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Improving clinical management of COVID-19: the role of prediction models

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Published Online
January 11, 2021
https://doi.org/10.1016/
S2213-2600(21)00006-0

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A year after the identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its related disease, COVID-19, in the Chinese province of Hubei, one of the most difficult-to-manage modern health-care crises has unfolded worldwide. WHO declared COVID-19 a pandemic in March, 2020, and the epidemiological severity has since been shown by the high incidence of infections, critical cases, and deaths from the disease and, indirectly, by tragic socioeconomic disruption.

The long wait to confirm the epidemiological effectiveness of immunisation against COVID-19, based on a confident estimation of vaccine efficacy and safety, should be accompanied by the retention of preventive interventions (ie, physical distancing, hand hygiene, face masks, ventilation), which have been the only effective measures available until now.

In addition, improvements in the diagnostic and therapeutic management of patients with COVID-19 are needed, including rapid, accurate, point-of-care diagnostic platforms and new effective and safe antiviral and anti-inflammatory drugs. These improvements present a scientifically fascinating challenge given the current scenario of a poor therapeutic armamentarium and suboptimal sensitive molecular tests.

Good clinical management further relies on accurate assessment of patients' prognoses, for which reliable predictive models can be a good scientific base. In *The Lancet Respiratory Medicine*, Gupta and colleagues describe the 4C Deterioration model, which can be used at hospital admission to estimate the risk of death or requirement for ventilatory support or critical care.[1]

The modelling effort by Gupta and colleagues follows an earlier study that tested 22 existing prognostic models and showed that none was of sufficient quality to inform the management of patients with COVID-19.[2] Multivariable prognostic models combine and give appropriate weights to diverse prognostic factors to calculate risks for individual patients, and therefore usually outperform individual risk factors. Surprisingly, the tested models were not more clinically useful than oxygen saturation on room air alone to predict deterioration, or than age alone to predict mortality. The most likely causes for the disappointing predictions are serious methodological flaws and shortcomings of the model development studies, as flagged by a living systematic review of COVID-19 models.[3]

The 4C Deterioration model is of high quality compared with earlier models.[2,3] A key strength is that the model has been developed and validated with a large, multicentre database of consecutive patients (over 66 000 patients for model development and 8000 patients for external validation), and that the authors transparently reported on their analysis process following the TRIPOD guidelines.[4] The model's reported C-statistic of 0·77 indicates that it can discriminate at hospital admission between patients likely and unlikely to deteriorate. Crucially, the authors also illustrate that the model's predicted risks are well calibrated (eg, among 100 patients with a deterioration risk of 10%, ten will deteriorate),[5] and that the model has utility for decision making in clinical practice.[6] The model works well in each of nine National Health Service (NHS) regions across England, Wales, and Scotland after updating to accommodate regional differences.[7]

The careful analysis and good results from external validation suggest that the 4C Deterioration model could be used to support clinicians in the decision to keep a patient in the hospital, admit a patient to critical care, or initiate therapy. However, care must be taken when interpreting the predicted risk: it does not reflect the risk of deterioration in the absence of such an intervention or the risk with an optimal intervention. Although it would be ideal, it is not straightforward to predict the risk of deterioration with and without intervention.[8] Readers and users should keep in mind that the risks predicted by the 4C Deterioration model reflect the probability of deterioration of a patient receiving similar care to that of patients in the development cohort, who were hospitalised in the UK between February and August, 2020. It follows that the risk model is likely to need updates as changes in the infected population and care occur over time. In addition, differences with respect to patient case-mix and care might necessitate local updates before the model can be transported to another setting. Further external validation of the published risk equation

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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Published **Online**
January 22, 2021
https://doi.org/10.1016/S2213-2600(20)30513-0

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