Secondary bacterial infections trigger New Onset Atrial Fibrillation in ICU Covid-19 ARDS patients

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Research

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Abstract

Background

Cardiac arrhythmias, mainly atrial fibrillation (AF), is frequently reported in COVID-19 patients, yet causality has not been explored. Intensive Care Unit patients frequently present AF during critical illness. Sepsis is one of the main contributors of AF occurrence in ICU patients. The aim of the study was to explore if Covid-19 myocardial involvement is the only contributor for New Onset Atrial Fibrillation (NOAF) in intubated ICU patients.

Methods

Consecutive intubated, Covid-19ARDS patients, were prospectively studied for factors triggering NOAF. Demographics, data on Covid-19 infection duration, severity of illness and ARDS are reported. Echocardiographic findings, troponin levels and secondary infection (sepsis/septic shock) data were collected on the day of AF and compared to the preceding days’ and/or ICU admission data. Comparison was also performed between NOAF and control group (no AF) on admission.

Results

Among 105 patients screened, 79 were eligible; nineteen presented NOAF (24%). Baseline characteristics did not differ between the NOAF and control groups. Troponin levels were mildly elevated upon ICU admission in both groups. NOAF occurred on the 18 ± 4.8 days from Covid-19 symptoms’ onset, and the 8.5 ± 2.1 ICU day. Seventeen patients in the NOAF group (89.5%) presented a septic secondary infection vs 25 (41.6%) in the control group (p < 0.001). In sixteen NOAF patients (84.2%), AF occurred concurrently with a secondary septic episode. Noradrenaline, lactate levels and inflammation biomarkers presented a gradual increase in the days preceding the AF day (all p < 0.05). Troponin increased compared to admission (p = 0.017). AF did not resolve or re-occurred if sepsis persisted. Upon ICU admission left ventricular ejection fraction was rather normal, yet, global longitudinal strain was equally impaired (< 16.5%) in 63% vs 78% in the NOAF and control groups, respectively. The right ventricle was mildly dilated, and 36 (45.6%) patients had pericardial effusion. Echocardiographic findings did not change on NOAF occurrence.

Conclusion

Secondary infections seem to be major contributors for NOAF in Covid-19 patients, probably playing the role of the “second hit” in an affected myocardium from Covid-19.

Backround
The main manifestation of coronavirus disease 2019 (Covid-19) is pneumonia leading to Acute Respiratory Distress Syndrome (ARDS) in 6% of cases [1]. Cardiovascular disease and complications are frequently reported in Covid-19 patients [2]. Yet, cardiac involvement is frequently based on mildly increased troponin levels [3–6]; more detailed examinations are still rather scarce [7, 8].

Cardiac arrhythmias, mainly atrial fibrillation (AF), are not uncommon in COVID-19 patients [9–11]. However, there is a lack of clear association of new onset AF (NOAF), to direct myocardial damage depicted with Cardiac Magnetic Resonance (CMR), histopathologic findings or even echocardiographic findings. In addition, Covid-19 myocarditis seems to be an uncommon finding [12].

Studies do not clearly report on the exact time that NOAF appeared [9, 10, 13–15]. However, NOAF is far more frequent in Intensive Care Unit (ICU) patients compared to patients in the ward [9, 10, 13–15]. Therefore, as respiratory worsening occurs after several days from symptom onset, AF seems to occur late in the course of the disease, when the patients have been admitted in the ICU [1, 13, 14]. Severe Covid-19 could be a risk factor, yet, in ICU, other-than SARS-CoV-2 trigger factors may be implicated, which have not yet been explored.

In the non-Covid-19 era, NOAF is a frequently encountered arrhythmia in ICU patients [16]. Multiple factors are implicated, leading to structural or electrical remodeling of the atria, triggering AF, sepsis being the leading one [16]. Sepsis could be a possible trigger factor in Covid-19 as well, as the incidence of ICU-acquired secondary infections is increased, partly attributed to the immunosuppressive drug protocols adopted [18–21].

In the present study we hypothesized that other factors than SARS-CoV-2 infection may contribute to NOAF occurrence in ICU patients with Covid-19 ARDS. Therefore, we aimed to evaluate in a cohort of intubated, ICU, Covid-19 ARDS patients: 1). the incidence of NOAF and investigate possible factors leading to its occurrence, 2). the course of NOAF during ICU stay, and 3). the cardiac involvement using echocardiography and troponin levels upon ICU admission.

**Methods**

**Study population.** Consecutive patients admitted in the ICU (March 2020-February 2021) at the University Hospital of Larissa, Greece with laboratory confirmed (real-time PCR) SARS-CoV-2 infection and ARDS were included in this prospective study. The study was approved by the local ethics committee (55951/2020), with a waiver for informed consent. All patients were admitted intubated, and evaluation included the period from the first ICU day until the 28th day (either still in the ICU, discharged or dead).

All eligible (according to inclusion/exclusion criteria) patients were divided in two groups: the NOAF group including patients with new onset AF during ICU stay without previous history of AF, and the control group, including all other patients not presenting AF. Patients were included in the NOAF group if they presented at least one AF episode lasting more than 10 minutes or suffered multiple AF episodes during a 24-hour period, or AF episodes needing direct electrical cardioversion due to hemodynamic instability.
Exclusion criteria were: 1). history of recent myocardial infarction or previous echocardiography presenting wall motion abnormalities indicating ischemic disease, 2). recent admission for either coronary artery bypass graft, cardiac surgery or percutaneous transluminal coronary angioplasty (PTCA), 3). severe aortic or mitral stenosis or regurgitation, 4). patients with a history of heart failure from any cause or previous echocardiographic findings indicating Left Ventricular Ejection Fraction (LVEF) below 45%, 5). known Right Ventricular (RV) dysfunction, 6). cardiomyopathy of any type, 7). presence of pacemaker, 8). congenital heart disease, 9). brief AF episodes not meeting inclusion criteria, 10). history of NOAF occurring in the ward or presenting upon ICU admission, 11). death during the first 48 hours of ICU admission, 12). permanent AF, 13) history of paroxysmal atrial fibrillation (PAF). However, PAF patients were analyzed separately (Appendix).

**Data collection.** Baseline characteristics and disease severity (APACHE II, SOFA score) were recorded on admission. Demographics, medical history, and data concerning COVID-19 infection prior to hospital admission were collected from patients’ medical records and/or next-of-kin. Laboratory findings [inflammation markers (CRP, ferritin), coagulation, electrolytes] and the SOFA score were recorded daily. Troponin levels were recorded on ICU admission, the NOAF day and whenever indicated, according to attending physicians.

Blood, urinary and endotracheal aspirate (ETA) cultures were collected on admission, every 3 days (per local protocol) and whenever indicated, according to the attending physicians, but always on the day of AF occurrence and the day after. Heart rhythm was assessed continuously from the patients’ monitor (General Electric, Carescape B850); ECG tracings (12-lead) could be reviewed for the preceding 72-hours (GE monitor’s software), while 12-lead ECG was performed daily.

All patients received enhanced prophylactic anticoagulation according to current suggestions for Covid-19, except in patients with contraindication (coagulation abnormalities, thrombocytopenia, active bleeding).

Echocardiography was performed on admission and whenever indicated, but always on the AF day, according to AHA guidelines [22], by trained operators (VT, NK, VV), (General Electric, Vivid E95). We used a standard procedure to assess LV and RV sizes, function and filling measurements (2D imaging, color doppler, Tissue Doppler Imaging (Appendix) [23]. Left ventricular myocardial performance was assessed using the two-dimensional speckle-tracking method [23].

In patients needing cardioversion after 24 hours due to AF persistence, a transesophageal echocardiography (TEE) preceded. If pulmonary embolism (PE) was suspected, Computed Tomography Pulmonary Angiography (CTPA) was performed.

All patients were assessed under satisfactory loading conditions (Appendix). Central Venous Oxygen Saturation (ScVO\textsubscript{2}) measurements were performed on admission, in episodes of hemodynamic instability, and whenever indicated according to attending physicians.
Definitions

Sepsis, septic shock, and types of infections were defined according to recently updated terms [24, 25]. Secondary infections included all hospital acquired Blood Stream Infections (BSI), Hospital/Ventilator-Associated Pneumonia (HAP/VAP) and Urinary Tract Infections (UTI) occurring after 48 hours of hospital admission (Appendix).

Atrial fibrillation management protocol

All NOAF episodes received amiodarone (750 mg daily) after a loading dose of 150–300 mg administration (± b-blockers for rate control). Direct electrical cardioversion was performed only in patients with hemodynamic instability, defined as a significant increase in vasopressor dosage after AF appearance, according to the attending physicians’ assessment. However, attending physicians were encouraged to postpone electrical cardioversion until the patient had received the amiodarone loading dose.

Statistical analyses. Results are given as mean (± Standard Deviation, SD) in normally distributed parameters and as median (± Standard Deviation, SD) in not normally distributed values. Normally distributed continuous indices were compared with Student’s t-test (between two groups) and one-way ANOVA (for multiple group and other repetitive variable measurement comparisons); non-normally distributed indices were compared via the Mann-Whitney-U and Wilcoxon test. Finally, Chi-square was used when testing categorical data. Data were analyzed using SPSS (IBM SPSS statistics version 25).

Results

Among one hundred and five patients with Covid-19 ARDS admitted in the ICU, seventy-nine patients were eligible for the study (Fig. 1). Nineteen patients presented NOAF (24%), constituting the NOAF group; the rest 60 patients comprised the control group. The two groups did not differ in baseline characteristics, Charlson comorbidity index, laboratory findings, disease severity upon admission and lung mechanics (Table 1). Troponin levels were mildly elevated upon ICU admission in both groups (0.17 ±0.4 vs 0.15 ±0.55, p=1) (Table 1). Thirteen (73%) in the NOAF and 54 (84%) in the control groups (p=0.08) received corticosteroids (Table 1). Five patients (26%) vs 19 (32%) had received Tocilizumab (p=0.66), while four (21%) vs 18 (30%) had received anti-IL-1 therapy (p=0.64), respectively. Six patients, in whom severe pulmonary embolism was suspected, underwent CTPA. One in the control and none in the NOAF group was diagnosed with significant PE.

New Onset AF occurred late in the course of hospitalization, 18±4.8 days from Covid-19 symptoms’ onset and on 8.5±2.1 ICU day. Only one patient (70-years-old) presented a short AF episode lasting 3 min (2\textsuperscript{nd} ICU day) and another two (65 and 72-years-old) presented with NOAF on ICU admission and were excluded. In all other patients, NOAF occurred after/on the 3\textsuperscript{rd} ICU day (range 3-23 ICU day).
Laboratory and clinical data on AF day, compared to data on the third preceding the AF day are presented in Table 2.

**Septic secondary infection episodes**

Twenty five (41.6%) patients in the control group (upon ICU admission in two) and 17 (89.5%) in the NOAF group presented at least one secondary infection episode during their ICU stay ($p<0.001$) (Fig. 1). Secondary infections occurred after the sixth ICU day in 30 (71.4%) patients.

**NOAF group.** Sixteen patients (84.2%) presented a septic secondary infection concurrently with NOAF, thirteen of whom (81.3%) presenting with septic shock. Eleven patients (57.9%) had primary bacteremia and five (26.3%) suffered ventilator-associated pneumonia (VAP)-two accompanied with bacteremia. Pan-drug resistant (PDR) or extensively drug resistant (XDR) Gram (-) bacteria (*Klebsiella pneumoniae* and/or *Acinetobacter baumannii*) were the main isolates. All NOAF patients had negative blood, urine and ETA cultures on admission. In 14/16 patients, NOAF presented during the first septic episode. Notably, antibiotics were added or modified in 18/19 patients, in the two preceding or the NOAF day, for suspected septic secondary infections, according to the attending physicians. Interestingly, in one of the two patients with NOAF upon ICU admission (excluded per protocol), the blood cultures drawn on admission revealed *Acinetobacter baumannii*.

Noradrenaline dose was increased from 0.08±0.06 μg/kg/min three days before NOAF to 0.44±0.22 μg/kg/min exactly before AF appearance ($p=0.01$), reaching the highest value (0.52±0.06 μg/kg/min) after NOAF ($p=0.033$ compared to the value on NOAF occurrence). Lactate increased (1.1±0.3 vs 2.3±0.5, $p<0.001$); in 13 patients lactate increased >2 mmol/l. No modification in sedation had been done that could have provoked hypotension. A positive fluid balance was noted in patients with sepsis in the preceding 3 days (6948.13±2829 ml), while ScVO$_2$ presented a significant rise on the day of AF compared to admission (75.8±3 vs 69.6±3.6%, $p<0.001$)(Table 2).

**Laboratory findings**

CRP values showed a gradual increase during the days preceding AF (Table 2) and a subsequent decrease thereafter.

Troponin levels significantly increased on the AF day compared to admission (0.64±1.04 vs 0.16±0.31 ng/dl, $p=0.017$). The highest value was observed in one patient (4.43 ng/dl) subsiding over the next days. This patient, with primary bacteremia presented laboratory and echocardiographic signs of septic cardiomyopathy.

**Echocardiographic findings**

Left Ventricular function did not differ between groups, although RV function was mildly impaired in the control group. (Table 3). Left Ventricular Global Longitudinal Strain (GLSLV) was -12±4% in patients without AF and -14±6% in NOAF patients. Noteworthy, GLSLV was abnormal (<16.6%) in 78% of the
patients in the control and 63% in the NOAF group [26]. Covid-19 patients presented moderate RV dilation (Right Ventricular End Diastolic Area/Left Ventricular End Diastolic Area > 0.6 in both groups). Twenty-six (43%) vs ten (52%) in the control and NOAF groups respectively, presented mild pericardial effusion ($p = 0.48$). Echocardiographic measurements did not significantly change on NOAF occurrence (Table 3).

**Outcome.**

**Arrhythmia** In all patients, NOAF lasted more than one hour. Sixteen patients (84%) returned to sinus rhythm (SR), 13 during the first 24 hours and the rest during 48 hours, although short recurrent AF episodes (after cardioversion), lasting less than 30 minutes were recorded in 4 patients. Only one patient, presenting severe hemodynamic instability, was electrically cardioverted, one hour after unsuccessful amiodarone infusion; in this patient, AF recurred, returning to sinus rhythm after 24 hours. Nine TEE were performed in five patients; in all, cardiac chambers, including the appendage were free from thrombi.

In six patients (including three in whom SR was not restored) signs of sepsis were not resolving until death. In three, AF recurred after 4-9 days on SR, coinciding with a new septic episode, returning to SR with sepsis resolution. Amiodarone infusion was continued until ICU discharge or death.

**Mortality:** In NOAF group, 28th day mortality was 47% (9/19) vs 41.7% (25/60) in the control group ($p = 0.57$). Three patients died without converting to SR. All ten survivors were discharged on SR, under amiodarone. Among them, we were able to contact three patients (aged 45, 56, 76 years) discharged home; patients are on SR (2-7 months later); amiodarone has been stopped.

**Discussion**

Our study demonstrates that myocardial dysfunction is present in intubated ICU patients with severe Covid-19 ARDS, as depicted by the echocardiographic findings of impaired left and right ventricular function, mild pericardial effusion and mild elevation of troponin levels. However, New Onset Atrial Fibrillation occurred in ICU, Covid-19 ARDS patients, mainly in relation to a secondary infection that led to severe sepsis/septic shock. Demographics, ARDS severity, respiratory system mechanics, mechanical ventilatory modes and electrolytes did not differ between groups, while hypoxemia degree was quite improving in NOAF patients on the day AF occurred. We suggest that sepsis triggered NOAF occurrence, in the setting of an affected, from Covid-19, myocardium; sepsis resolution was crucial to maintain SR (under amiodarone infusion).

Our understanding on the cardiovascular effects of Covid-19 is still limited [4]. In our cohort, Left Ventricular EF was rather normal, although impaired global longitudinal strain indicated occult myocardial injury in the majority (74%) of Covid-19 ARDS patients upon ICU admission; abnormal GLSLV (< 16.6%) has been reported in 42% of Covid-19 patients admitted in the ward, while data on ICU patients are scarce [26–29]. In addition, a moderate RV enlargement was observed, which is in accordance with various Covid-19 reports [30, 31]. However, multiple factors may explain this finding apart from Covid-19; RV dilation is exacerbated by mechanical ventilator settings (PEEP), especially when lung compliance is
preserved [32, 33]. Interestingly, 45.6% of the patients had a mild pericardial effusion. Pericardial effusion incidence has not been thoroughly evaluated in Covid-19 [34, 35]. In addition, troponin levels were elevated on ICU admission, a finding that has been linked to myocardial involvement in Covid-19 [3–6]. The above data support the notion that a degree of myocardial injury is present in severe Covid-19 patients, admitted in the ICU [36]. However, there was no difference between the NOAF and control group, in any parameter concerning the cardiac involvement.

Among atrial arrhythmias, AF is the most frequent in Covid-19 patients; NOAF prevalence varies between 3–10% in non-ICU patients [10, 11]. In our study, NOAF incidence was 24%, which is in accordance with the higher incidence reported in ICU patients [9–11, 13, 37–39]. Colon et al, noted a NOAF incidence of 16.5% in ICU patients [14]. However, no reference is made on possible secondary conditions and the timing of arrhythmia occurrence. Increased inflammatory markers and vasopressor need were reported during AF appearance, without specifying whether AF occurrence was coincidental to a secondary infection episode [2, 9]. Other studies confirm the increased NOAF incidence in ICU Covid-19 patients, varying between 16.5–40%, yet, without specifying whether the virus or other factors, frequently present in critically-ill patients, are associated to its occurrence [9, 10, 11, 13–15, 37–39]. Similarly, existing data lack information about the exact time of NOAF appearance in the course of Covid-19 [10, 11, 13, 14, 37–39]. An early, in the course of the infection, virally driven hyperinflammation-cytokine storm has been proposed as a possible mechanism, partially explaining NOAF occurrence in patients hospitalized in the wards [2, 9]. In our study, NOAF appeared late in the course of the disease, approximately during the 18th post symptom onset day (8th ICU day), when COVID-19 symptoms usually subside [39]. Although myocarditis has also been suggested as a possible mechanism for arrhythmias in Covid-19, histological findings indicate macrophage infiltration, with no clear association to myocardial injury, and, although troponin is high, myocarditis is established in only 4.5% of the severely ill, Covid-19 patients with heart failure, undergoing endomyocardial biopsies; thus, the virus does not seem to directly invade the cardiac cells in order to initiate AF [12, 40]. Our findings support that non cardiac causes, such as systemic infection, may contribute to NOAF.

New-onset AF is a common arrhythmia in non-Covid-19 ICU patients, occurring in 19–35% of patients, sepsis being the main triggering factor [16, 41, 42]. Walkey et. al, reported an increased incidence (35%) of NOAF among septic patients, further increasing with disease severity [16]. In our study, 84.2% of the patients presented sepsis and 68.4% had septic shock on NOAF episodes. Inflammation markers, vasopressor need, and lactate levels presented a gradual increase in the preceding the AF days. The positive fluid balance during the last three days, and the rise in ScVO₂ values, further supported NOAF’s association to sepsis-induced vasodilation [43].

An increased incidence of secondary infections has been observed in our cohort; 42% in the control group and 89% in the NOAF group, consistent with recent reports. Buetti et al, reported an increased daily risk (HR 4.5) to acquire an ICU-BSI in Covid-19 compared to non-Covid-19 patients; BSIs usually occurred after the 7th ICU day [17]. Similarly, Rouze et al, reported that ventilator associated lower respiratory tract infections were more frequent in Covid-19 ARDS patients (50.5%) compared to influenza (30.3%) and ICU
patients with non-viral infections (25.3%), similarly occurring after the 7th ICU day [18]. Corticosteroids, Tocilizumab and Anakinra, used in COVID-19 ARDS, may be partly responsible [17, 18, 44]. In our study, NOAf occurred on the 8.5 ± 2.1 ICU day, mostly coinciding with the first BSI/VAP septic episode. We suggest that sepsis, with adrenergic overstimulation, due to endogenous elevated catecholamine levels and exogenous catecholamine administration (as in septic shock), constitutes the second “hit”, to trigger AF in a diseased/affected, from SARS-CoV-2, myocardium [2, 16]. Interestingly, patients in both groups were of comparable age and did not present factors indicating apparent cardiovascular disease, known to increase AF occurrence risk [11].

Troponin levels were significantly raised on the AF day compared to admission, further supporting the association of NOAf to secondary sepsis. Troponin elevation has been repeatedly reported in bacterial sepsis, reflecting altered cardiomyocyte permeability or some degree of necrosis, frequently associated with cardiac dysfunction [45, 46]. Sepsis induced myocardial dysfunction is very frequent, attributed to increased circulating catecholamine and cytokine levels, found in severe sepsis and septic shock [47, 48]. However, decreased systemic vascular resistance may mask the altered myocardial performance. We believe that sepsis-induced vasoplegia is responsible for the apparently preserved LVEF in our patients when NOAf appeared.

Rhythm control has been found more beneficial than rate control in ICU patients [42]. Most patients in our study returned to sinus rhythm with pharmacologic cardioversion (amiodarone); AF could not be restored in patients with non-resolving sepsis or re-occurred in those with recurrent septic episodes.

Our study has limitations. It was conducted in a single center serving an urban population, thus the number of patients is limited. However, although our findings may not be generalizable across the world, they may have particular importance in South Europe and other countries with an increased incidence of nosocomial infections from PDR/XDR, as in our study [49]. In addition, we consider an advantage that the study population was rather homogenous: we prospectively enrolled consecutive, intubated patients with severe Covid-19, with no obvious preexisting cardiovascular disease in order to eliminate known factors triggering AF. Cardiac Magnetic Resonance tomography was not performed, but its utility in ICU is limited by the out-of-hour availability and the requirement for some breath-holding, while no patients underwent endomyocardial biopsy (caring inherent risks), as it is not suggested due to the low incidence of myocarditis in Covid-19 [12]. Instead, in all patients, troponin levels and a full echocardiographic examination were performed, which seem appropriate to reveal cardiac involvement in Covid-19.

**Conclusion**

In conclusion, myocardial function is altered in Covid-19 patients, probably lowering the threshold for arrhythmogenicity. Secondary infections seem to be major contributors for NOAf occurrence in ICU Covid-19 ARDS patients, probably playing the role of the “second hit” in an affected myocardium. Sepsis should be suspected in case of late NOAf occurrence in these patients. Furthermore, AF did not resolve or re-
occurred if sepsis persisted. Further research on the arrhythmogenicity of COVID-19 in severe ICU Covid-19 ARDS patients is needed.

**Abbreviations**

A: late diastolic ventricular filling velocity with atrial contraction; AHA: American Heart Association; AF: atrial fibrillation; ANOV: Analysis Of Variance; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute Respiratory Distress Syndrome; BSI: Blood Stream Infection; CAD: Coronary Artery Disease; Covid-19: Coronavirus Disease 2019; CMR: Cardiac Magnetic Resonance; CRP: C-Reactive Protein; CTPA: Computed Tomography Pulmonary Angiography; E: left ventricular early diastolic peak velocity, E': early diastolic tissue Doppler velocity; ECG: Electrocardiography; EF: Ejection Fraction; ETA: Endotracheal Aspirate; GLS: Global Longitudinal Strain; GLSLV: global longitudinal strain of the left ventricle; HAP: Hospital Acquired Pneumonia; HF: Heart Failure; ICU: Intensive Care Unit; IL-1: Interleukin-1; NOAF: New Onset Atrial Fibrillation; LV: Left Ventricle; LVOT VTI: Velocity Time Integral in the Left Ventricular Outflow Tract; MI: Myocardial Infarction; PAF: Paroxysmal Atrial Fibrillation; PCR: Polymerase Chain Reaction; PE: Pulmonary Embolism; PEEP: Positive End Expiratory Pressure; PDR: Pan-drug resistant; PTCA: Percutaneous Transluminal Coronary Angioplasty; RV: Right Ventricle; RVEDA/LVEDA: Right Ventricular End Diastolic Area to Left Ventricular End Diastolic Area; RVFAC: Right Ventricular Fractional Area Change; RV s': Tissue doppler peak systolic velocity at the tricuspid annulus, S': systolic tissue Doppler velocity; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ScVO$_2$: Central Venous Oxygen Saturation; SOFA: Sequential Organ Failure Assessment; SR: Sinus Rhythm; TAPSE: Tricuspid Annular Plane Systolic Excursion; TEE: Transesophageal Echocardiography; TTE: Transthoracic Echocardiography; UTI: Urinary Tract Infection; VAP: Ventilator Associated Pneumonia; XDR: Extensively Drug Resistant;

**Declarations**

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**Conflict of Interest:** None

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**Authors’ contributors**

GEZ contributed to the concept, design, and data collection; conducted the analyses; and drafted the manuscript. VT contributed to concept and design, data collection, and critical revisions of the manuscript. DM contributed to concept and design, data collection, and critical revisions of the manuscript. NK, GD, VV and KM, contributed to concept and design and critical revisions of the manuscript. GV contributed to statistical analysis and critical revisions of the manuscript.
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Availability of data and materials

The data set used for this manuscript will be available from the corresponding author upon reasonable request.

Ethics approval and consent to participate.

This study was approved by the Institutional Ethics Committees of the University Hospital of Larissa (55951/2020), with a waiver for informed consent.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: Demographics and baseline characteristics in patients without AF (controls) and NOAF patients upon ICU admission.
| Demographics | Control (n=60) | NOAF (n=19) | p     |
|--------------|---------------|-------------|-------|
| Age          | 68.2 ± 3.1    | 69.7 ± 3.1  | 0.64  |
| Males N (%)  | 46 (76%)      | 14 (74%)    | 0.88  |
| Charlson comorbidity index | 3.2 ± 0.4 | 3.8 ± 0.88  | 0.11  |
| Hypertension | 46 (76.6%)    | 10 (52.6%)  | 0.05  |
| Corticosteroids (N) (%) | 54 (84%) | 14 (74%)    | 0.075 |
| Clinical Data |              |             |       |
| APACHE II    | 16.9 ± 1.8    | 14.4 ± 2.8  | 0.12  |
| SOFA         | 8 ± 1.3       | 7.4 ± 1     | 0.63  |
| P_{\text{aO}_2}/F_{\text{tO}_2}, \text{mmHg} | 111.2 ± 45.7 | 124.6 ± 42.2 | 0.35  |
| CRS          | 36.7± 2.5     | 37.1± 8.9   | 0.89  |
| Noradrenaline (µg/kg/min) | 0.39 ± 0.18 | 0.24 ± 0.13 | 0.27  |
| Laboratory Data |          |             |       |
| D-Dimers (ng/mL) (<300) | 819 ± 398.5 | 895 ± 353.6 | 0.52  |
| Ferritin, (ng/ml), (< 330) | 1,205.7 ± 952.8 | 1,380 ± 801.5 | 0.28  |
| WBC, 10^3/L (<10 x 10^3/L) | 9,273.2 ± 6498 | 9,543.8 ± 2108 | 0.08  |
| CRP (mg/dL), (<0.5) | 8.4 ± 0.4 | 10.9 ± 4.2 | 0.13  |
| Troponin, ng/ml (<0.04) | 0.15 ± 0.34 | 0.16 ± 0.31 | 1.0   |

Table 2: NOAF group: Clinical and laboratory data on the day of AF compared to data three days before AF occurrence.
### Clinical Data

|                        | Day -3 of AF occurrence | Day of AF occurrence | p   |
|------------------------|--------------------------|----------------------|-----|
| **PaO₂/FiO₂, mmHg**    | 162.3 ± 24.3             | 199.05 ± 35.5        | 0.056 |
| **Heart rate**         | 65.9 ± 14.6              | 100 ± 6.8            | 0.002 |
| **Noradrenaline (µg/kg/min)** | 0.08 ± 0.06             | 0.44 ± 0.22          |     |
| **Lactate, mmol/l**    | 1.1 ± 0.4                | 2.3 ± 0.5            | <0.001 |
| **ScVO₂, %ᵃ**         | 69.6 ± 3.6               | 75.8 ± 3             | <0.001 |

| **WBC, 10⁹/L (<10x 10⁹/L)** | 8,680 ± 2,679          | 10,627 ± 1,972       | 0.71 |
| **CRP (mg/dl) (<0.5)**    | 7.41 ± 4.3             | 12.33 ± 4.1          | 0.01 |
| **Ferritin (ng/ml) (<330)** | 1,188 ± 453            | 999 ± 787            | 0.46 |
| **Na (mmol/l)**          | 143.6 ± 4.7            | 145.6 ± 3.8          |     |
| **K (mmol/l)**           | 4.3 ± 0.3              | 4.4 ± 0.3            |     |
| **Troponin, ng/ml lᵃ (<0.02)** | 0.16 ± 0.31         | 0.64 ± 1.04          |     |

| **Positive blood culture, n(%)ᵇ** | 0                  | 13 (81%)             |
| **Positive ETA, N(%)**           | 0                  | 5 (26%)              |

ᵃFor troponin and ScVO₂, the value in the first column refers on admission data

ᵇEleven patients presented primary bacteremia on the day NOAF occurred. Two more patients diagnosed with VAP on NOAF day, presented positive blood cultures, with the same isolate as the one responsible for VAP (bacteremic VAP)

**Table 3.** Comparison of echocardiographic variables between the control and NOAF group on admission, and between admission and the NOAF day, in the NOAF group.
|                                | Control Group (n=60) | NOAF group (n=19) | ICU Admission | ICU admission | AF Day |
|--------------------------------|----------------------|-------------------|--------------|---------------|--------|
| **Left atrial area, cm²**      | 19.7±3.1             | 21.2±3.6          | 22.2±4.7     |                |        |
| **Left Ventricular End Diastolic Diameter, cm** | 4.5±0.7             | 4.6±0.4           | 4.6±0.5      |                |        |
| **Left Ventricular EF (Simpson method) (%)** | 59.9±14.4           | 55.1±19.5         | 56.6±15      |                |        |
| **GLSLV, %**                   | -12.3 ± 4.2          | -14.7 ± 5.5       | -11.9 ± 3.1  |                |        |
| **GLSLV <16.6%, n (%)**        | 47 (78%)             | 12 (63%)          | 0.075        |                |        |
| **VTI_{LVOT} cm**              | 22.2 ± 5.4           | 21.6 ± 7.1        | 22.8 ± 5.3   |                |        |
| **E, cm/s**                    | 63 ± 21              | 74± 8             | 76 ± 16      |                |        |
| **A, cm/sec**                  | 67± 8                | 72 ± 15           |              |                |        |
| **E’, cm/s**                   | 8 ± 2                | 7 ± 1             | 8 ± 2        |                |        |
| **E/E’**                       | 7.4 ± 5.1            | 9.9± 2.3          | 10.1 ± 2.3   |                |        |
| **S’, cm/s**                   | 10 ± 3               | 8 ± 1             | 8 ± 2        |                |        |
| **RVEDA/LVEDA**                | 0.7 ± 0.2            | 0.7 ± 0.4         | 0.7 ± 0.3    |                |        |
| **RV FAC, %**                  | 38.7 ± 13.3*         | 51 ± 21.4         | 36.3 ± 10    |                |        |
| **TAPSE, mm**                  | 22.1±5.1             | 25.4±5.9          | 21.1±5       |                |        |
| **RV s’, cm/sec**              | 15 ± 4*              | 19 ± 3#           | 13 ± 5       |                |        |
| **Pericardial effusion**       | 26/60 (43%)          | 10/19 (52%)       | 11/19 (58%)  |                |        |

A: late diastolic ventricular filling velocity with atrial contraction; AF, Atrial Fibrillation; EF: Ejection Fraction, E, left ventricular early diastolic peak velocity, E’, early diastolic tissue Doppler velocity; ICU, Intensive Care Unit; GLSLV, global longitudinal strain of the left ventricle; RVEDA/LVEDA, Right Ventricular End Diastolic Area to Left Ventricular End Diastolic Area; RVFAC, Right Ventricular Fractional Area Change; S’, systolic tissue Doppler velocity; RV s’, Tissue doppler peak systolic velocity at the tricuspid annulus; TAPSE: Tricuspid Annular Plane Systolic Excursion; VTI_{LVOT}, Left Ventricular Outflow Tract Velocity Time Integral;

Data are expressed as mean ± standard deviation.

*: p<0.05 for comparisons between the control and NOAF group upon ICU admission

#: p<0.05 for comparisons between echocardiographic data on admission and the NOAF day, in the NOAF group

Figures
Figure 1

Study Flowchart AF, atrial fibrillation; CAD, Coronary Artery Disease; Covid-19, Coronavirus disease-2019; ECHO, Echocardiography; EF, Ejection Fraction; HF, Heart Failure; ICU, Intensive Care Unit; MI, Myocardial Infarction; NOAF, New Onset Atrial Fibrillation.
Figure 2

Time course of vasopressor dose in the period around NOAF occurrence. Noradrenaline dose was increased from 0.08±0.06 μg/kg/min three days before NOAF to 0.44±0.22 μg/kg/min exactly before AF appearance (p=0.01), reaching the highest value (0.52±0.06 μg/kg/min) after NOAF occurrence (p=0.033, compared to NOAF occurrence). Comparisons have been performed with the Day-3 (reference value) and, also, between each day. *: p=0.01 refers to the difference between the noradrenaline dose on the day AF occurred (just before AF appearance) and the dose that the patients were receiving on the Day -3 (reference day).

Supplementary Files

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