New-Onset Atrial Fibrillation Independently Predicts In-Hospital Mortality In Critically Ill COVID-19 Patients Admitted To The Intensive Care Unit

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Abstract

***Background*:** In view of high prevalence of cardiac arrhythmias in patients admitted with COVID-19 disease, we investigated whether new-onset atrial fibrillation (AF) in critically ill Covid-19 patients predicts mortality.

Results: A retrospective analysis of consecutive PCR-positive COVID-19 patients who were admitted to the ICU in Al Kuwait Hospital, Dubai, UAE during the period between September 2020 and March 2021. Patients with AF (group 1) were compared with patients without AF (group 2) and analyzed for mortality risk using multivariate statistical analysis (using Logistic Regression). 149 patients were studied. 16.1% had atrial fibrillation. Mean age 59.3 years (range 27-91 years), 74.5% males, 44.4% obese, 52.3% diabetic and 50.3% hypertensive. Compared with the non-AF group, the AF patients had higher mean ferritin levels; there was no difference in age, gender, comorbidities and rest of the lab results. Among outcomes, mortality rate as well as incidence of shock, acute cardiac injury, acute kidney injury, acute liver injury and mechanical ventilation were significantly higher among the AF group. Multivariate analysis by Logistic Regression revealed the odds ratio for mortality with AF to be 3.058 (95% CI 0.745-12.550), after adjusting for age, gender, body mass index, diabetes mellitus, hypertension, ferritin, c-reactive protein and troponin levels.

Conclusions: Our single center study found that 16.1% of the COVID-19 hospitalized ICU patients experienced new-onset AF. Presence of atrial fibrillation independently predicts in-hospital mortality, after adjusting for age, gender, body mass index, diabetes mellitus, hypertension, ferritin, c-reactive protein and troponin levels.

Keywords: Atrial Fibrillation, COVID-19, Mortality.

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), has caused widespread morbidity and mortality across the globe since it was first reported in Wuhan, China in December 2019 [1]. As of 30 June 2021, the total number of confirmed cases worldwide are 181,813,645 with 3,937,983 confirmed deaths, whereas, United Arab Emirates (UAE) has 631,160 confirmed cases with 1,807 deaths (Johns Hopkins Coronavirus Resource Center) [2]. A wide range of arrythmias have been reported to occur in COVID-19 patients as a result of multiple viral mechanisms that incur injury to the cardiac conduction system including cardiac fibrosis, altered intercellular coupling, downregulation of K^+ channels, interstitial edema and abnormal Ca^{+2} handling [3]. A global cross-sectional survey done by the Heart Rhythm Society in 2020 has shown that the most common reported tachyarrhythmia among hospitalized COVID-19 patients was atrial fibrillation (AF) [4]. Russo et al [5] found that the mechanisms possibly related to AF include systemic infection, hypoxia, direct viral cardiomyocyte injury, sympathetic nervous system over-activity and existing susceptibility due to advanced age and comorbidities.

However, there is scarce data describing the impact of AF on mortality in COVID-19 Intensive Care Unit (ICU) patients. Hence, we conducted this study to investigate the epidemiology of AF in COVID-19 patients and its impact on adverse in-hospital outcomes including mortality.

II. METHODS

Study participants:

The study was conducted at Al Kuwait Hospital, Dubai, UAE between September 2020 and March 2021. This involved a retrospective analysis of all consecutive patients who were admitted to the ICU at our hospital with laboratory-confirmed COVID-19 disease. It included all patients who had positive COVID-19 PCR test and were aged 18 years or more. We excluded patients with only suspicion of COVID-19 disease without laboratory confirmation.

The laboratory used Sacace Real Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) test to diagnose COVID-19 disease. The test was performed on patients' nasopharyngeal swabs. RNA was extracted using SaMag Viral Nucleic Acid Extraction system. Extracted RNA was amplified using BGI- Real Time Fluorescent RT-PCR kit for the detection of COVID-19.

Data collection and management:

Data was extracted from the hospital electronic medical records retrospectively. This included basic demographics (age, gender, ethnicity), clinical data (comorbidities), admission laboratory parameters (complete blood count, coagulation tests, inflammatory markers, electrolytes, cardiac and liver enzymes), end organ complications and outcomes including death. All data was independently reviewed and entered into the computer excel sheet by two analysts. The access to the data excel sheet was provided only to the authors.

Statistical analysis:

Categorical variables were presented as counts and percentages. Continuous variables were presented as mean (standard deviation in their original units. Univariate statistical analysis was done using Stat Plus statistical program version 7 for Mac. Groups were compared using statistical tests (chi-square for categorical variables and t-tests for comparing means of continuous variables). P-value <0.05 was considered statistically significant. Multivariate statistical analysis (using Logistic Regression) was performed according to study-level relevant baseline characteristics (age, gender, body mass index, diabetes mellitus, hypertension, ferritin, c-reactive protein and troponin level) to identify if the presence of AF or any of the other factors is associated with inpatient mortality. It was implemented using the MedCalc Version 20.006 statistical software for Windows. Results were presented as odds ratio (with 95% confidence interval).

Ethical approval: The study was approved by the Ministry of Health and Prevention Research and Ethics Committee, UAE and informed consent was waived off.

III. RESULTS

Baseline characteristics:

A total of 149 patients were included in the study. 24/149 (16.1%) had Atrial Fibrillation. Mean age was 59.3 years (range 27-91 years), 74.5% were males, 44.4% were obese (Body Mass Index >30 kg/m^2), 52.3% were diabetic and 50.3% had hypertension. UAE has a culturally diverse population and we found that 53% of the patients were Middle Eastern and 35.6% were South Asian.

Comparison between AF and non-AF groups:

Compared with the non-AF group, the AF patients had higher mean ferritin levels (2526.6 vs. 1095.9, p=0.018); there was no difference in age, male gender, nationalities, comorbidities and rest of the lab results. The mortality rate was higher among AF patients compared to the Non-AF group (83.3% vs. 40.8%, p <0.001). Shock (83.3% vs. 43.2%, p <0.001), Acute Cardiac Injury (75% vs. 36.8%, p <0.001), Acute Kidney Injury (75% vs. 34.2%, p <0.001), Acute Liver Injury (50% vs. 26.4%, p=0.021) and Mechanical Ventilation (91.7% vs. 41.6%, p <0.001) were significantly higher among the AF group (Table 1).

Table 1:

Atrial fibrillation vs. non-Atrial Fibrillation – comparison of baseline characteristics, laboratory tests and in-hospital complications.

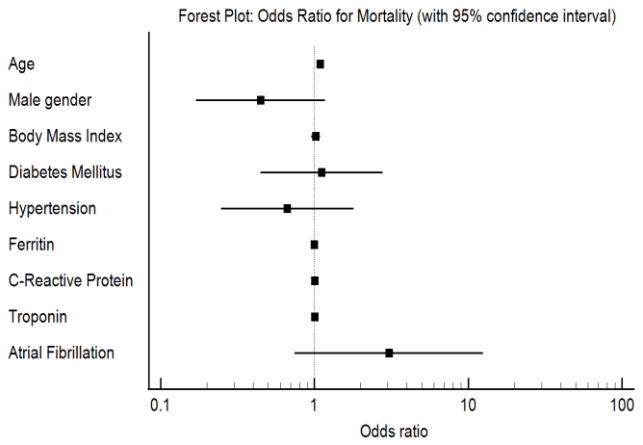
Characteristic	Overall (n=149)	AF present (n=24/149)	No AF (n=125/149)	p-value
Age, years, mean (±SD)	59.3 (±15.4)	72.4 (±13.8)	56.8 (±14.4)	2.804
Males, no./total no. (%)	111/149 (74.5)	17/24 (70.8)	94/125 (75.2)	0.653
Nationalities				
Middle East, no./total no. (%)	79/149 (53)	14/24 (58.3)	64/125 (51.2)	0.812
South Asia, no./total no. (%)	53/149 (35.6)	9/24 (37.5)	46/125 (36.8)	
Comorbidities				
DM, no./total no. (%)	78/149 (52.3)	10/24 (41.7)	68/125 (54.4)	0.253
HTN, no./total no. (%)	75/149 (50.3)	13/24 (54.2)	62/125 (49.6)	0.682
BMI >30 kg/m^2, no./total no. (%)	66/149 (44.3)	4/24 (16.7)	62/125 (49.6)	0.003
Laboratory results on ICU admission				
Hb, g/dL, mean (±SD)	13.4 (±8.5)	12.3 (±2.4)	12.8 (±1.9)	0.175
WCC, x10^3 /mcL, mean (±SD)	9.1 (±4.9)	9.1 (±3.8)	9.1 (±5.1)	0.962
PL, x10^3 /mcL, mean (±SD)	236 (±100.6)	207.8 (±76.0)	241.2 (±104.1)	0.136
INR, mean (±SD)	1.1 (±0.13)	1.2 (±0.2)	1.1 (±0.1)	<0.001
D-dimer, mg/dL, mean (±SD)	2.0 (±4.3)	1.8 (±2.5)	2.0 (±4.6)	0.955
eGFR, mean (±SD)	72.2 (±28.5)	63.7 (±26.1)	73.8 (±28.8)	0.113
Ferritin, mcg/L, mean (±SD)	1326.3 (±2724.3)	2526.6 (±6305.8)	1095.9 (±1072.5)	0.018
CRP, mg/L, mean (±SD)	107.5 (±73)	96.6 (±69.5)	109.6 (±73.7)	0.423
Pro-calcitonin, ug/L, mean (±SD)	0.64 (±2.0)	0.5 (±0.8)	0.7 (±2.2)	0.629
HS Troponin-I, ng/L, mean (±SD)	128.6 (±609.3)	295.7 (±1311.5)	96.5 (±343.1)	0.143
Pro-BNP, ng/L, mean (±SD)	2654.3 (±6188.6)	3825.2 (±6158.3)	2429.5 (±6193.6)	0.313
Sodium, mmol/L, mean (±SD)	135.6 (±6.0)	135.7 (±6.8)	135.6 (±5.9)	0.929
Potassium, mmol/L, mean (±SD)	4.4 (±2.9)	5.6 (±7.1)	4.2 (±0.7)	0.676
Magnesium, mmol/L, mean (±SD)	0.88 (±0.16)	0.9 (±0.2)	0.9 (±0.2)	0.460
ALT, IU/L, mean (±SD)	55.4 (±48.0)	57.8 (±80.9)	55.0 (±39.1)	0.791
AST, IU/L, mean (±SD)	59.9 (±55.3)	73.1 (±110.9)	57.4 (±36.4)	0.202
Complications				
Death, no./total no. (%)	71/149 (47.7)	20/24 (83.3)	51/125 (40.8)	<0.001
Shock, no./total no. (%)	74/149 (49.7)	20/24 (83.3)	54/125 (43.2)	<0.001
Acute cardiac injury, no./total no. (%)	64/149 (43.0)	18/24 (75)	46/125 (36.8)	<0.001
Acute kidney injury, no./total no. (%)	61/149 (40.9)	18/24 (75)	43/125 (34.2)	<0.001
Acute liver injury, no./total no. (%)	45/149 (30.2)	12/24 (50)	33/125 (26.4)	0.021
Mechanical ventilation, no./total no. (%)	74/149 (49.7)	22/24 (91.7)	52/125 (41.6)	<0.001

Results are expressed as number (percentages) for categorical variables, and as mean (standard deviation) for continuous variables.

Analysis of risk factors for mortality in the intensive care unit:

Multivariate analysis by Logistic Regression to determine factors related to mortality revealed the odds ratio for AF to be 3.058 (95% CI 0.745-12.550), after adjusting for age, gender**,** body mass index, diabetes mellitus, hypertension, ferritin, c-reactive protein and troponin levels (Figure 1).

Figure 1:
Multivariate analysis by Logistic Regression showing Odds Ratio for mortality.



IV. DISCUSSION

Our study investigated the incidence of new-onset AF in critically ill COVID-19 patients and its association with adverse outcomes including mortality. We found the incidence of new-onset AF in our study to be 16.1%. This is in accordance with the study by Colon et al [6] who reported a 16.5% incidence of atrial arrhythmias in a study of 115 patients with COVID-19, all of whom were admitted to ICU. A meta-analysis of 31 studies including 187,716 patients by Romiti et al [7] showed the prevalence of AF in COVID-19 patients to be as high as 8% (95% CI:6.3-10.2%) with heterogeneity between studies. AF patients in our study were older (mean age 72.4 years vs. 56.8 years), but no difference in the prevalence of diabetes and hypertension. However, a study showed AF patients were likely to be older, diabetic, hypertensive, with history of coronary heart disease and associated with 5-fold greater chance of critical COVID-19 illness [7].

Higher degrees of inflammation have been related to the incidence of AF . Peltzer [8] reported marked elevations of troponin, brain natriuretic peptide (BNP), C-reactive protein (CRP), d-dimer, erythrocyte sedimentation rate (ESR) and ferritin in an observational cohort study of 1,053 COVID-19 patients. Similarly, Zylla at el [9] found higher CRP and interleukin-6 levels in COVID-19 patients with AF as compared to patients without AF. However, we found that serum ferritin was the only inflammatory marker that was found to be statistically more in AF patients compared to without AF. The rest of the markers including CRP and procalcitonin were not statistically different. We found that AF was associated with adverse clinical outcomes like shock, acute cardiac injury, acute kidney injury, acute liver injury and risk of mechanical ventilation due to acute respiratory distress syndrome, compared to non-AF patients. Although, these associated complications would together lead to increased mortality, we found that presence of atrial fibrillation independently predicted in-hospital mortality, after adjusting for age, gender, body mass index, diabetes mellitus, hypertension, ferritin, c-reactive protein and troponin levels. This is in accordance with previous studies that have shown that the presence of AF is associated with a 4-fold higher risk of death [7] and independently associated with 30-day mortality [8]. Gauzzi et al [10] has mentioned that apart from the associated high degree of inflammation and existing comorbidities, AF may directly contribute to hemodynamic instability, thromboembolism and increased endothelial dysfunction and hence associated with increased mortality.

The study has certain limitations. This is a retrospective study where data is obtained via patient electronic records, which may be subject to error. We did not study the timing of diagnosis of AF which would have allowed to explore the temporal relationship between the onset of AF and clinical events such as intubation or death. We did not examine the impact of type of intervention, that is rate control versus rhythm control of AF, on the outcomes. We did not follow the patients post-discharge and hence no information is gathered regarding the recurrence of arrhythmias after discharge. And finally, this is a single-center study with small sample size, hence needs further larger studies to validate the results.

V. CONCLUSIONS

Atrial fibrillation is common in critically ill COVID-19 patients. We found an AF incidence of 16.1% in our single center study of COVID-19 patients admitted to the intensive care unit. Presence of atrial fibrillation independently predicted in-hospital mortality, after adjusting for age, gender, body mass index, diabetes mellitus, hypertension, serum ferritin, C-reactive protein and troponin levels. Early recognition and management of AF in COVID-19 is critical to improved outcomes.

VI. ABBREVIATIONS

AF - atrial fibrillation; SARS-Cov-2 - Severe Acute Respiratory Syndrome Coronavirus 2, CRP - C-reactive protein.

VII. REFERENCES

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