

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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

For the **PRAISE score online**

calculator see https://praise.

hpc4ai.it

colleagues must be congratulated for developing a comprehensive and well designed score for integrating thrombotic and bleeding risks in patients with ACS. Compared with previous scoring approaches (appendix), the PRAISE score is based on one of the largest study populations and shows superior performance when externally validated. The variables included in the score are easily accessible from patient discharge information. Therefore, the score is simple, intuitive, and easy to implement in everyday clinical practice, also thanks to the PRAISE score calculator available online. Of note, previous scores have often been derived from cohorts of patients admitted for both stable coronary artery disease and ACS.⁴⁻⁶ As these two clinical entities are likely to be associated with different risk profiles, the training and validation of the PRAISE score on cohorts of only patients with ACS should be considered as an additional strength. Although the ability of machine learningbased models to overcome limitations of traditional regression-based risk prediction systems remains a subject of debate, D'Ascenzo and colleagues' study⁷ does not allow conclusions to be drawn in this regard, since a comparison with conventional statistical models is lacking.8-11

The study of D'Ascenzo and colleagues surely represents a considerable step forwards in enhancing the risk stratification of patients with ACS. Nevertheless, some caution must be applied when analysing the results. There might be confounding by indication due to the observational design of the derivation cohorts. Also, the prediction of events based on clinical features (eg, age, haemoglobin concentration, eGFR, and LVEF) that correlate with both outcomes (ie, ischaemia and bleeding events) might mean that the model does not always lead to therapeutic decisions that ultimately improve prognosis. Whereas the PRAISE models were

derived on a heterogeneous cohort including patients from five continents, validation was done on patients mainly enrolled from Italian centres. Therefore, further validation on additional cohorts remains desirable. Finally, the effectiveness of the PRAISE score in improving patient outcomes should be prospectively tested in randomised controlled trials.

We declare no competing interests.

*Christian Templin, Davide Di Vece

christian.templin@usz.ch

University Heart Center, Department of Cardiology, University Hospital Zurich, 8091 Zurich, Switzerland

- Ducrocq G, Schulte PJ, Budaj A, et al. Balancing the risk of spontaneous ischemic and major bleeding events in acute coronary syndromes. Am Heart J 2017; 186: 91–99.
- 2 Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000; 284: 835–42.
- 3 Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004; 291: 2727–33.
- Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016; 67: 2224–34.
- 5 Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016; 315: 1735–49.
- Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017; **389**: 1025–34.
- D'Ascenzo F, De Filippo O, Gallone G, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. *Lancet* 2021; **397:** 199–207.
- Motwani M, Dey D, Berman DS, et al. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J* 2017; **38:** 500–07.
- Tokodi M, Schwertner WR, Kovács A, et al. Machine learning-based mortality prediction of patients undergoing cardiac resynchronization therapy: the SEMMELWEIS-CRT score. *Eur Heart J* 2020; **41:** 1747–56.
- 10 Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. J Clin Epidemiol 2019; 110: 12–22.
- 11 Gravesteijn BY, Nieboer D, Ercole A, et al. Machine learning algorithms performed no better than regression models for prognostication in traumatic brain injury. J Clin Epidemiol 2020; **122**: 95–107.

Long-term follow-up of recovered patients with COVID-19

7

By early January, 2021, COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had resulted in more than 83 million confirmed cases and more than 1.8 million deaths. The clinical spectrum of SARS-CoV-2 infection is wide, encompassing asymptomatic infection, fever, fatigue, myalgias, mild upper respiratory tract illness, severe

life-threatening viral pneumonia requiring admission to hospital, and death.¹ Physicians are observing persisting symptoms and unexpected, substantial organ dysfunction after SARS-CoV-2 infection in an increasing number of patients who have recovered, as previously observed in the SARS outbreak.² However, COVID-19 is a new disease and uncertainty remains regarding the



Published Online January 8, 2021 https://doi.org/10.1016/ S0140-6736(21)00039-8

See Articles page 220

For more on **number of confirmed cases and deaths** see https://coronavirus.jhu.edu/ map.html



3arcroft Media/Getty Images

possible long-term health sequelae. This is particularly relevant for patients with severe symptoms, including those who required mechanical ventilation during their hospital stay, for whom long-term complications and incomplete recovery after discharge would be expected. Unfortunately, few reports exist on the clinical picture of the aftermath of COVID-19.

The study by Chaolin Huang and colleagues³ in The Lancet is relevant and timely. They describe the clinical follow-up of a cohort of 1733 adult patients (48% women, 52% men; median age 57.0 years, IQR 47.0-65.0) with COVID-19 who were discharged from Jin Yin-tan Hospital (Wuhan, China). 6 months after illness onset, 76% (1265 of 1655) of the patients reported at least one symptom that persisted, with fatigue or muscle weakness being the most frequently reported symptom (63%, 1038 of 1655). More than 50% of patients presented with residual chest imaging abnormalities. Disease severity during the acute phase was independently associated with the extent of lung diffusion impairment at follow-up (odds ratio 4.60, 95% CI 1.85-11.48), with 56% (48 of 86) of patients requiring high-flow nasal cannula, non-invasive ventilation, and invasive mechanical ventilation during their hospital stay having impaired pulmonary diffusion capacity.3

These findings are consistent with those from earlier small studies that reported lingering radiological and pulmonary diffusion abnormalities in a sizeable proportion of COVID-19 patients up to 3 months after hospital discharge.^{4,5} Evidence from previous coronavirus outbreaks suggests that some degree of lung damage could persist, as shown in patients who recovered from SARS, 38% of whom had reduced lung diffusion capacity 15 years after infection.²

Although SARS-CoV-2 primarily affects the lungs, several other organs, including the kidney, can also be affected.⁶ Therefore, Huang and colleagues assessed the sequelae of extrapulmonary manifestations of COVID-19. Unexpectedly, 13% (107 of 822) of the patients who did not develop acute kidney injury during their hospital stay and presented with normal renal function, based on estimated glomerular filtration rate (eGFR) during the acute phase, exhibited a decline in eGFR (<90 mL/min per 1.73 m²) at followup.³ However, this finding must be interpreted with caution. Because repeated GFR measurement using a gold-standard technique-such as plasma clearance of iohexol or iothalamate-would presumably have been unfeasible in such a large cohort of patients, GFR-estimating equations, such as that used in the present study, do not enable a sound assessment of renal function, which can be overestimated or underestimated compared with measured GFR.7 Importantly, deep venous thrombosis was not diagnosed in any of the patients who underwent ultrasonography at follow-up.³ This is an encouraging finding, in light of the frequent development of venous thromboembolism in patients with COVID-19 who are critically ill while in hospital.⁶

Even though the study offers a comprehensive clinical picture of the aftermath of COVID-19 in patients who have been admitted to hospital, only 4% (76 of 1733) were admitted to an intensive care unit (ICU),³ rendering the information about the long-term consequences in this particular cohort inconclusive. However, previous research on patient outcomes after ICU stays suggests that several patients with COVID-19 who were critically ill during their hospital stay will subsequently face impairments regarding their cognitive and mental health or physical function far beyond their hospital discharge.⁸

Outpatient clinics that are dedicated to following up on lasting disabilities in the large number of patients who previously had COVID-19 are opening in many hospitals, especially in areas where large SARS-CoV-2 outbreaks have occurred. However, this initiative implies a further burden on the health-care system in terms of human and economic resources, in addition to conventional health-care services. Unfortunately, these clinics are largely unaffordable in most low-income or middle-income countries that have also been severely affected by the COVID-19 pandemic. However, the success of this approach to monitoring and treating patients with COVID-19 who have recovered creates an opportunity to concomitantly conduct integrated multidisciplinary research studies during 1-2 years of follow-up, as is currently happening in the UK and USA.⁹ These studies will improve our understanding of the natural history of COVID-19 sequelae and the factors or mediators involved, and enable us to assess the efficacy of therapeutic interventions to mitigate the long-term consequences of COVID-19 on multiple organs and tissues. This is consistent with the syndemic nature of the COVID-19 pandemic,¹⁰ and has implications for the long-term follow-up of COVID-19 sequelae, which in most instances should be interpreted against a background of an array of non-communicable diseases and social and income inequalities that exacerbate the adverse effects of each of these diseases in many communities.

GR reports personal fees and non-financial support from Alexion Pharmaceuticals Inc, Janssen Pharmaceutical, Akebia Therapeutics, Alnylam, Boehringer Ingelheim, Inception Sciences Canada, Omeros, and Catalyst Biosciences, all outside of the submitted work. MC and NP declare no competing interests.

Monica Cortinovis, Norberto Perico, *Giuseppe Remuzzi giuseppe.remuzzi@marionegri.it

Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 24126 Bergamo, Italy

- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; **395:** 1054–62.
- 2 Zhang P, Li J, Liu H, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res 2020; 8: 8.
- Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; published online Jan 8. https://doi.org/10.1016/S0140-6736(20)32656-8.
- Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res* 2020; 21: 163.
- Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463.
- 5 Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol 2020; 17: 46–64.
- 7 Porrini E, Ruggenenti P, Luis-Lima S, et al. Estimated GFR: time for a critical appraisal. Nat Rev Nephrol 2019; **15:** 177–90.
- Marra A, Pandharipande PP, Girard TD, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. Crit Care Med 2018; 46: 1393–401.
- 9 Marshall M. The lasting misery of coronavirus long-haulers. Nature 2020; 585: 339-41.
- 10 Horton R. Offline: COVID-19 is not a pandemic. Lancet 2020; 396: 874.

Organophosphorus poisoning: the wet opioid toxidrome

In The Lancet, David Steindl and colleagues describe the case of a 44-year-old man who was poisoned by a novichok organophosphorus nerve agent.¹ The man was a passenger on a domestic flight in Russia when he became confused, and vomited and collapsed unconscious; 2 h later, he was hospitalised in Omsk, Russia, and treated for respiratory failure and coma. After transfer by air ambulance to Berlin, Germany, features of the cholinergic toxidrome (ie, small or pinpoint pupils, bradycardia, sweating, and hypersalivation) allowed a diagnosis of organophosphorus poisoning to be made. Assessments done by a doctor from the air ambulance crew before transfer to Germany did not indicate that organophosphorus poisoning had yet been diagnosed or antidotes used. However, atropine was later detected in urine. With administration of antidotes and intensive care at Charité-Universitätsmedizin Berlin, the man made a full recovery.

Organophosphorus compounds inhibit acetylcholinesterase at cholinergic synapses in the CNS, autonomic nervous system, and neuromuscular junctions, causing accumulation of acetylcholine and overstimulation of cholinergic receptors (acute cholinergic crisis).² A diagnosis was made in Germany based on clinical features and severely inhibited cholinesterase activity and was later confirmed by detection of novichok compounds in blood samples (data not in the public domain). This case is exceptionally well documented, showing typical cholinesterase inhibition, neuromuscular dysfunction, and antidote administration.

This case report draws parallels with incidents from 2018 of novichok poisoning in Salisbury and Amesbury in the UK.^{3,4} In Salisbury, a woman and man were found unresponsive in a public place; initially thought to have taken opioids, they were stabilised at the scene by paramedics and taken to hospital. A policeman also became ill; all affected individuals



Published Online December 22, 2020 https://doi.org/10.1016/ S0140-6736(20)32749-5 See **Case Report** page 249