
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.

in other countries should be done to assess the inter-country variability.

The main clinical advantage of this predictive model is its predictors, which can be easily collected as part of daily routine care and inform stratification of patients on the basis of clinical severity. The 4C Deterioration and Mortality models could be combined and included in the programmatic standard of care adopted by hospitals to better identify the most appropriate clinical pathways for patients with COVID-19. Reliable predictive models can be a means to improve clinical management and, consequently, to better allocate human and economic resources.

We declare no competing interests.

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# Nebulised heparin for patients on ventilation: implications for COVID-19 pneumonia

Pulmonary coagulopathy is intrinsic to pulmonary inflammation, occurs in patients with different types of lung injury, and is one of the potential mediators of harm caused by mechanical ventilation.[1] Locally applied anticoagulants, such as heparin, could affect bronchoalveolar haemostasis, including fibrin deposition in the alveoli and possibly also in the vascular compartment.[1] Although several clinical studies have shown that nebulised heparin mitigates both onset and progression of lung injury, one meta-analysis[2] did not confirm any benefit.

In *The Lancet Respiratory Medicine*, Barry Dixon and colleagues[3] report the results of the CHARLI study, a multicentre, phase 3, randomised controlled trial on the effect of nebulised heparin on self-reported clinical outcomes in invasively ventilated patients with acute respiratory distress syndrome (ARDS) or those who were at risk of ARDS. Initially, the findings imply that nebulised heparin has no benefit. Indeed, the primary endpoint, the Short Form 36 Health Survey (SF-36) Physical Function Score of survivors at day 60—a patient-reported numeric scale—was not affected by the intervention (mean score 53·6 in the heparin group *vs* 48·7 in the placebo group; difference 4·9 [95% CI −4·8 to 14·5]; p=0·32). It is, however, debatable whether the SF-36 is an appropriate outcome measure for this study. Although the SF-36 is perhaps beneficial as a numeric score allowing a smaller sample size,[4] use of the SF-36 also come with challenges; for example, the SF-36 can only be scored in patients who survive and can also not be obtained from patients lost to follow-up. The loss to follow-up is of concern since it could be caused by a poor functional status. Moreover, the impact on global functioning of a treatment that targets a single organ could be limited or influenced by confounding factors.

While secondary outcomes should always be interpreted carefully, the CHARLI study does suggest some potential benefits of nebulised heparin. A faster improvement in the Murray Lung Injury Score suggests faster recovery of lung function, and the finding that fewer patients at risk for ARDS actually developed ARDS suggests a prophylactic effect of nebulised heparin. Also, patients who received the intervention were discharged home at day 60 more often than those who received standard care.

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These results fit with the results of an earlier study[5] by these investigators, namely that nebulised heparin is associated with fewer days of invasive ventilation in a similar cohort of patients.

More studies are needed that use clinically relevant outcomes, such as mortality, duration of ventilation, or length of stay in the intensive care unit, and these studies should be adequately powered. The CHARLI study helps somewhat in these aspects—it is important to see that nebulised heparin at dosages of 25 000 UI every 6 h, as used in most studies to date,[2] is a safe strategy, with concomitant use of systemic low molecular weight or unfractionated heparin. Despite the increase in the activated partial thromboplastin time (aPTT), suggesting some systemic effect of nebulised heparin, the number of transfusions and major bleeding events was not affected. Withholding of treatment was only necessary in small proportion of patients in response to blood-tinged sputum or an excessive prolongation of aPTT. Conversely, in another study[6] of burn patients with inhalation trauma, a much higher withholding rate related to the presence of blood-tinged sputum was seen than that seen in the CHARLI study.[3] It could be that this difference is the result of the specific lung injury.

Pulmonary coagulopathy is once again receiving attention because pulmonary thrombosis is frequently seen in patients with COVID-19 pneumonia,[7,8] causing increased dead space and severe hypoxaemia. The promising findings of the CHARLI study[3] underline the importance of considering studies of nebulised heparin in patients with COVID-19 pneumonia,[9] and some studies have already been registered on ClinicalTrials.gov (NCT04397510, NCT04530578). The CHARLI study investigators discuss the need for future studies in more homogeneous populations and we could not agree more; the surges of COVID-19 pneumonia in many countries should trigger the scientific community to test nebulised heparin in these large, uniform populations.

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# Trends in COVID-19-related in-hospital mortality: lessons learned from nationwide samples

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SARS-CoV-2 infectivity remains widespread across the world, with the resulting disease, COVID-19, causing devastating sequelae. With disease-modifying therapy but no cure, and a long road to developing immunity through vaccination, understanding and identifying risk factors contributing to mortality must remain a priority. In *The Lancet Respiratory Medicine*, two Articles—one from England,[1] the other from Brazil[2]—offer insights into nationwide trends for inpatient mortality due to COVID-19.

These Articles contribute considerably to the growing literature on the markedly diverse inpatient mortality due to COVID-19 across jurisdictions, by providing nationwide, high-quality, population-level health-system