Right ventricular dysfunction in patients with COVID-19 pneumonitis: replies

We thank Flower et al. for their thoughtful response [1] to our article examining right ventricular (RV) dysfunction in ventilated patients with COVID-19 infection [2]. We agree that the definition of RV dysfunction is critical when examining this important topic and will be one of the main determinants of prevalence. Further, as they point out, there is no widely accepted definition of RV dysfunction, a situation where we agree that consensus would benefit the researcher and clinician alike. The term is often used to describe abnormal echocardiographic or biomarker findings where cardiac output is preserved, a setting of "pre-" RV failure. Counterintuitively, right ventricular failure (RVF) is perhaps easier to define but more difficult to diagnose clinically; RVF is "a complex clinical syndrome characterised by insufficient delivery of blood from the RV in the setting of elevated systemic venous pressure at rest or exercise" [3]. This definition isn't dependent on any single imaging parameter and relies on the integration of imaging along with the clinical findings of systemic hypoperfusion and congestion.

We recognise the importance of the PRICES statement for conducting and reporting of critical care echocardiography studies [4]. As part of our a priori protocol for secondary analyses [5], all imaging performed was transferred to a central "echo lab" where additional quantitative methods of assessing RV function, such as tricuspid annular plane systolic excursion (TAPSE), pulsed Doppler S wave (S') and fractional area change (FAC), along with speckle tracked strain assessment were performed (a manuscript reporting these data is in submission). Whilst these quantitative methods of interrogating RV function are important study endpoints and help provide insight to mechanisms, as discussed in our manuscript, the primary outcome of the study was intentionally pragmatic, rather than quantitative. Our focus was on providing an endpoint that could be delivered by critical care clinicians at the bedside; these clinicians are the people who are making real-time management decisions regarding these critically ill patients.

We also appreciate the considered response by Zawadka et al. [6]. The ECHO-COVID study is one of the largest critical care echo studies in patients with COVID-19 and contributes significantly to our knowledge regarding this patient population, but the results are not directly comparable with our study [7]. The ECHO-COVID study was retrospective, meaning imaging was performed as per clinical necessity (often at times of haemodynamic instability) and not on every patient, risking significant selection bias and limiting its generalisation. Our study reports results on 24% of all ventilated patients with COVID-19 infection admitted to participating ICU's during the study period, where imaging was performed per-protocol, regardless of clinical necessity. Further, the ECHO-COVID study

was also performed on a mixed cohort of patients requiring, or not requiring, mechanical ventilation. The higher prevalence of septal flattening (or paradoxical septal motion as described in ECHO-COVID) may be as a result of the retrospective nature of ECHO-COVID. The ECHO-COVID study, however, is commendable for providing data on *quantitative* RV size in the majority (76.4%) of participants. This quantitative assessment may account for the lower prevalence of severe RV dilatation seen in their cohort. As highlighted by Zawadka et al., RV size is often over-estimated on visual assessment, meaning that the prevalence of true severe RV dilatation (if assessed quantitatively) in our study may be lower.

Although a wide-range of echocardiography expertise in our study is highlighted; the majority (82%) had either focused critical care echocardiography *mentor* status or British Society of Echocardiography accreditation. Echocardiography reporting in our study comes from clinicians who regularly perform focused echo assessment in their clinical practice and who are treating and making real-time management decisions based on their results. We thought that any definition of RV dysfunction needed to be sufficiently pragmatic [8] to empower these clinicians to make the diagnosis. Although lower than seen in some previous reports, we feel our estimate is robust, and that the prevalence of 6% is in keeping with previous work in ventilated patients with ARDS by Mekontso Dessap et al. where *severe* acute cor pulmonale (the definition used in our study) was present in 7% and, as in our study, was associated with mortality [9]. When reporting an alternative definition of RV dysfunction (supporting information); severe RV dilatation *and/or* septal flattening, the prevalence of RV dysfunction of was higher at 30%. This prevalence is perhaps more in keeping with other studies, but importantly was not associated with survival in this cohort. As Flower et al suggest, this definition may include the "less sick." Although the definition of RVD used, undoubtedly impacts on prevalence, other aspects of study design are also important. More than 50% of the studies in the meta-analysis by Corica et al. [10] are retrospective, which can be susceptible to ascertainment bias with a reliance on clinically indicated echocardiograms (often performed at times of haemodynamic instability) leading to higher observed rates of RV dysfunction.

We agree that the end-point of "*radiologically-confirmed*" or "*clinically-suspected*" pulmonary thromboembolism (PTE) is not perfect. As described in our manuscript, the association described is at high risk of type II error and should be treated as exploratory only. Design of the study was that the radiologically confirmed or clinically suspected PTE was in the period *prior* to their *study* echocardiogram. This part of the case report form asked for presence of confirmed or suspected PTE in the period from hospital admission to 08:00 on the day of their study echocardiogram. This finding

should not therefore have been influenced by their subsequent *study* echocardiogram. Despite this, there will have been patients who had additional imaging prior to COVID-RV enrollment, as clinically indicated, which may have influenced clinicians to perform (or not perform) investigations for PTE. The fact that most imaging societies recommend the use of more than one parameter for assessment of RV function reflects there being no single measure that will accurately reflect "RV dysfunction". The future is likely to include the integration of dynamic and non-dynamic imaging parameters, biomarkers and clinical findings to highlight patients with "RV dysfunction" or at risk of RV failure, allowing interventions to be targeted at those most likely to benefit. However RV dysfunction or failure is defined, to maximally benefit these patients, its diagnosis must be deliverable at the bedside.

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