INCIDENCE AND PROGNOSTIC IMPACT OF NEW-ONSET ATRIAL FIBRILLATION IN PATIENTS WITH SEVERE COVID-19: A RETROSPECTIVE COHORT STUDY

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Abstract

Background Corona virus disease 2019 (COVID-19) contributes to cardiovascular complications including arrhythmias due to high inflammatory surge. Nevertheless, the common types of arrhythmia amongst severe COVID-19 is not well described. New onset atrial fibrillation (NOAF) is frequently seen in critically ill patients and therefore we aim to assess the incidence of NOAF in severe COVID -19 and its association with prognosis. Methods This is a retrospective multicentre study including 109 consecutive patients admitted to intensive care units (ICU) with confirmed COVID-19 pneumonia and definitive outcome (death or discharge). The study period was between 11th March and 5th May 2020. Results Median age of our population was 59 years (IQR 53-65) and 83% were men. Nearly three-fourth of the population had two or more comorbidities. 14.6% developed NOAF during ICU stay with increased risk amongst older age and with underlying chronic heart failure and chronic kidney disease. NOAF developed earlier during the course of severe COVID-19 infection amongst non-survivors than those survived the illness and strongly associated with increased in-hospital death (OR 5.4; 95% CI 1.7-17; p=0.004). Conclusion In our cohort with severe COVID-19, the incidence of new onset atrial fibrillation is comparatively lower than patients treated in ICU with severe sepsis in general. Presence of NOAF has shown to be a poor prognostic marker in this disease entity.

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ABSTRACT

Background

Corona virus disease 2019 (COVID-19) contributes to cardiovascular complications including arrhythmias due to high inflammatory surge. Nevertheless, the common types of arrhythmia amongst severe COVID-19 is not well described. New onset atrial fibrillation (NOAF) is frequently seen in critically ill patients and therefore we aim to assess the incidence of NOAF in severe COVID -19 and its association with prognosis.

Methods

This is a retrospective multicentre study including 109 consecutive patients admitted to intensive care units (ICU) with confirmed COVID-19 pneumonia and definitive outcome (death or discharge). The study period was between 11th March and 5th May 2020.

Results

Median age of our population was 59 years (IQR 53-65) and 83% were men. Nearly three-fourth of the population had two or more comorbidities. 14.6% developed NOAF during ICU stay with increased risk amongst older age and with underlying chronic heart failure and chronic kidney disease. NOAF developed earlier during the course of severe COVID-19 infection amongst non-survivors than those survived the illness and strongly associated with increased in-hospital death (OR 5.4; 95% CI 1.7-17; p =0.004).

Conclusion

In our cohort with severe COVID-19, the incidence of new onset atrial fibrillation is comparatively lower than patients treated in ICU with severe sepsis in general. Presence of NOAF has shown to be a poor prognostic marker in this disease entity.

Keywords:

COVID-19 pneumonia, New onset Atrial Fibrillation, In-hospital mortality.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread globally causing COVID-19 since the first reported cases in Wuhan, China in December 2019 [1-3]. The majority with COVID-19 remain asymptomatic or with mild symptoms, however around 20 % will have severe symptoms with multi-organ failure triggered by cytokine storm [4]. Several recent studies have demonstrated the deleterious effects of COVID 19 on cardiovascular system comprising acute myocardial injury, myocarditis, cardiomyopathies, arrythmias, cardiogenic shock and cardiac arrest [5-8].

New onset atrial fibrillation (NOAF) is the commonest arrythmia seen in patients treated in intensive care unit (ICU) and is a sequelea of critical illness. The incidence of NOAF is reported between 20-46% amongst

patients treated for sepsis in ICU with a strong association with mortality [9-12]. Inflammation per se is likely a trigger for initiation, maintainance and perpetuation of AF [13] and we hypothesised the incidence of NOAF will be higher in COVID-19 due to high inflammatory state secondary to cytokine release syndrome. In a study by Wang et al, arrythmia amongst COVID-19 were more common in ICU patients (44.4%) than the counterpart [14], however the nature of the arrythmias was not described. There is paucity in the emerging literatures with regard to the nature of common arrythmias attributed by COVID-19 in ICU and there is no literature so far reporting the frequency of NOAF in severe COVID-19. Therefore the purpose of our study is to explore the incidence and clinical characteristics of patients with NOAF in severe COVID-19 admitted to ICU and to evaluate its prognostic impact with respect to mortality.

METHODS

Study design and participants

This is a retrospective observational multicentre study, encompassing two major COVID 19 ICU centres in London; including St Bartholomew's Hospital and the Nightingale Hospital London which was the field hospital intensive care unit for COVID-19 during first wave of the pandemic. The study population comprised of consecutive patients (over the age of 18 years) admitted to COVID-19 intensive care units between 11^{th} March and 05^{th} May 2020 with definitive clinical outcome either discharge or death. 113 patients [St Bartholomew's Hospital (73) and Nightingale Hospital (40)] were included fulfilling the above criteria, however 4 patients were excluded due to pre-existing diagnosis of permanent or persistent AF.

All patients had a laboratory confirmed diagnosis with detection of SARS-CoV-2 RNA on swab (nasal/throat) results. Demographic, clinical, laboratory and imaging data were extracted from the electronic medical records (Cerner Millennium- registered clinical portal of the institutions) and the details regarding premorbid conditions were also cross referenced with their respective general practitioner's (GP) records.

Definition:

In this study NOAF was defined as episodes of paroxysmal or persistent AF occurred during ICU stay with no previous diagnosis of AF. All patients were attached to continuous cardiac monitor and episodes were confirmed on 12 lead electrocardiography. Chronic kidney disease was classified in stages by eGFR according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines. Acute kidney injury was also classed according to the KDIGO clinical practice guidelines.

Acute cardiac injury was diagnosed if serum levels of cardiac biomarker (Troponin T) were above the 99^{th} percentile of the upper reference range and if new abnormalities were shown in echocardiography or electrocardiogram. Patients with heart failure with reduced ejection fraction (HFrEF) as per ESC guidelines (left ventricular ejection fraction less than 40%) were classed under chronic heart failure. The linear dimension (anteroposterior measurement on parasternal long axis view) was taken into consideration for measuring left atrial (LA) size and was categorised according to the reference values from British Society of Echocardiography. Extra corporeal membrane oxygenation (ECMO) was offered to patients with acute severe and potentially reversible respiratory failure despite ventilator support who fulfilled the NHS England ECMO guidelines (version 1- revised in response to the COVID-19 pandemic). All documented diagnoses of pulmonary embolism (PE) were confirmed radiologically following computed tomography pulmonary angiogram (CTPA). The highest value of the laboratory markers prior to the AF episode were taken into account for the purpose of analysis in **table 2.**

Statistical analysis

Categorical variables were described as frequency (percentage) and continuous variables as median (interquartile range). Continuous and categorical variables were compared using Mann-Whitney U test and the χ^2 test respectively. Fisher exact test was used when the data were limited. Univariate and multivariable logistic regression models were used to explore the association between NOAF with in-hospital mortality. A 2-sided α of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software, version 26.0 software (IBM SPSS Statistics).

RESULTS:

The study population included 109 ICU patients with confirmed COVID-19 out of which 107 (98%) required invasive mechanical ventilation and the remainder were treated with non-invasive ventilation. All had radiological evidence of acute respiratory distress syndrome (ARDS) or pneumonia. Out of total, 3 patients (3%) admitted to ICU after been treated for myocardial infarction during the index admission and 2(2%) were diagnosed following cardiac surgery. Primary cause of admission for the rest was symptoms of COVID-19 pneumonia. The median age was 59 years (IQR 53-65; range 30-79 years) and 83% were men. Two or more comorbidities were observed in 72 % of patients (Table 1).

Clinical characteristics during admission

NOAF was found in 16 patients (14.6%) within this cohort which also includes one post cardiac surgical patient. Clinical characteristics between patients developed NOAF were further studied with comparison to the group of patients without AF. Majority (70 [64%]) had acute kidney injury and of which 36% patients required renal replacement therapy. Major laboratory markers were traced during course of illness and cardiac troponin T was raised in 91% of the study group above the 99^{th} percentile upper reference limit (URL). Nevertheless, median Left ventricular systolic function on echocardiography was within normal range (60%; IQR 55-65) (Table 2). Echocardiography was performed based on clinical grounds in patients (83%) with suspected acute cardiac injury evidenced by serial troponin rise, electrocardiographic changes, arrhythmia or haemodynamic instability/shock. Deterioration in left ventricular systolic function from baseline was observed only in three patients of which two admitted following acute myocardial infarction (AMI) and one developed AMI during COVID-19 illness due to an acute thrombus evident on coronary angiogram.

12% of our study population required ECMO for severe respiratory failure. Locally adopted guidelines were followed for management of venous thromboprophylaxis in COVID-19 and a modified anticoagulation regime with increased dose was advocated for patients with D-Dimer more than 3mg/L (normal range 0-0.5 mg/L). However a small proportion of our study group (7 patients; 6%) received therapeutic dose of anticoagulation assessed by their thrombosis risk especially when the D-Dimer levels were extremely high (>80 mg/L). 65 % of patients had D-Dimer levels 10 fold above the upper limits of normal (median 17 mg/L; IQR 6-59). Venous and arterial thromboembolism was one of the commonly observed complications [24 patients (22%)] with 76% diagnosed with pulmonary embolism on CTPA. 7 patients (44%) received therapeutic anticoagulation amongst NOAF group for AF, venous and arterial embolism and unusually elevated level of d-dimer.

One-third of patients (33%) did not survive the illness and the median time from admission to ICU discharge was 35 days (IQR 22-42) (Table 2).

Clinical characteristics between patients with and without new onset atrial fibrillation

Patients who developed NOAF (n=16) during their ICU stay in comparison to non AF counterpart (n=93), were significantly older (median 65 year [IQR 59-71] vs 58 years [IQR 51-64]; p =0.001) and were high likely to have underlying chronic heart failure (2 [33%] vs 2[2%]; p =0.03) and chronic kidney disease (7 [44%] vs 15[16%]; p =0.004). Other comorbidities did not show any statistical significance between these two groups (Table 1). AKI has been more prevalent amongst the NOAF (94 % vs 59%; p =0.028) and nearly half of them required renal replacement therapy during ICU admission. Left atrium was enlarged above the normal limits in more than half of NOAF group (56% NOAF vs 28 % without NOAF; p = 0.032).Length of stay in ICU was significantly longer amongst survivors with NOAF than who remained in sinus rhythm (42 days [IQR 37-44 days] vs 32 days [IQR 21-40 days]; p =0.03) (Table 2). Increased in-hospital mortality was associated with presence of NOAF (OR 5.4; 95% CI 1.7-17; p =0.004) on univariate analysis and also when adjusting for covariates such as age, gender and comorbidities (p =0.042). One patient amongst the NOAF group died following an ischaemic stroke.

Survivors and non survivors of new onset atrial fibrillation

Temporal pattern of daily laboratory blood markers amongst patient who developed NOAF, revealed raised median values for C-reactive protein, Ferritin, Creatinine kinase and troponin in non survivors than the

survivors. However the difference did not reach statistical significance probably because of the size of the group (Figure 1). Electrical cardioversion was performed in 2 of the 16 patients with NOAF due to haemodynamic instability with rapidly conducted AF and all patients received antiarrhythmic (amiodarone) and rate control drug therapy (bisoprolol, non dihydropyridine calcium channel blockers or/and digoxin) in the absence of contraindications . Restoration of sinus rhythm was achieved in 87% prior discharge or death (14 patients). 1 patient remained in persistent AF on discharge.

Incidence of NOAF was observed earlier during the course of illness among non-survivors (7 days; IQR 6.5-11.0 days vs 17days; IQR 11.0-23days) in comparison to patients who survived the illness ($p<0.005$).

DISCUSSION:

To our knowledge this is the first study demonstrating the incidence and outcome of new onset atrial fibrillation in patients with severe COVID-19 treated in ICU. There is increased evidence that the systemic inflammatory response per se is a predominant trigger of NOAF in critically ill patients [13]. In the literatures available on cardiovascular complications related to critically ill patients with COVID-19, the nature and classification of the arrhythmogenic events and their mechanisms have not yet well described. Our retrospective multicentre study assessing NOAF, showed an incidence of 14.6% amongst patients with COVID-19 treated in ICU and this is comparatively lower than the occurrence of NOAF reported in studies relating to severe sepsis in ICU in general [9-11]. This raises the question of whether the mechanism triggering AF in COVID-19 differ from other forms of sepsis despite high systemic inflammatory milieu by pro-inflammatory cytokine storm and possible direct viral invasion into cardiomyocytes through angiotensin-converting enzyme 2 (ACE2) receptors [15].

A systematic review by Kuipers et al, described that advanced age, male gender, obesity, organ failure were associated with development of AF during sepsis. In contrast to reported associations in the general population, diabetes and hypertension were not identified as risk factors in sepsis [16,17]. In our study advanced age, chronic heart failure and chronic kidney disease have shown to be a risk factor for development of NOAF among severely ill patients with COVID-19. Presence of diabetes, obesity or hypertension has not been identified as trigger for NOAF in our cohort (Table 1).

Patients with and without NOAF did not have any significant difference in the trend of inflammatory markers or troponin, however AKI was a risk for NOAF in patient with severe form of COVID-19 infection.

Just over 90% of our study population showed raised troponin T level above the normal range, but there was no significant association with NOAF or indeed left ventricular systolic function. Further detailed studies with cardiac MRI may help to assess the degree of myocardial involvement through tissue characteristics. There is compelling evidence that LA size is an independent predictor for atrial fibrillation in general population [18-20] and likewise in our cohort with severe COVID-19, enlarged LA size certainly remained a risk factor for NOAF.

Uncontrolled activation of coagulation cascade following lung injury contributes to lung inflammation in ARDS [21]. In general, significantly higher D-Dimer levels are found in patients with severe pneumonia/ARDS and also shown to be a predictor of poor clinical outcome and mortality [22]. COVID-19 data from recent studies described similar findings [14, 23] and our data reveal very high levels of D-Dimer in our cohort with more than one-third having levels >50mg/L. This indicates the severity of COVID-19 infection and the thrombosis risk in our study population, however did not achieve statistical significance when considering the in-hospital death.

The manifestation of even a single episode of AF is associated with increased mortality and poor outcome in critically ill patients with sepsis [10,11,16]. In this study the occurrence of NOAF was strongly associated with poor outcome. Patients who develop NOAF earlier during the course of COVID-19 illness had worse outcome and this may be a useful marker for physicians to predict prognosis.

Patients with severe sepsis who developed NOAF have a greater risk of in-hospital stroke than patients with pre-existing AF or individuals without history of AF [15,24]. We have reported one case of ischaemic stroke

amongst the group developed NOAF with poor outcome. However, it was difficult to ascertain the contribution by AF, as COVID-19 infection per se has risk of arterial thromboembolism due to hypercoagulable state.

Anticoagulation significantly reduces the risk of stroke amongst patients with high risk factors, based on CHA_2DS_2 VASc score (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease and sex). However there is not much evidence to support anticoagulating critically ill patients in ICU which may expose them to risk of bleeding during sepsis [25,26] or invasive intensive care management. Virally driven hyper-inflammation with cytokine release will lead to hypercoagulable state and propensity for disseminated intravascular coagulation (DIC) in severe COVID-19 [27]. This is increasingly evident as substantial proportion of patients develop venous and arterial thromboembolic complications which was seen in our cohort. This may in turn could increase the risk of stroke in patients who develop NOAF with severe COVID-19, and careful assessment regarding decision on anticoagulation is warranted in these patients irrespective of CHA_2DS_2 VASc score. However further studies are needed to determine the value of anticoagulation in treating NOAF in severe COVID-19 patients.

LIMITATIONS:

We have only included 109 patients confirmed with COVID-19 treated in ICU and a larger cohort is required to verify our conclusions. We had incomplete data on echocardiography as they were performed if suspected acute cardiac injury or arrhythmia during ICU stay. Our study does not include patients with existing AF and to patients in non-ICU setting with COVID-19.

CONCLUSION:

Incidence of new onset atrial fibrillation evidenced to be less frequent in patients with severe COVID-19 regardless of inflammatory burden, however it proves to be a marker of poor prognosis. Despite understanding the hypercoagulable milieu of the disease, the benefit of anticoagulation for prevention of stroke during the course of severe COVID-19 remains unclear. Furthers larger studies are warranted to assess the incidence of stroke associated with NOAF in severe COVID-19 infection.

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LEGENDS:

Table 1. Baseline Characteristics of patients treated in ICU with COVID-19

Abbreviations: COVID 19, Corona Virus Disease 2019 caused by SARS-CoV-2; ICU, intensive care unit; NOAF, new onset atrial fibrillation; IQR, interquartile range; eGFR, estimated glomerular filtration rate.

Data are presented as n (%), or n/N (%) unless specified**.** P values indicate difference between patients with NOAF and those without NOAF in ICU. $P<0.05$ was considered statistically significant.

Table 2. Clinical, laboratory and outcome findings of patients treated in ICU with COVID-19

Abbreviations: COVID 19, Corona Virus Disease 2019 caused by SARS-CoV-2; ICU, intensive care unit; NOAF, new onset atrial fibrillation; IQR, interquartile range; AKI, acute kidney injury; RRT, renal replacement therapy; LV, left ventricle; LVSD, left ventricular systolic dysfunction; ECMO, ;d, days.

Data are presented as n (%), or n/N (%) unless specified as median (IQR)**.** P values indicate difference between patients with NOAF and those without NOAF in ICU. $P<0.05$ was considered statistically significant.

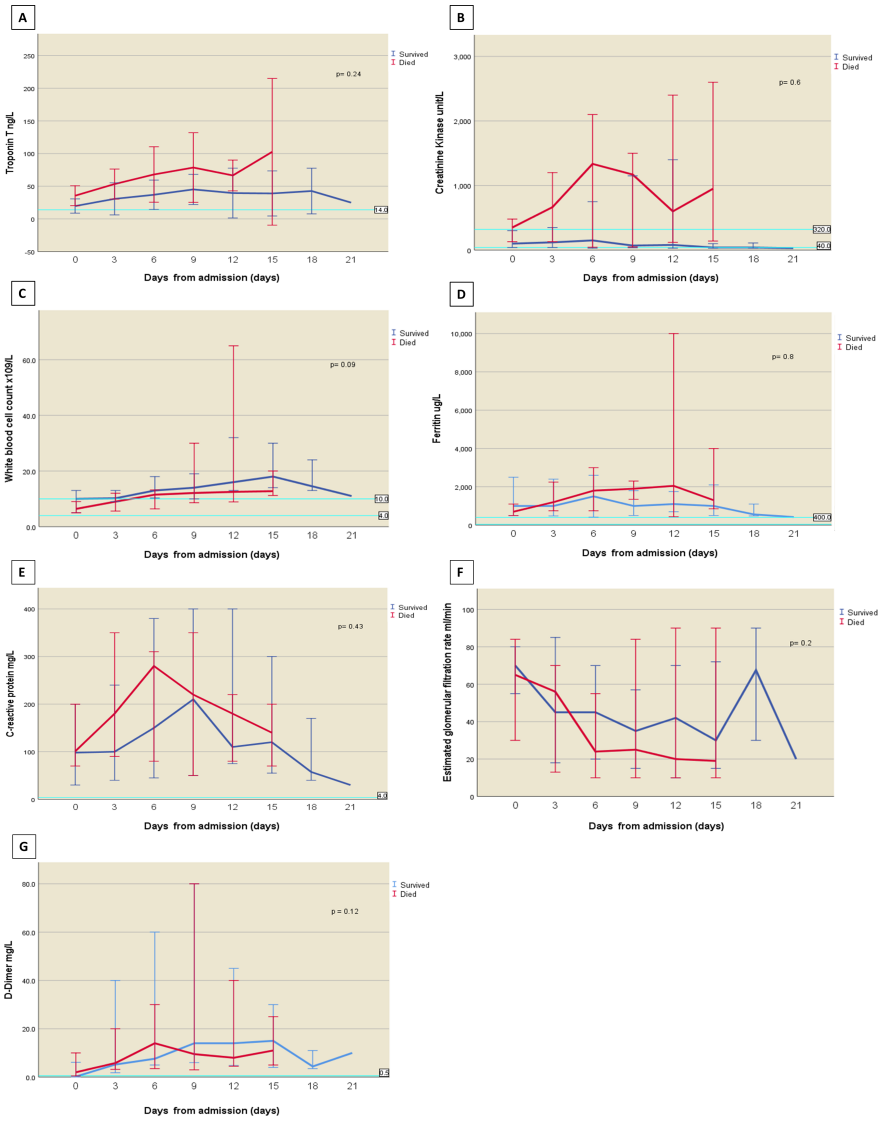
*Echocardiography was only performed in 90 patients (16 NOAF group and 74 without NOAF group) and the percentage is expressed accordingly.

** Only 2 patients received therapeutic anticoagulation for NOAF based on CHA_2DS_2 VASc score in the ICU setting.

*** Therapeutic anticoagulation commenced in some patients with high thrombotic risk based on clinical assessment and with extremely elevated D-Dimer levels in the context of COVID-19 (7 patients).

Figure 1. Temporal pattern of laboratory parameters illustrating the trend between survivors (7 patients) and non survivors (9 patients) from admission till onset of NOAF

A, Troponin; B, Creatinine kinase; C, White blood cell count; D, Ferritin; E, C-reactive protein; F , Estimated glomerular filtration rate; G, D-Dimer. Light blue solid line refers to the reference values for the blood markers where appropriate.



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