from the fact that patients with CAF are vulnerable to critical illness, due to concomitant diabetes, kidney, and cardiovascular diseases [4]. Furthermore, NOAF can be triggered by critical conditions among individuals admitted to the ICU with sinus rhythm [4]. NOAF episodes in the ICU usually result in further destabilization of a patient's status. Decreased cardiac output due to NOAF can manifest, for example, in hypotension, shock, heart failure, decreased urine output, acute kidney injury, and altered mental status. It is noteworthy that thromboembolic events triggered by NOAF, mainly stroke, can lead to unfavorable outcomes. The need for anticoagulation due to NOAF can also be challenging in several clinical situations [4]. NOAF during an ICU stay is also a sign of organ damage in critical illness [6,7] and should be perceived similarly to other signs of organ dysfunction, such as impaired consciousness, decreased pO2/FiO2 index, need for inotropic agents, acute kidney injury, and elevated serum lactates [7]. In-hospital morbidity is only the beginning, as NOAF has the tendency do reoccur after hospital discharge, with a 1-year risk of relapse from 16% to even 55%, when a patient develops sepsis during hospitalization [5]. These observations are also true for patients with COVID-19. NOAF and CAF have been investigated as risk factors in this group of patients, with inconsistent results [8-17].

Given that patients with COVID-19 can require ICU admission and that NOAF is common among critically ill patients, we decided to investigate the association between NOAF and several clinical parameters that may serve as potential triggers, as well as the effect of NOAF on patient outcomes. COVID-19 is a disease caused by infection with novel coronavirus SARS-CoV-2 [18]. COVID-19 can manifest with interstitial pneumonia and acute respiratory distress syndrome (ARDS), which is a condition resulting in refractory hypoxemia [19]. ARDS related to COVID-19 is treated primarily with oxygen therapy, high-flow nasal oxygen therapy, and invasive mechanical ventilation [20]. At first, COVID-19 was perceived mostly as a pulmonary disease [19]. Soon, clinicians treating COVID-19 reported complications from the cardiovascular system [21]. COVID-19 is a relatively new phenomenon in medicine, and there is still little research on its prognostic factors. It is known that patients with significant comorbidity are at greater risk of death in the course of SARS-CoV-2 infection. However, there is still no complete data on what medical conditions pose the greatest threat to patients with COVID-19, as well as to what extent the conditions increase the risk of death. The aim of this study was to estimate the odds ratios of death associated with the de novo appearance of AF during disease onset. AF has been identified as a disease with a very high incidence in the ICU, which, at the same time, indicates numerous abnormalities in the body's homeostasis.

Taking the above into consideration, we decided to retrospectively study the linkage of AF with morbidity and mortality among patients with COVID-19 hospitalized in a single center.

Material and Methods

Study Design

This retrospective, case control study was conducted in the specialist COVID Hospital of Military Institute of Medicine, Warsaw, Poland. We decided to set dichotomous outcomes: in-hospital death and survival. Survival was defined as discharge home or transfer to a ward outside of our COVID-treating hospital. The exposure analysis included 3 groups: the control group, which had sinus rhythm throughout the hospital stay; the NOAF group, for which no information about prior AF was provided by the patient or their relatives, or found in the discharge charts; and the CAF group, for which a history of prior AF was reported by the patient or their relatives, or documented in the discharge charts. Using clinical judgement, we decided to analyze all laboratory tests that were done in most patients that could measure severity of the disease, including markers of inflammation, including ferritin, white blood cells count (WBC), and C-reactive protein (CRP), and markers of global hypoperfusion, including lactates, alanine transaminase, aspartate

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

transaminase, and urea. Based on the literature linking pulmonary hypertension with NOAF, we included the severity of ARDS, as measured by computed tomography (CT) scans, in the analysis [8,22]. All patients admitted consecutively between March 2021 and June 2021 were assessed for eligibility to participate in the study.

Study Population

All patients were adults above the age of 18 years. Women in reproductive age with pregnancy were excluded. As a reference center for severe COVID-19 cases, the hospital had 48 high-dependency beds and 12 ICU beds. All patients were treated by a multidisciplinary team, including an internal medicine specialist, cardiologist, and intensivist. All patients included in this study were admitted to our COVID-19 hospital due to respiratory failure caused by SARS-CoV-2 pneumonia. SARS-CoV-2 infection was confirmed with a polymerase chain reaction test (GeneFinder COVID-19 Plus RealAmp Kit; OSANG Healthcare, Korea). Electrocardiogram (ECG) and medical records were examined for the presence of AF, and a medical interview was obtained from patients and/or from patients' relatives. All patients with AF were treated according to the existing European Society of Cardiology (ESC) guidelines [3]. This included immediate synchronized DC shock for all unstable arrhythmias and intravenous amiodarone as the first-line treatment for stable patients with NOAF. If amiodarone infusion failed to restore sinus rhythm or to control ventricular rates, patients were administered intravenous metoprolol, or, if patients received a high dose of inotropes, they were administered intravenous digoxin. Patients in stable condition with CAF usually had their long-term therapy prescribed. All patients with NOAF or unstable arrhythmia had their ions corrected. All patients, if indicated, were prescribed a full dose of enoxaparine in 2 doses, adjusted to kidney function. All patients were treated in accordance with the current actual Polish standards at that time, consistent with international COVID-19 treatment guidelines [23]. All treatment strategies for COVID-19, including extracorporeal membrane oxygenation (ECMO), were used as needed. Patients who needed conventional oxygen therapy or high-flow nasal oxygen therapy stayed in the high-dependency unit. Patients who needed mechanical ventilation, vasoactive support, or ECMO were transferred to the ICU. All ICU patients had severe ARDS, neuromuscular blockade, multiple lung recruitment, and prone positioning. All ICU patients needed vasoactive medications, mostly norepinephrine. In the studied sample of 334 patients, 20 patients needed ECMO life support.

Measures

The patients' ECGs were evaluated with the ESC diagnostic criteria for AF [3]. AF was defined as (1) information about the diagnosis of AF found in medical records from previous hospital

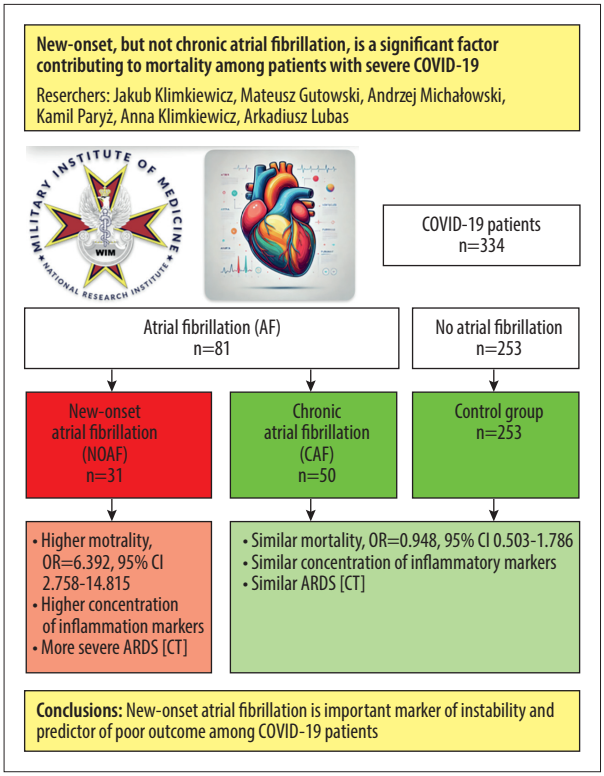

Figure 1. Diagram showing the flow of patients.

or emergency department visits; (2) AF >30 s captured on bedside monitoring; (3) AF documented with 12-lead ECG; or (4) AF resulting in pharmacotherapy or electrotherapy documented in medical records. We did not categorize AF into the subgroups proposed by the ESC, as this was not found to be useful for the purpose of this study [3]. Medical interview and review of medical records was used to identify comorbidities.

The severity of radiological findings was based on the chest CT scale by Francone et al [24]. In this scale, every lung lobe is assessed separately, with 0 points for no changes and 5 points for changes including over 75% of lung parenchyma. The minimal score is 0 points, and the maximal score is 25 points. A total score of 16 or more points indicates very severe ARDS [24]. Laboratory tests and CT scans were performed at admission.

Data Collection

The medical records of every patient admitted were reviewed, if suitable data were extracted from the hospital information system. We excluded 29 patients due to missing data or an important medical problem, such as polytrauma, severe traumatic brain injury, cerebrovascular incidents, and out-of-hospital cardiac arrest, ongoing with mild or asymptomatic COVID-19. Finally, we analyzed the charts of 334 patients. A diagram showing the flow of patients is shown in **Figure 1**.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Statistics

Results were presented as the mean with standard deviation or as median with interquartile range (IQR), according to the normal distribution criteria. Categorical variables were presented as numbers with the occurrence. The Shapiro-Wilk test, which has high power, especially for smaller groups, was used to check the normality of investigated variables. Differences between variables were analyzed with the *t* test for parametric data, and otherwise with the Mann-Whitney U test. Differences in categorical data were analyzed with the chi-square test. If the number of observations was low, Fisher's exact test was performed. Univariable and multivariable logistic regression were used to assess associations between dichotomous and continuous data. Only variables significantly differentiating groups and associated with the odds ratios in univariable logistic regression were considered for multivariable analysis. Due to the missing data, multivariable logistic regression analysis could not consider all significantly associated variables simultaneously. Therefore, exclusively for this analysis, missing data from blood sample results were completed with a median, with the abovementioned exception, and raw data were considered for statistics. Two-tailed $P<0.05$ was considered significant, and $P\geq0.05$ but <0.1 was defined as "trend toward significance". We used Statistica 13.3 software package (Tibco, USA).

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Military Institute of Medicine. Authors made an effort to ensure absolute anonymity of used data. Once the database was created, all variables that could possibly jeopardize patients' anonymity were permanently deleted from the dataset. Datasets were transferred only inside our institution.

Results

Descriptive statistics are presented in **Table 1**. We performed analysis to identify discrepancies between the groups. The comparison of the NOAF and control groups is presented in **Table 2**.

The NOAF group had a trend toward significance of being older than the control group and having a higher occurrence of obesity. The sex distribution and hospital stay were not different between the groups. The frequency of comorbidities was similar in terms of hypertension, ischemic heart disease, heart failure, previous myocardial infarction, cerebrovascular disorders, and chronic kidney disease. In both groups, pulmonary embolism was diagnosed with CT with the same frequency during the hospital stay. More patients from the NOAF group had diabetes. Parameters describing the severity of COVID-19 were statistically different in the NOAF group. Inflammation markers CRP, ferritin, and WBC were higher in the NOAF group. Also, the NOAF group had a lower albumin level and higher urea level. Furthermore, severity of lung impairment measured with CT was higher in the NOAF group. Finally, the NOAF group had higher mortality than did the control group.

The comparison between the CAF and control groups is presented in **Table 3**. The patients in the CAF group were older than those in the control group. The sex distribution and hospital stay were not different between the groups. The CAF group had a higher frequency of comorbidities, with ischemic heart disease, heart failure, previous myocardial infarction, cerebrovascular disorders, and chronic kidney disease. Pulmonary embolism was diagnosed with CT with the same frequency in both groups during the hospital stay. The occurrence of hypertension was similar in both groups. The CAF group had more diabetes, with a trend toward statistical significance. Urea levels were higher in the CAF group than in the control group. Inflammation markers, albumin levels, and CT abnormalities did not differ between the groups. Also, mortality in the CAF group was similar to that of the control group.

Finally, we compared the NOAF and CAF groups. The differences between the NOAF and CAF groups are shown in **Table 4**. The NOAF population was younger. The sex distribution and hospital stay were not different between the groups. The frequency of comorbidities was similar in terms of obesity, diabetes, hypertension, cerebrovascular diseases, and chronic kidney disease. Ischemic heart disease and heart failure were more frequent in the CAF group. Previous myocardial infarction in the CAF group showed a trend toward being more frequent. The inflammation markers CRP and ferritin were higher in the NOAF group. WBC and urea level were similar. Albumin level showed a statistical trend toward being lower in the NOAF group. The NOAF group had significantly more severe lung involvement on CT. Finally, mortality in the NOAF group was dramatically higher than that in the CAF group. To assess the link between AF occurrence and in-hospital mortality, logistic regression was performed (**Table 5**). AF was found to be related with the risk of in-hospital death. When the OR was calculated for NOAF and CAF separately, NOAF remained a strong predictor of death, but CAF did not.

To identify factors associated with NOAF, univariable logistic regression analysis was performed. We included variables with substantial differences observed between the NOAF and control groups (**Table 2**). Then, the variables significantly associated with NOAF were included in the multivariable logistic regression analysis (**Table 6**). Only severity of CT changes and serum albumin levels were independently associated with the risk of NOAF.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Descriptive statistics of the examined population.

Variable	Mean or n	SD or %	Median	IQR
Demographics				
Age (years)	65.8	15	68	19
Female gender	140/334	41.9%		
Male gender	194/334	58.1%		
Comorbidities				
Obesity (BMI >35)	69/334	20.6%		
Diabetes	85/334	25.4%		
Hypertensio	191/334	57.1%		
ischemic heart disease	53/334	15.9%		
heart failure	37/334	11.1%		
History of MI	23/334	6.9%		
Cerebrovascular disorders	33/334	9.9%		
Chronic kidney fisease	42/334	12.6%		
Pulmonary embolism	22/334	6.5%		
Disease severity markers				
ALT (U/l)	77	256	37	35
AST (U/l)	109	45	45	41
CRP (mg/l)	10.5	8.3	8.9	11.8
Ferritin (mcg/l)	1510	2101	830	1183
WBC (10^9/l)	10.5	8.83	8.15	6.79
Urea (mg/dl)	68	57	49	56
Albumin (g/dl)	3	0.57	3	0.8
CT scan severity index (points)	14.7	6	15	10
Treatment results				
Hospital stay (days)	11.8	8	10	9
Survival	217/334	65%		
Deaths	117/334	35%		

BMI – body mass index.

Discussion

AF is the most common arrhythmia in the ICU [4], especially among older patients with chronic conditions, who are prone to critical illness [4]. It is believed that, among the general population (not only patients with COVID-19), the process of AF onset consists of 2 steps. The first step is remodeling of the atria, due to chronic medical conditions. The substrate for arrhythmia is created in the atria, usually by fibrosis of the atrial wall or electrical remodeling. Remodeling comprises changes in intracellular calcium ion handling and ion channel expression [25-27]. Then, AF is triggered by electrolyte imbalance as hypokalemia, hypomagnesemia, and changes in fluid status, autonomic nervous system activity, mechanical ventilation, inotropes, and vasopressors [4,28]. Occurrence of AF in the ICU can lead to complications, including decreased cardiac output, hypotension, heart failure, and cardiogenic shock [4]. Additionally, NOAF is a long-term predictor of morbidity and mortality among ICU survivors. It is well documented that NOAF is a risk factor for in-hospital and post-discharge mortality and stroke [6]. AF during sepsis can contribute to "post-ICU syndrome" [7]. Walkey et al stated that AF should be treated as a cardiac complication of severe infection. They point out that NOAF can be missed in organ function calculations. Infection-related organ dysfunction can be underdiagnosed, and risk of death can be underestimated this way [7].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Comparison of new-onset atrial fibrillation (NOAF) group and control group.

	NOAF n=31 Mean±SD Median [IQR] or n (%)	Control n=253 Mean±SD Median [IQR] or n (%)	p-value
Demographics			
Age (years)	69.3 SD 8.6 69 [9]	63.6 ±15.7 67 [22]	0.073
Female gender	14 45.2%	102 40.3%	0.604
Male gender	17 54.8%	151 59.7%	0.604
Comorbidities			
Obesity	10 32.2%	47 18.6%	0.07
Diabetes	12 38.7%	56 22.1%	0.041
Hypertension	18 (58%)	140 (55.3%)	0.772
Ischemic heart disease	3 9.7%	32 12.6%	0.634
Heart failure	3 9.7%	16 6.3%	0.480
History of myocardial infarction	1 3.2%	14 5.5%	0.587
Cerebrovascular disorders	3 (9.7%)	21 8.3%	0.794
Chronic Kidney Disease	4 12.9%	25 9.9%	0.599
Pulmonary embolism	32 9.6%	16 6.3%	0.480
Disease severity markers			
ALT (U/l)	203±688 26 [5; 3036] 36	70±176 39 [7; 1697] 37	0.255
AST (U/l)	325±1060 41 [10; 4661] 78	94±240 45 [9; 2317] 41	0.797
CRP (mg/l)	14.5±9.5 13.6 [0.8; 38.9] 9.8	10.4±8.3 8 [0.1; 59.2] 11.4	**0.026**
Ferritin (µg/l)	2617±2994 1442 [507; 11712] 1268	1432±2024 812 [21; 17118] 1234	**0.002**
WBC (10^9/l)	13,8±12.07 10.44 [2.72; 59.54] 8.19	9.87±8.03 7.95 [1.46; 64.85] 6.06	**0.035**
Urea (mg/dl)	89±80 67 [21; 417] 45	64±55 44 [7; 360] 46	**0.013**

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2 continued. Comparison of new-onset atrial fibrillation (NOAF) group and control group.

	NOAF n=31 Mean±SD Median [IQR] or n (%)	Control n=253 Mean±SD Median [IQR] or n (%)	p-value
Albumin (g/dl)	2.7±0.6 2.8 [1.1; 3.4] 0.6	3.1±0.5 3.1 [1.9; 4.3] 0.9	**0.021**
CT scan severity index (points)	17.9±5.1 19 [6; 23] 7	14.5±5.9 15 [0; 25] 9	**0.004**
Treatment results			
Hospital stay (days)	12 SD 7.6 Median 11.7 IQR 9.8	11.6 SD 7.7 Median 10.3 IQR9.7	0.492
Deaths	23 (74.2)	77 (30.4)	**<0.001**

Several specific pathways promoting NOAF in patients with COVID-19 are proposed. In addition to mechanisms that apply to general ICU patients, the literature describes mechanisms of triggering AF by SARS-CoV-2, which can directly interact with cardiac pericytes, causing micro-vascular leakage, inflammation, and thrombosis. Pericytes and endothelial cells release substances contributing to local inflammation and disturbances in cardiac electrophysiology [29]. Interaction of SARS-CoV-2 with ACE-2 receptors causing disturbances in the renine-angiotensin-aldosterone system is another possible mechanism leading to NOAF [29,30]. SARS-CoV-2 infection can result in hemodynamic changes, leading to immune response from cardiac tissue. Atrial immune response can cause increased concentration of CD-4 T cells, which corresponds with NOAF in patients with cardiac surgery and heart failure [31,32]. Finally, ARDS causes pulmonary vascular dysfunction and proinflammatory mediators' release, microvascular remodeling, and vascular thrombosis, promoting lung parenchyma pathology [29,33,34]. This can lead to pulmonary hypertension and stretching of the right atrium [29,34]. Also, left atrial stretch measured as the left atrium volume index, higher pulmonary artery systolic pressure, and AF were found to be predictors of in-hospital death in patients with COVID-19 [8].

Our results support the findings of other authors studying the correlation of NOAF with the morbidity and mortality in patients with COVID-19 [8-11]. Several authors found NOAF to be a predictor of bad outcomes in the ICU setting or in the general hospital population with COVID-19. Abdulrahman et al found that NOAF was a predictor of bad outcomes, namely death or ICU transfer, in COVID-19 patients, with an OR of 3.96 (95% CI: 1.05-14.98; *P*=0.042) [9]. A study of 171 high-risk COVID-19 patients showed that AF during the ICU stay was a predictor of in-hospital death, with hazard ratio of 2.38 (95% CI: 1.52-3.71; *P*<0.001) [10]. D'Andrea et al found NOAF to be a major risk factor contributing to unfavorable results. In their study, NOAF was a strong predictor of death, with OR: 2.5; (95% CI: 1.22-5.4; *P*<0.001) [8].

A large study identified NOAF to be associated with a poorer prognosis [11]. Mountantonakis et al found NOAF to be a predictor of in-hospital mortality, with an OR of 1.18 (95% CI: 1.04-1.33; *P*=0.009) [12]. However, not every publication supports our findings. In a Turkish study, NOAF was not a risk factor for in-hospital mortality, with an OR 1.42, (95% CI: 0.40-5.09; *P*=0.582) [13]. Contrary to our findings, CAF was risk factor among hospitalized patients with COVID-19. In a study by Paris et al, a history of AF was related with elevated risk of death (OR 2.47, 95% CI: 1.73-3.53; *P*<0.001) [14]. A systematic review and meta-analysis of 12 studies by Zuin et al found CAF to be risk factor of short-term mortality, with an OR of 2.22, (95% CI: 1.47-3.36; *P*<0.0001) [15]. Other systematic reviews also report AF as a risk factor of unfavorable results. In contrast with our results, authors did not find a difference between CAF and NOAF [16,17]. We believe that the main differences in results can come from repowering bias, as most patients with COVID were treated during the peak of the pandemic. Also, selection bias can be an important contributing factor, since in the busiest period, many patients were disqualified from treatment, as there was a need to choose which patients would receive high-flow nasal oxygen therapy or ICU admission.

In our study, the patients in the CAF group were older than the those in the control group and had more cardiovascular comorbidities, but had similar severity of COVID as the control group, measured with markers of inflammation and severity of ARDS. Mortality in the CAF group was not significantly

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. Comparison of chronic atrial fibrillation (CAF) group and control group.

	CAF n=50 (n, %)	Control n=253 (n, %)	p-value
Demographics			
Age (years)	75 SD 11.6 Median 75.5 IQR 16	63.6 SD 15.7 Median 67 IQR 22	**<0.001**
Female gender	24, 48%	102, 40.3%	0.313
Male gender	26, 52%	151, 59.6%	0.313
Comorbidities			
Obesity	12, 24%	47, 18.6%	0.376
Diabetes	17, 34%	56, 22.1%	0.073
Hypertension	33, 66%	140, 55.3%	0.163
Ischemic heart disease	18, 36%	32, 12.6%	**<0.001**
Heart failure	18, 36%	16, 6.3%	**<0.001**
History of myocardial infarction	8, 16%	14, 5.4%	**0.009**
Cerebrovascular disorders	9, 18%	21, 8.3%	**0.016**
Chronic kidney disease	13, 26%	25, 9.9%	**<0.001**
Pulmonary embolism	3, 6%	16, 6.3%	0.931
Disease severity markers			
ALT (U/l)	36±23 29 [9; 102] 28	70±176 39 [7; 1697] 37	0.063
AST (U/l)	46±23 49 [14; 109] 33	94±240 45 [9; 2317] 41	0.610
CRP (mg/l)	8.1±6.2 7.4 [0.1; 21.1] 11.1	10.4±8.3 8 [0.1; 59.2] 11.4	0.141
Ferritin (µg/l)	886±819 600 [80; 3024] 711	1432±2024 812 [21; 17118] 1234	0.133
WBC (10^9/l)	10.97±9.18 7.95 [2.22; 46.6] 7.83	9.87±8.03 7.95 [1.46; 64.85] 6.06	0.669
Urea (mg/dl)	75 ±40 69 [17; 185] 64	64 ±55 44 [7; 360] 46	**0.011**
Albumin (g/dl)	3.1±0.6 3.2 [2.1; 4.1] 0.7	3.1±0.5 3.1 [1.9; 4.3] 0.9	0.829
CT scan severity index (points)	13.2±6.7 14 [2; 24] 13	14.5±5.9 15 [0; 25] 9	0.330
Treatment results			
Hospital stay (days)	12.5 Sd 10 Median 11 IQR 11	11.6 SD 7.7 Median 10.3 IQR9.7	0.601
Deaths	17, 34%	77, 30.4%	0.610

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 4. Comparison of new-onset atrial fibrillation (NOAF) group and chronic atrial fibrillation (CAF) group.

	NOAF group n=31	CAF group n=50	p-value
Demographics			
Age (years)	69.3 SD 8.6 Median 69 IQR 9	75 SD 11.6 Median 75.5 IQR 16	**0.008**
Female gender	14, 45.2%	24, 48%	0.803
Male gender	17, 54.8%	26, 52%	0.803
Comorbidities			
Obesity	10, 32.2%	12, 24%	0.416
Diabetes	12, 38.7%	17, 34%	0.667
Hypertension	18, (58%)	33, (66%)	0.47
Ischemic heart disease	3, 9.7%	18, 36%	**0.009**
Heart failure	3, 9.7%	18, 36%	**0.009**
History of myocardial infarction	1, 3.2%	8, 16%	0.075
Cerebrovascular disorders	3, 9.7%	9, 18%	0.305
Chronic kidney disease	4, 12.9%	13, 26%	0.159
Pulmonary embolism	3, 9.7%	3, 6%	0.539
Disease severity markers			
ALT (U/l)	203±688 26 [5; 3036] 36	36±23 29 [9; 102] 28	0.773
AST (U/l)	325±1060 41 [10; 4661] 78	46±23 49 [14; 109] 33	0.639
CRP (mg/l)	14.5±9.5 13.6 [0.8; 38.9] 9.8	8.1±6.2 7.4 [0.1; 21.1] 11.1	**0.004**
Ferritin (µg/l)	2617±2994 1442 [507; 11712] 1268	886±819 600 [80; 3024] 711	**<0.001**
WBC (10^9/l)	13,8±12.07 10.44 [2.72; 59.54] 8.19	10.97±9.18 7.95 [2.22; 46.6] 7.83	0.223
Urea (mg/dl)	89±80 67 [21; 417] 45	75±40 69 [17; 185] 64	0.898
Albumin (g/dl)	2.7±0.6 2.8 [1.1; 3.4] 0.6	3.1±0.6 2 [2.1; 4.1] 0.7	0.072
CT scan severity index (points)	17.9±5.1 19 [6; 23] 7	13.2±6.7 14 [2; 24] 13	**0.006**
Treatment results			
Hospital stay (days)	12 SD 7.6 Median 11.7 IQR 9.8	12.5 Sd 10 Median 11 IQR 11	0.774
Deaths	23, 74.2%	17, 34%	**<0.001**

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 5. Results of univariable logistic regression concerning association of atrial fibrillation (AF) and in-hospital deaths.

	OR	95% CI	p-value
Total AF	2.230	1.337-3.718	**0.002**
NOAF	6.392	2.758-14.815	**<0.001**
CAF	0.948	0.503-1.786	0.868

Table 6. Results of new-onset atrial fibrillation (NOAF) univariable and multivariable regression.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	P
Diabetes	1.990	0.922-4.294	0.079			
CRP	1.055	1.011-1.100	**0.012**	1.024	0.975-1.075	0.343
Ferritin	1.000*	1.000-1.000	**0.027**	1.000#	1.000-1.000	0.238
WBC	1.035	1.001-1.071	**0.046**	1.013	0.969-11.060	0.566
Urea	1.005	1.000-1.011	0.065			
Albumin	0.291	0.115-0.738	**0.009**	0.266	0.078-0.903	**0.034**
CT scan severity index	1.123	1.033-1.220	**0.006**	1.116	1.024-1.217	**0.013**

* Ferritin OR=1.000230 and 95% CI: 1.000060-1.000400; # Ferritin OR=1.000108 and 95% CI: 0.999285-1.000288.

different than that in the control group. One explanation can be that, in the CAF group, CAF itself could have been one of the components resulting in hospitalization. In other words, mild to moderate COVID resulted in the need of in-hospital treatment, because elderly individuals with limited cardiovascular reserve could not tolerate it. Another possible hypothesis is that the CAF in patients who developed COVID-19 can be a condition to which they are relatively well adapted, in contrast to NOAF. Moreover, those patients with CAF probably had received appropriate pharmacological treatment in advance of the infection, especially since antithrombotic treatment used in CAF can be a factor in reducing the risk of thrombosis in small vessels. Thrombosis is an important pathomechanism in organ damage and the development of complications in the course of COVID-19, and CAF in patients is usually managed with anticoagulants prior to admission. Anticoagulation used at home before admission can had limited microthrombosis, with organ ischemia. Also, anticulaguation used at home can lead to the limited occurrence of major cardiovascular events, mainly stroke, during a hospital stay. However, CAF, being a disease with which patients develop COVID-19, does not constitute a signal of deterioration of their condition, as is the case with NOAF. Further studies on this may provide more information.

Patients in the NOAF group had less comorbidities than patients in the CAF group; however, COVID-19 was critically severe among them. Inflammation markers in the NOAF group were significantly higher than those in the control and CAF groups. Also, CT abnormalities were more advanced in the NOAF group. In the other words, patients with similar comorbidities to control, but with a critical COVID-19 course, formed the NOAF group. NOAF in this group can be perceived as a sign of cardiovascular, respiratory, and metabolic destabilization.

The findings support the thesis that NOAF should be perceived as a symptom of organ damage due to critical illness. Our results are consistent with data suggesting that patients developing NOAF during sepsis generally do not have a high burden of cardiovascular comorbidities associated with risk of CAF [35]. A strength of our study was the low risk of heterogeneity, as patients were mostly Polish citizens and therapeutic protocols were consistent. At the time of the study, the *delta* type of virus was the dominating strain in Poland [36].

To conclude, we believe that CAF and NOAF should be viewed as separate clinical conditions. CAF might still be perceived mostly on a cardiovascular background, as it used to be. NOAF should be perceived as a marker and result of a critical condition. Also, despite its cardiac manifestation, NOAF is rather an indicator for extracardiac problems, namely the critical mismatch between oxygen delivery and consumption, anaerobic metabolism, and extreme tissue hypoperfusion.

Limitations

This study had limitations. First, when interpreting the results of this study, it must be considered that the research was designed as a case-control study and had a limited sample size.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Second, the study was conducted at a single center and had a retrospective design, with the examined population almost limited to the Polish nationality. Third, in order to include all patients and significantly associated variables in the multivariable regression analysis, we completed missing data with median values, which could influence the achieved results. Therefore, a similar analysis performed on a larger group without missing data could provide more adequate and complete results.

Conclusions

It seems justified to investigate NOAF as sign of organ damage in critically ill patients. Large, multicenter, randomized trials are needed to determine whether NOAF should be perceived as a sign of circulatory instability in systems of risk stratification.

The results of our study, although conducted on just over 300 patients, constitute a significant argument for including AF in the stratification of the risk of death in patients with COVID-19. Given the results, it seems justified to create a risk assessment scale for such patients, which will include the occurrence of a new episode of AF. Also, it seems prudent to test NOAF as a risk factor for death among the general population, for example, in patients with bacterial sepsis.

At the same time, similar relationships can be expected in other serious diseases; however, this requires further research in ICU patient populations with other diseases. In our opinion, it is justified to conduct further studies, preferably prospective ones, on much larger groups of patients with more diverse ethnicities, ages, and comorbidities. Further research would clarify which of the factors and pathomechanisms linking COVID-19 with NOAF are responsible for such a significantly increased mortality in this group of patients.

Acknowledgements

This manuscript was reviewed and corrected as the Capstone Project during the Clinical Scholars Research Training Poland 2024 course by Harvard Medical School. The authors would like to thank to the faculty, staff, and peers for their support.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J Stroke. 2021;16(2):217-21 [Erratum in: Int J Stroke. 2020;15(9):NP11-NP12
2. Fernando SM, Mathew R, Hibbert B, et al. New-onset atrial fibrillation and associated outcomes and resource use among critically ill adults-a multicenter retrospective cohort study. Crit Care. 2020;24(1):15
3. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2021;42(5):373-498
4. Bosch NA, Cimini J, Walkey AJ. Atrial fibrillation in the ICU. Chest. 2018;154(6):1424-34
5. Klein Klouwenberg PM, Frencken JF, Kuipers S, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. Am J Respir Crit Care Med. 2017;195(2):205-11
6. Xiao FP, Chen MY, Wang L, et al. Outcomes of new-onset atrial fibrillation in patients with sepsis: A systematic review and meta-analysis of 225,841 patients. Am J Emerg Med. 2021;42:23-30
7. Walkey AJ, McManus D. When rhythm changes cause the blues: New-onset atrial fibrillation during sepsis. Am J Respir Crit Care Med. 2017;195(2):152-54
8. D'Andrea A, Russo V, Manzo G, et al. Association of atrial fibrillation and left atrial volume index with mortality in patients with COVID-19 pneumonia. Eur J Prev Cardiol. 2022;29(2):e44-e46
9. Abdulrahman A, Hussain T, Nawaz S, et al. Is atrial fibrillation a risk factor for worse outcomes in severe COVID-19 patients: A single center retrospective cohort. J Saudi Heart Assoc. 2021;33(2):160-68
10. Ip RJ, Ali A, Baloch ZQ, et al. Atrial fibrillation as a predictor of mortality in high risk COVID-19patients: A multicentre study of 171 patients. Heart Lung Circ. 2021;30(8):1151-56
11. Offerhaus JA, Joosten LPT, van Smeden M, et al. CAPACITY-COVID collaborative consortium. Sex- and age specific association of new-onset atrial fibrillation with in-hospital mortality in hospitalised COVID-19 patients. Int J Cardiol Heart Vasc. 2022;39:100970
12. Mountantonakis SE, Saleh M, Fishbein J, et al. COVID-19 Research Consortium. Atrial fibrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection. Heart Rhythm. 2021;18(4):501-7
13. Ergün B, Ergan B, Sözmen MK, et al. New-onset atrial fibrillation in critically ill patients with coronavirus disease 2019 (COVID-19). J Arrhythm. 2021;37(5):1196-204
14. Paris S, Inciardi RM, Lombardi CM, et al. Implications of atrial fibrillation on the clinical course and outcomes of hospitalized COVID-19 patients: Results of the Cardio-COVID-Italy multicentre study. Europace. 2021;23(10):1603-11
15. Zuin M, Rigatelli G, Bilato C, et al. Pre-existing atrial fibrillation is associated with increased mortality in COVID-19 Patients. J Interv Card Electrophysiol. 2021;62(2):231-38
16. Lee JH, Hwang YM, Cho Y, Oh IY. Prognostic impact of atrial fibrillation in patients with severe acute respiratory syndrome coronavirus 2 infection. Medicine (Baltimore). 2021 Aug;100(33):e26993
17. Szarpak L, Filipiak KJ, Skwarek A, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: A systematic review and meta-analysis. Cardiol J. 2022;29(1):33-43
18. Khan M, Adil SF, Alkhathlan HZ, et al. COVID-19: A Global challenge with old history, epidemiology and progress so far. Molecules. 2020;26(1):39
19. Batah SS, Fabro AT. Pulmonary pathology of ARDS in COVID-19: A pathological review for clinicians. Respir Med. 2021;176:106239
20. Attaway AH, Scheraga RG, Bhimraj A, et al. Severe COVID-19 pneumonia: Pathogenesis and clinical management. BMJ. 2021;372:n436
21. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666-87

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

22. Tsapenko MV, Tsapenko AV, Comfere TB, et al. Arterial pulmonary hypertension in noncardiac intensive care unit. Vasc Health Risk Manag. 2008;4(5):1043-60
23. Polish diagnostic, therapeutic and organizational recommendations for the care of individuals infected with SARS-CoV-2 or exposed to a SARS-CoV-2 infection. Agency for Health Technology Assessment and Tariff System. Available from: https://www.aotm.gov.pl/media/2020/07/Covid_FINAL-v-1.1-_wersja-EN-1.pdf. [Access: 25.11.2022]
24. Francone M, Iafrate F, Masci GM, et al. Chest CT score in COVID-19 patients: Correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808-17
25. Moss TJ, Calland JF, Enfield KB, et al. New-onset atrial fibrillation in the critically ill. Crit Care Med. 2017;45(5):790-97
26. Aldhoon B, Melenovský V, Peichl P, Kautzner J. New insights into mechanisms of atrial fibrillation. Physiol Res. 2010;59(1):1-12
27. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res. 1997;81(4):512-25
28. Lu YY, Cheng CC, Chen YC, et al. Electrolyte disturbances differentially regulate sinoatrial node and pulmonary vein electrical activity: A contribution to hypokalemia- or hyponatremia-induced atrial fibrillation. Heart Rhythm. 2016;13(3):781-88
29. Stone E, Kiat H, McLachlan CS. Atrial fibrillation in COVID-19: A review of possible mechanisms. FASEB J. 2020;34(9):11347-54
30. Jansen HJ, Mackasey M, Moghtadaei M, et al. Distinct patterns of atrial electrical and structural remodeling in angiotensin II mediated atrial fibrillation. J Mol Cell Cardiol. 2018;124:12-25
31. Sulzgruber P, Thaler B, Koller L, et al. CD4+CD28null T lymphocytes are associated with the development of atrial fibrillation after elective cardiac surgery. Sci Rep. 2018;8(1):9624
32. Sulzgruber P, Koller L, Winter MP, et al. The impact of CD4+CD28null T-lymphocytes on atrial fibrillation and mortality in patients with chronic heart failure. Thromb Haemost. 2017;117(2):349-56
33. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-22
34. Dongaonkar RM, Stewart RH, Geissler HJ, Laine GA. Myocardial microvascular permeability, interstitial oedema, and compromised cardiac function. Cardiovasc Res. 2010;87(2):331-39
35. Walkey AJ, Greiner MA, Heckbert SR, et al. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. Am Heart J. 2013;165(6):949-955.e3
36. Marczyńska M, Pokorska-Śpiewak M, Talarek E, et al. Updated principles of prevention, diagnosis and treatment of COVID-19 in children in Poland – recommendations for paediatricians and family medicine doctors. Pediatria Polska – Polish Journal of Paediatrics. 2022;97(2):71-80.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]