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Incidence and predictors of cardiac arrhythmias in patients with COVID-19 induced ARDS

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Abstract
Introduction: Recent studies suggest cardiac involvement with an increased incidence of arrhythmias in the setting of coronavirus disease 2019 (COVID-19). The aim of this study was to evaluate the risk of potentially lethal arrhythmias and atrial fibrillation in patients with COVID-19-induced acute respiratory distress syndrome (ARDS) and to elicit possible predictors of arrhythmia occurrence.

Methods and results: A total of 107 patients (82 male, mean age 60 ± 12 years, median body mass index 28 kg/m²) treated for COVID-19-induced ARDS in a large tertiary university hospital intensive care unit between March 2020 and February 2021 were retrospectively analyzed. Eighty-four patients (79%) had at least moderate ARDS, 88 patients (83%) were mechanically ventilated, 35 patients (33%) received vvECMO. Forty-three patients (40%) died during their hospital stay. Twelve patients (11%) showed potentially lethal arrhythmias (six ventricular fibrillation, six significant bradycardia). Atrial fibrillation occurred in 27 patients (25%). In a multivariate logistic regression analysis, duration of hospitalization was associated with the occurrence of potentially lethal arrhythmias (p = 0.006). There was no association between possible predictive factors and the occurrence of atrial fibrillation. Invasive ventilation, antipsychotics, and the QTc interval were independently associated with acute in-hospital mortality, but this was not arrhythmia-driven as there was no association between the occurrence of arrhythmias and mortality.

Conclusion: In this relatively young population with COVID-19-induced ARDS, the incidence of potentially lethal arrhythmias was low. While overall mortality was high in these severely affected patients, cardiac involvement and arrhythmia occurrence was not a significant driver of mortality.

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possible. The present study was therefore conducted to elicit the incidence and possible predictive factors of cardiac arrhythmias in a patient population severely affected by COVID-19 by analyzing all consecutive patients admitted to a tertiary university hospital intensive care unit (ICU) for COVID-19-induced acute respiratory distress syndrome (ARDS).

Methods

The study was conducted in accordance with the declaration of Helsinki and was designed as a retrospective analysis including all patients admitted to the internal medicine intensive care unit of a large tertiary university hospital for COVID-19-induced ARDS between 03/2020 and 02/2021. All patients admitted during this time were analyzed concerning the occurrence of cardiac arrhythmias during their stay on the ICU and possible predictors were recorded.

Therapy of COVID-19-induced ARDS

All included patients had at least moderate ARDS at the time of ICU admission. Patients were treated according to the state of evidence at the time of admission, especially concerning the status of noninvasive ventilation, the time of intubation, and the use of dexamethasone, which was administered according to the RECOVERY or DEXA-ARDS protocols as appropriate [9,10]. In all patients with a \( \text{pO}_2/\text{FiO}_2 < 1.5 \), prone ventilation was attempted for 5 cycles of 16 h each [11]. If patients were not mechanically ventilated, this was done as awake proning [12]. Patients with a \( \text{pO}_2/\text{FiO}_2 < 1.0 \) were evaluated for veno-venous extracorporeal membrane oxygenation (vv-ECMO) therapy, which was administered either with the Maquet Rotaflow (Maquet, Rastatt, Germany) or Getinge Cardioplegia (Getinge, Göteborg, Sweden) systems. Antiviral agents such as remdesivir were not routinely administered during intensive care treatment as there was no evidence of benefit in this severely affected population [13]. All patients received a transthoracic echocardiography and a control of cardiac laboratory parameters on admission and when clinically indicated.

Statistical analysis

Data were stored using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) while SPSS Version 27 (IBM Corporation, Somers, NY, USA) and MedCalc Version 19.6.4 (MedCalc Software Ltd., Ostend, Belgium) were used for statistical analysis. Univariate analyses were conducted using Mann-Whitney U, chi-square, or Fisher exact tests as appropriate. A multivariate logistic regression model was used for multivariate analysis. Statistical significance was defined as a two-sided alpha level of 0.05 or less.

Results

One-hundred and seven patients were included. Patient characteristics are shown in Table 1 and relevant previous medical history is listed in Online Table 1. The patient population included 82 male patients (77%), mean age was 60 ± 12 years, and the median duration of ICU stay was 11 days (interquartile range: 5–16 days). Eighty-four patients (79%) had at least moderate ARDS, 59 patients (55%) received at least one proning session with a median of 4 proning sessions per patient, and 35 patients (33%) received a vvECMO during their course of treatment. Online Table 2 displays relevant medication use in the patient population during the ICU treatment. Forty-three patients (40%) died during their hospital stay.

Ventricular tachycardias

Six patients (6%) developed ventricular tachycardia (VT) during their intensive care treatment. Median age was 64 years and median body mass index 30 kg/m². In all of these patients, a monomorphic VT was documented (see Fig. 1). Five of six patients were male, all were mechanically ventilated and four of six patients received a vvECMO during their treatment course. Only two patients had previously known coronary artery disease. In two patients cardiopulmonary resuscitation (CPR) was needed but all patients survived their episode(s) of VT. However, three of the six patients later died due to end-stage pulmonary COVID-19 involvement and, in one case, fungal superinfection.

Two of the patients with ventricular tachycardia exhibited increased serum troponin and reduced left ventricular function on echocardiography. In one of these patients the most likely cause of the cardiac involvement was deemed to be a septic cardiomyopathy caused by Candida sepsis and left ventricular ejection fraction (LVEF) improved after antifungal treatment. The other patient had COVID-induced myocarditis with a regeneration of LVEF after resolution of COVID-induced ARDS. A cardiac magnetic resonance imaging conducted six months after first diagnosis was able to document a reduced cardiac perfusion reserve in this patient.

Atrial fibrillation

Twenty-seven patients (25%) developed at least one episode of atrial fibrillation (AF) during their intensive care treatment. AF was previously

### Table 1

Clinical characteristics of the included patient population.

| Characteristic                                  | Number of patients |
|------------------------------------------------|--------------------|
| Number of patients                             | 107                |
| Gender (male/female)                           | 82/25 (77%/23%)    |
| Age in years (mean ± SD)                       | 60 ± 12            |
| Time from first diagnosis to ICU admission (IQR)| 8 (3–12)           |
| Length of ICU stay in days (IQR)               | 11 (5–16)          |
| BMI in kg/m² (IQR)                             | 28 (25–33)         |
| Severity of ARDS                               |                    |
| - Mild                                         | 23 (21%)           |
| - Moderate                                     | 38 (36%)           |
| - Severe                                       | 46 (43%)           |
| Mechanical ventilation                         | 88 (82%)           |
| vv-ECMO                                       | 35 (33%)           |
| Number of patients with proning                | 59 (55%)           |
| - Median number of proning sessions (IQR)      | 4 (3–5)            |
| Number of patients on hemodialysis             | 31 (29%)           |
| ECG on admission                               |                    |
| - PQ (IQR)                                     | 140 (130–160)      |
| - QRS (IQR)                                    | 82 (80–90)         |
| - QT (IQR)                                     | 440 (420–460)      |
| Arrhythmias                                    |                    |
| - Ventricular tachycardia                      | 6 (6%)             |
| - Bradycardiac (AVB, sinus arrest, asystole)   | 6 (6%)             |
| - Atrial fibrillation                          | 27 (25%)           |
| Death during hospital stay                     | 43 (40%)           |

AVB, atrioventricular block; BMI, body mass index; ECG, electrocardiogram; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; vv-ECMO, veno-venous extracorporeal membrane oxygenation.
known in three of these twenty-seven patients (11%). Nineteen patients (70%) were male with a mean age of 62 ± 9 years. Twenty-one patients (78%) received betablockers, 18 patients (66%) were treated with amiodarone, and 5 patients (19%) received cardiac glycosides. Twelve patients (44%) were electrically cardioverted during their treatment course.

Predictors of cardiac arrhythmias

Possible predictors of cardiac arrhythmias were recorded in all patients and analyzed in a univariate analysis and a multivariate logistic regression model. Table 2 displays the relevant results. Because of the substantially different impact for affected patients, we decided to analyze predictors of potentially lethal arrhythmias (ventricular tachycardia and relevant bradyarrhythmias) separately from predictors of AF.

On univariate analysis, duration of ICU treatment and the use of antipsychotics showed a significant association with the occurrence of lethal arrhythmias. In the multivariate logistic regression model, only duration of ICU treatment remained as an independently associated factor (see Table 2). None of the recorded possible predictors showed a significant association with the development of AF. Not surprisingly, betablockers and amiodarone were used more often in patients with AF.

Predictors of mortality

Recorded parameters were analyzed for an association with mortality in a univariate analysis and a logistic regression model. On univariate analysis, QTc, invasive ventilation, proning, vv-ECMO, and the use of catecholamines, amiodarone, antipsychotics, and sedatives showed a significant association with mortality. In the multivariate model, QTc,
invasive ventilation, and the use of antipsychotics remained independently associated with mortality. The association between the QTc interval and mortality was not arrhythmia-driven, as there was neither an association of QTc with potentially lethal arrhythmias nor an association of potentially lethal arrhythmias to mortality in our population. Nevertheless, the association of QTc with mortality remained statistically significant in the multivariate regression model even when corrected for QRS duration [14]. Additionally, sensitivity analyses with clinically relevant QTc cutoff values of 450 ms ($p = 0.003$) and 470 ms ($p = 0.007$) also showed a statistically significant association with mortality. Antipsychotics showed an inverse relationship to mortality, possibly indicating patients who survived a prolonged treatment course and became delirious during the weaning period.

**Discussion**

The present study including 107 patients suffering from COVID-19 with at least moderate ARDS documents an overall low incidence of life-threatening arrhythmias. While mortality was high in this previously healthy and comparatively young patient population, our analyses suggest that this was not primarily driven by arrhythmia occurrence.

Concerning AF, our reported incidence in this patient population is comparable to the results of a recent study analyzing the incidence of AF in a large general intensive care cohort [15], indicating that the occurrence of AF corresponds to the overall severity of disease and not to SARS-CoV-2 infection specifically. The reported association between the occurrence of AF and amiodarone or betablockers is most likely a reverse causality, as patients received the medication as treatment for AF. Our findings support the idea that despite possible myocardial involvement, arrhythmia occurrence mainly corresponds to the severity of illness including hypoxia and systemic inflammation rather than viral infection. After multivariate adjustment, only duration of invasive care treatment was associated with the occurrence of ventricular tachycardias and significant bradycardia, indicating a higher incidence in patients requiring prolonged treatment due to their critical course of illness. Importantly, mortality was not associated with the occurrence of arrhythmias and all patients survived their acute arrhythmic events. While recent studies suggest the possibility of myocardial involvement due to direct SARS-CoV-2 effects including elevated troponin levels and pericardial and myocardial late enhancement in magnetic resonance imaging, our analyses were unable to show a corresponding increased risk of cardiac arrhythmias despite our severely affected patients. It is therefore questionable whether cardiac arrhythmias represent a significant factor in COVID-19 mortality, with previous studies likely reporting imaging abnormalities with little clinical impact [16]. Additionally, tissue damage related to COVID-19 might not only be the result of local inflammatory mechanisms but also possibly the result of vascular-related damage, such as capillary leakage and vessel thrombosis [17].

We found a significant association between a slightly increased QTc interval at the time of admission and in-hospital mortality on multivariate analysis, which was not arrhythmia-driven. The QTc interval could therefore be a marker for subclinical cardiac injury and reduced cardiac reserve respectively. Correspondingly, QTc prolongation was previously shown to be a predictor of cardiovascular mortality and morbidity in patients with known cardiovascular disease [18]. In our center, patients were not routinely treated with azithromycin or other QTc-prolonging medications for COVID-19. Therefore a systemic effect of the COVID-19 specific medical therapy on QTc interval seems unlikely. While invasive ventilation is likely a surrogate for disease severity in general and lung involvement in particular, the use of antipsychotics displayed an inverse relationship to mortality in our data. This is most likely explained by many COVID-19 patients exhibiting a prolonged weaning phase with a high incidence of delirium after having survived the most life-threatening phase of their illness.

**Limitations**

The presented results may be limited because of the relatively short inclusion period and our study’s single center design. Since we present a relatively young population with few previously known comorbidities, findings may not be generalizable to a general population with COVID-19, especially in the absence of ARDS. In addition, there was no long-term follow-up to evaluate possible future health effects of arrhythmia occurrence. However, few data are available concerning the impact of arrhythmia on overall COVID-19 mortality with no long-term follow-up available because of the novelty of the disease.

**Conclusion**

In a relatively young and previously healthy population with COVID-19-induced ARDS, the incidence of potentially lethal arrhythmias during intensive care treatment was low. Only duration of ICU stay was found to be independently associated with the occurrence of lethal arrhythmias in a multivariate logistic regression analysis. While the overall mortality was high in these severely affected patients, arrhythmias did not seem to be a significant driver of mortality. In addition to invasive ventilation, a prolonged QTc on admission electrocardiogram was associated with increased mortality, potentially indicating subclinical myocardial injury or reduced cardiac reserve.

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**Declaration of competing interest**

None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.04.010.

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