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.

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

data. Although hospital admission rates and mortality were high in both studies during the early stage of the pandemic, mortality declined notably only in England over the study period (March 1 to May 31, 2020). Older age, male sex, and the presence of comorbidities were identified as significant risk factors for inpatient mortality in both studies. In Brazil, the findings suggest that a strained health-care system—indicated by regional differences in access to resources, compounded by overburdened hospital systems—contributed to greater in-hospital mortality during the study period (Feb 16 to Aug 15, 2020, with mortality peaking between March and May). In England, there was a reduction in mortality over time in older patients, particularly those aged 70 years and older. Contextualising these findings related to in-hospital mortality would depend on a number of factors, including socioeconomic status, ethnicity, and literacy, as well as other community and in-hospital factors (figure), which neither study fully addressed.

Social determinants of health contributed to differential mortality rates in both countries. In Brazil, although older age portended high mortality—greater than 55% in those older than 70 years—mortality was 12% in patients younger than 40 years. Comparing death rates across populations is difficult, but this figure is unexpectedly high compared with previously published data for this age demographic, including the findings from England, which show 2·9% mortality in those younger than 40 years. In the Brazilian study, there were higher death rates in those who were illiterate, those located in the resource-limited North and Northeast regions of Brazil, and those who identified as Black or Brown. By contrast, in England, deprivation scores had only a modest effect on inpatient mortality, and only Asian ethnicity was associated with increased in-hospital mortality. It is possible that socioeconomic status and other factors might have a different role across different jurisdictions, dependent on the adequacy of and access to the health-care system.

The high death rate during the initial phase of the pandemic in both countries might have been due, in part, to the high prevalence of SARS-CoV-2 infection throughout the community, with initial low levels of physical distancing and mask wearing before such practices became more widely adopted, leading to more severe disease in the setting of potentially greater viral inocula or multiple-hit exposures.[3] In addition, host genetic factors could have contributed to the high age-specific infection fatality rates.[4,5]

England's temporal mortality reductions in older adults across the early pandemic were impressive, with more than a 50% decrement in patients older than 80 years. Although the magnitude of this trend might seem difficult to explain, a study from the UK showed an 11·8% reduction in adjusted 28-day inpatient mortality over time for critically ill patients, with fewer intensive care unit admissions for those aged 75 years and older.[6] This raises the possibility that older adults might have remained in the community longer earlier in the pandemic, perhaps not reaching the hospital. For example, it appears that patients residing in care homes might have been less likely to be transported to a hospital setting, potentially accounting for a portion of the high mortality seen in care homes during the peak of the pandemic.[7,8] Additionally, improvements in in-hospital mortality over time might reflect decreased strain on hospital systems and changes in clinical practice as providers learned how best to manage the disease.

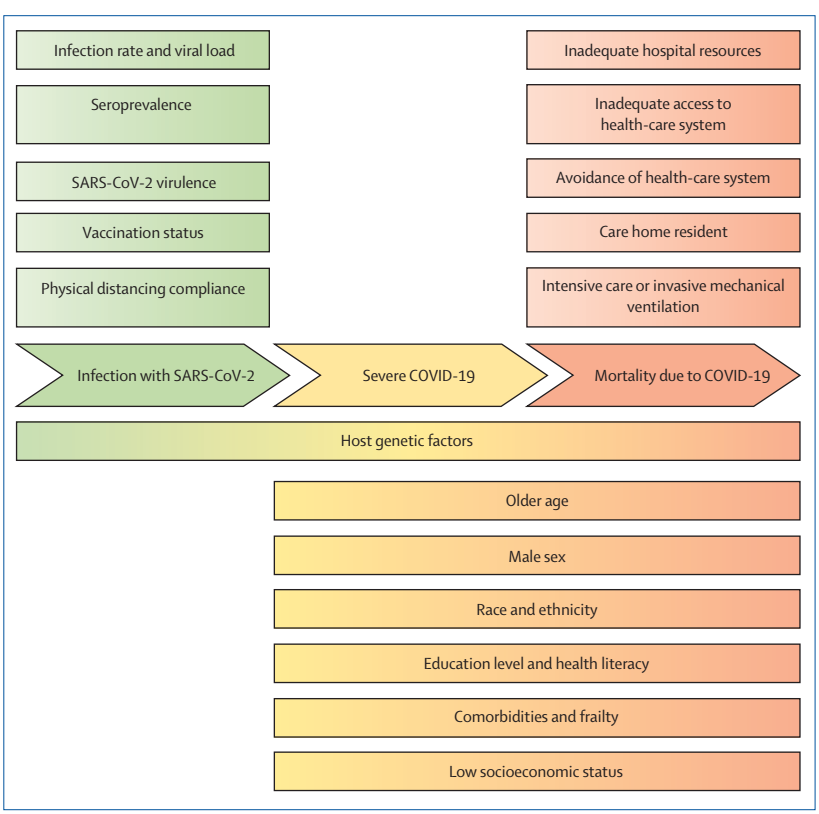

Figure: **Risk factors associated with transmission of SARS-CoV-2 and the development of severe COVID-19 leading to in-hospital mortality**

Both studies highlight the importance of ascertaining the true prevalence of COVID-19 in the community to obtain accurate rates of morbidity and mortality. Even the perception of a strained health system can lead to unintentional excess deaths, from COVID-19 and other conditions, because individuals might avoid seeking care until later stages of disease or might die at home, leading to underestimates of the true mortality burden attributable to COVID-19. Cultural preferences related to treatment intensity, social determinants of health affecting the ability to access health care, health literacy, and implementation and adherence to public health policy standards all affect community trends in disease morbidity and mortality, and need to be considered in the interpretation of in-hospital mortality data.

Future studies should focus on linking community SARS-CoV-2 seroprevalence data, community viral load (for example, using wastewater-based screening), COVID-19 surveillance data, patient viral load data, and the role of nosocomial transmission from health-care workers acquiring infection in the community with hospital admission outcomes to model the progression of the pandemic and determine the concurrent infection fatality risk.[5,9,10] For example, in areas of high community transmission and high coinciding hospital admission and death rates, interventions to improve self-quarantining, health literacy, access to health care and full protective equipment, and frequent testing for hospital staff (to prevent nosocomial infection) could be prioritised and implemented. To be successful, this approach, in turn, would need better understanding of community transmission dynamics. As we continue to battle COVID-19, identifying high-risk patients in hospital and community settings will be crucial, as will insights from population-based studies, helping to focus our community-based and hospital-based public health initiatives.

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Use of point-of-care testing for respiratory viruses in hospital

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In *The Lancet Respiratory Medicine*, Tristan Clark and colleagues report the results of a randomised controlled trial of point-of-care testing for influenza in patients in two UK hospitals in Hampshire, UK.[1] Before the emergence of COVID-19, influenza was the most important cause of admission to hospital with a respiratory virus. In England, influenza is estimated to have caused an average of 11 300 deaths per year between the 2015–16 and 2019–20 influenza seasons.[2] Influenza often goes undiagnosed in hospital, in part because of an absence of routine testing of patients with respiratory illness in this setting. For example, a study from Canada found that only around a quarter of patients with hospital admissions due to influenza