The evolution of cardiovascular COVID-19 research

Reply to: The Janus of COVID-19: from registry data to prospective studies

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We thank Sykes et al for their interest in our recent publication\textsuperscript{1} regarding mechanisms of myocardial injury following recovered severe COVID-19 infection with troponin elevation. We acknowledge the survivorship bias due to significant in-patient mortality associated with troponin-positive COVID-19 infection, but this remains difficult to overcome in future studies without imaging critically unwell patients. The importance of our findings, and of future studies, is to characterize the sequelae of severe COVID-19 infection in survivors.

Defining troponin negativity is challenging. Our study leveraged clinical data, with the vast majority having troponin checked at presentation based upon early indicators suggesting troponin as a prognostic marker\textsuperscript{2}. Additional troponin measurements were performed only if clinically indicated. Whilst classifying patients as troponin-positive requires only one abnormal measurement, troponin-negative patients can only be defined with serial measurements throughout hospital admission, which does not seem to be a feature in future studies.

Our decision to use historical pre-pandemic controls was both to minimize unnecessary visits to hospital during a pandemic, and to eliminate the risk of undiagnosed or asymptomatic COVID-19 infection featuring in the control and healthy volunteer groups, a challenge that will face any future studies using contemporary control groups unless antibody testing is performed. Our strategy was anchored by robust phantom testing which confirmed excellent stability over the time period between historical controls and convalescent COVID-19 patients.

The unexpected emergence of COVID-19 as a global healthcare emergency in early 2020 resulted in research being driven by constantly changing needs which have evolved during the course of the pandemic. The evolution of COVID-19 research over the past year can be considered in phases. Initially, there was urgency to focus on isolating and sequencing the virus, defining and limiting transmission with societal intervention, understanding pathophysiology of infection, developing rapid testing and setting up multicentre therapeutic trials. We have now reached the phase where we can shift the focus to assess disease sequelae on multiple organs. With each step over the past year there has been study refining. Early publications were predominantly case series without controls followed by single-centre retrospective studies\textsuperscript{3}, and we are now moving towards prospective multicentre phantom control studies. Each step along this journey provides additional incremental information and we look forward to the COVID-HEART study in which patients will undergo serial CMR
scans providing information on recovery of cardiac abnormalities, and the CISCO-19 study which uses a multisystem multimodality approach with the additional inclusion of troponin-negative patients.

We share Sykes et al.’s aspiration for precise media reporting of COVID-19 research and continue to emphasise that nearly half of our study cohort had no significant cardiac abnormality despite being some of the sickest patients reported in the literature (all required hospitalisation and a third required intensive care for ventilatory support). It is plausible that the overall prevalence of convalescent cardiac abnormalities in a broader group recovered from less severe COVID-19 infection may be much lower. We look forward to upcoming studies of troponin-negative and non-hospitalised COVID-19 patients to provide further insight in this regard.


