Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COMMENTARY

Atrial Fibrillation in COVID-19: Therapeutic Target or Grave Omen?

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To date, the ongoing Coronavirus disease 2019 (COVID-19) pandemic has afflicted nearly 147 million people, resulting in 3.1 million deaths [1]. Despite mass global vaccination campaigns, a significant global disparity in access to vaccines remains [2]. In this setting, the emergence of new COVID-19 variants with lower vaccine efficacy [3] threatens to continue to fuel the pandemic. Risk stratification and management of critically ill COVID-19 patients remains an urgent clinical challenge.

Initial reports from China suggested an overall incidence of cardiac arrhythmias of 17% in patients hospitalised with COVID-19, with rates of up to 44% in those admitted to the intensive care unit (ICU) [4]. Besides the direct cardiac effects of the virus, COVID-19 related systemic inflammatory response and therapeutic agents including hydroxychloroquine contribute to proarrhythmic risk observed in patients hospitalised due to COVID-19 [5]. Comprehensive data on outcomes amongst critically ill COVID-19 patients with atrial fibrillation (AF) is lacking.

In this issue of *Heart, Lung and Circulation*, Ip and colleagues report on a multicentre cohort of 171 patients admitted to the intensive care unit (ICU) [6]. The total burden of AF reported in these patients was 34.5%, with over half of these (54%) not having a prior diagnosis of AF. Overall mortality was 46.2%, with adjusted mortality risk more than two-fold (HR: 2.38, $p<0.01$) higher identified were age and endotracheal intubation status, both of which are well established risk markers in COVID-19. While patients with AF did tend to be older, and both those with a prior history of AF (63%) or new onset AF (76%) required endotracheal intubation more commonly than those who remained in sinus rhythm (40%), the independent prognostic significance of AF remained.

The burden of pre-existing and new onset atrial fibrillation observed by Ip and colleagues is 15.8% (95% CI: 10.3–21.3%) and 18.7% (95% CI: 15.7–21.7%) respectively. Adding Ip et al.'s 171 COVID-19 patients to a previously group of 12 studies analysed by Zuin et al. [7], and conducting a random effects meta-analysis for this invited commentary, we estimate a pooled prevalence of pre-existing AF in 13 studies [6,8–19] with 15,731 COVID-19 patients of 11.2% (95% CI: 8.3–15.1%), (unpublished data; Figure 1). However, the 34.5% total burden of AF reported by Ip et al. greatly exceeds previous reports ranging between 3.6% to 24.9% [20–22]. The greater AF burden likely reflects greater illness severity of the study cohort, as evidenced by 50% of patients requiring mechanical ventilation. The risk of incident AF has previously been reported to be more than four-fold higher in COVID-19 ICU patients versus those admitted to non-ICU wards [20], likely explaining the observed arrhythmia burden.

The higher burden of AF observed by Ip and colleagues was correspondingly associated with poorer survival, with mortality occurring in 78% of patients with pre-existing AF and 74% of patients with new onset AF, compared to a mortality of 31% in those remaining in normal sinus rhythm. Zuin et al.'s meta-analysis of recent publications has estimated higher risk of death in patients with preexisting AF (OR 2.2, 95% CI (1.5–3.4) [7], and new-onset AF has also been shown to be an independent risk factor for mortality in patients admitted to the ICU with severe sepsis or shock, with OR 1.6 (CI 1.4–1.7) for in-hospital mortality amongst these patients [23].

The study by Ip and colleagues, in the context of mounting evidence of the prognostic significance of AF in COVID-19 patients, leads to the question of whether the reported association reflects causality or if AF is a mere marker of

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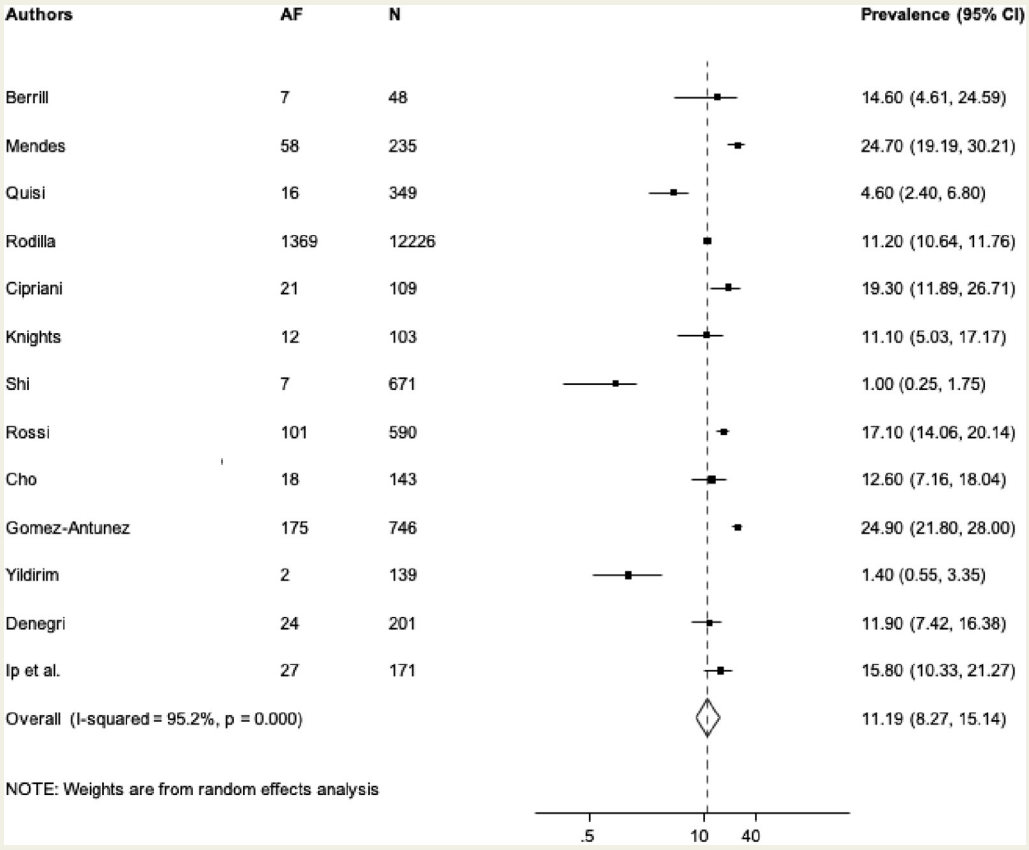

Figure 1 Prevalence of pre-existing atrial fibrillation in hospitalised COVID-19 patients (unpublished data; [6–19]).

disease severity. While it is beyond the capacity of observational studies to establish causation, ascertainment of cause-specific mortality may have provided additional evidence of causation. Onset of AF in a critically ill patient has deleterious haemodynamic effects that in the setting of a COVID-19 infection related hypercoagulable state may further increase thromboembolic events [24]. There is little evidence to support rhythm control of AF in critically ill patients [25]. Whereas the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial led to an era of relative equipoise between rate control and rhythm control for management of AF [26], a growing body of literature establishing the superiority of rhythm control, particularly for patients with recently diagnosed AF [27], and those patients with congestive heart failure [28], raises the question of whether the poor prognosis associated with AF in critical illness can be attenuated by arrhythmia related intervention. Critically ill COVID-19 patients with AF are generally treated with a rate-controlled strategy and receive anticoagulation. Consideration of interventions such as transoesophageal echocardiograms and cardioversions is challenging in any critically ill patient, and consideration of these interventions in COVID-19 patients would be further complicated due to exposure risk.

While arrhythmia related interventions could only be pursued in an investigational setting at this time, improved understanding of the prognostic importance of AF in COVID-19 patients may allow greater refinement of risk stratification. At present, several risk scores have been developed to predict important clinical outcomes in COVID-19 patients (https://covid-calculator.com) and incorporate variables such as age, sex, coronary artery disease, diabetes mellitus, body mass index, statin use and SpO_2:FiO_2 ratio [29]. Development of these and other risk models have not evaluated AF as a predictor. At present, risk models have only fair discrimination of 0.79–0.84 for mortality [29]. Improvement in risk stratification may help better target therapies towards those at the highest category of risk, particularly when resources are constrained—as they have been too often during this global pandemic.

Health care systems around the world are overwhelmed by COVID-19 patients and AF further complicates their course. Potentially important areas for future investigation include rhythm control with amiodarone, anticoagulation strategies and their relation to the timing of the development of AF, and interaction of comorbidity index with AF. To the question of whether AF represents a grave omen or a therapeutic target in COVID-19 patients, we would say that it is

almost certainly the former, but that there is also hope for the latter.

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