Edited by Dr Anisa Jafar on behalf of the RCEM COVID-19 CPD team

Following from the successful ‘RCEM weekly top five’ series starting in April 2020, this is the fourth of a monthly format for Emergency Medicine Journal (EMJ) readers. We have undertaken a focused search of the PubMed literature using a standardised COVID-19 search string. Our search between 1 January and 31 January 2020 returned 4138 papers limited to human subjects and English language. We also searched high impact journals for papers of interest.

Our team have narrowed down the most interesting, relevant and important of the papers and provided a critical snapshot of five of those we felt most deserved EMJ reader attention. Importantly, we have highlighted not only the main findings from the papers but key limitations and considerations for EM clinicians when interpreting the work. In doing so, we have created an accessible window into what is ready for prime time.

The papers are ranked in one of three categories, allowing you to focus on the papers that are most vital to your practice:

► Worth a peek—interesting, but not yet ready for prime time.
► Head turner—new concepts.
► Game changer—this paper could/should change practice.

This month’s searches were undertaken by the Emergency Medicine Academic Group in Leicester. We look forward to next month’s instalment from our friends and colleagues down the M69 in Coventry.

Development and validation of the ISARIC 4C deterioration model for adults hospitalised with COVID-19: a prospective cohort study

Topic: prognosis

Racing: head turner

Prognostic models for risk of deterioration in acute COVID-19 could inform clinical management decisions, plan appropriate treatment escalation for patients and forecast resource needs for hospitals. This paper from the International Severe Acute Respiratory and Emerging Infecions Consortium Coronavirus Clinical Characterisation Consortium (ISARIC4C) group developed and validated a predictive model for hospital deterioration defined as any requirement for ventilatory support, critical care or death.

Adults (n=74 944) with COVID-19 were prospectively recruited from 260 hospitals in the UK across 9 NHS regions. Of the 66 705 patients included in the multivariable logistic regression model, 31 924 had an in-hospital clinical deterioration, at a median time of 4 days from admission. The ‘4C’ model included age; sex; nosocomial infection; GCS; peripheral oxygen saturation (SpO₂) at admission; whether breathing room air or supplemental oxygen (contemporaneous with SpO₂ measurement); RR; urea; C reactive protein; lymphocyte count; and presence of radiographic chest infiltrates.

The model performed consistently across the eight regions used to derive the score and the validation C-statistic of 0.77 showed promising performance for 4C’s ability to predict deterioration (where a score of 0.5 would have been the equivalent of a coin toss). The model’s performance, participant numbers and robustness of reporting are notable among a plethora of such scores which in the main have been of inconsistent quality.

The study was conducted in 260 hospitals and while most contributed data in order to derive the model, the hospitals in the London region were initially excluded in order to be used to internally validate the model. However, the model has yet to be validated beyond the study. The applicability to low-resource settings is also limited due to reliance of some parameters on blood testing. The 4C utility in the ED would stretch beyond the population it was derived from; therefore, we need to be cautious in adopting and applying it without due consideration of this limitation.

Bottom line

The 4C deterioration model can help predict clinical deterioration of admitted patients—giving an additional factor to use in holistic treatment planning and forecasting resource requirements.

Asymptomatic hypoxia in COVID-19 is associated with poor outcome

Topic: prognosis

Rating: worth a peek

Hypoxia without dyspnoea (the so-called ‘happy hypoxemia’) in COVID-19 has become well recognised; however, outcomes in this group have not previously been defined. This retrospective case series is from an “Infectious Diseases Institute” in Marseille, France. From 3737 admissions, 1712 (46%) were selected as they had complete data for: the presence/absence of shortness of breath on presentation, a CT chest scan, oxygen saturation and outcome. Two-thirds (1107) of the patients did not have dyspnoea on admission, of these a subset (160) had at least one blood gas of which 28% (27/96) had hypoxia (defined as oxygen saturations <=95%) without dyspnoea. These patients did not appear to have good outcomes—the mortality figures in the abstract, suggest that 25.9% died.

There are a number of significant limitations in interpreting this study—namely the lack of information about the 54% with incomplete data. There is no comparative figure given for mortality in the hypoxic dyspnoeic group and there is no clear Consolidated Standards of Reporting Trials diagram of study participants to explain discrepancies in the numbers provided. It is unclear how patients were selected for admission (and thus ended up in the study in the first place). Generalisability is limited, as the included group: was relatively young (only 20% aged >65 years); had low disease severity (only 16% had oxygen saturation ≤95%); and mostly (98.4%) survived. Importantly,
the key mortality figure in the hypoxia without dyspnoea group was not clear from the main result section despite being stated in the abstract.

This study appears to suggest that hypoxia without shortness of breath has a poor prognosis in COVID-19 but the lack of clarity in the data presented seriously limits any definitive conclusions.

Bottom line
In the patient with hypoxic COVID-19, a lack of subjective shortness of breath is not reassuring but more robust evidence is needed to explore this.

What is the relationship between validated frailty scores and mortality for adults with COVID-19 in acute hospital care? A systematic review

Topic: prognosis
Rating: worth a peek
Frailty has been validated as an independent risk factor for outcome in a general intensive care population, but the evidence in COVID-19 is still emerging.1

In this systematic review of 26 papers (until December 2020), the majority of the studies showed that frailty was associated with COVID-19 related mortality in people over 65 hospitalised with COVID-19 illness. However, this was not consistent across all cohorts—with some showing a more complex interaction between frailty and COVID-19 status.

There was little evidence of whether frailty and age should be considered independent risk factors. Furthermore, there was considerable heterogeneity of methods and outcomes with mortality varying from 14% to 65%. Most of the studies included were from Europe (half from the UK) which limits international generalisability. Also, the focus on hospitalised patients means that selection bias is likely to have been introduced into this review if the most frail patients had end of life care delivered in the community rather than being transported to hospital, or indeed remained at home and had good outcomes.

The authors suggest that, on the basis of inconsistent evidence, frailty should not be used as a sole marker of predicting mortality or tool for deciding who would or would not benefit from higher levels of care. Instead, they advocate that it should be used as a part of a holistic assessment to assess prognosis and optimise care.

Bottom line
Frailty assessment should be one part of a holistic assessment, including discussion with the patient/relatives, to determine optimal aims of care for an individual

Targeted rapid testing for SARS-CoV-2 in the ED is associated with large reductions in uninfected patient exposure time

Topic: diagnosis
Rating: worth a peek
Prevention of hospital acquired infection with SARS-CoV-2 by separation of patients with COVID-19 from those with similar symptoms is especially difficult during the period between presentation and definitive diagnosis.2

This study looked at exposure time and resource implications of rapid COVID-19 testing. Hinson et al undertook a retrospective cohort study in three US EDs including 9018 patients. As expected, rapid testing provided results around 6 hours earlier than standard tests. This was associated with a decrease (65%) in exposure time of uninfected patients to other potentially infected patients—a median of 12.6 hours. Ninety per cent of rapid test results were available during the ED stay (compared with just over half with standard tests), allowing appropriate inpatient assignment direct from the ED. Length of ED stay was not clarified in the study; however, it appeared that rapid test results had more potential to be efficiently acted on because they were available in the ED rather than once admitted (which adds the complexity and administration of arranging movement from one ward to another).

Rapid testing was estimated to have prevented 100 000 clinician/patient interactions under isolation precautions. The authors estimated that this translated into cost-savings of US$650 000 in non-reusable personal protective equipment (PPE) alone.

This study presents data only from a single hospital system and the testing criteria shifted though the study period. Furthermore, we cannot be sure of the accuracy of the rapid diagnostic test—this is important given the potential reassurance of a ‘false negative’ rapid test.

Bottom line
Rapid COVID-19 testing in ED could decrease the potential for ED transmission of SARS-CoV-19 infection and save costs of PPE but the risk of false negatives needs weighing up alongside.

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa and the UK

Topic: prevention
Rating: game changer
Vaccination continues to be the bedrock of finally shifting the COVID-19 narrative. The ChAdOx1 nCoV-19 (or ‘AstraZeneca’ as it is informally known) vaccine has been licensed for use following interim analysis of this pooled data set of four ongoing blinded randomised controlled trials (RCTs) from three countries.3

In combination, 23 848 adult patients were included in the study to date. Approximately half of these (from one of the UK studies and the Brazilian study) were included in the efficacy analysis having been offered either 2 doses of the adenoviral vector AstraZeneca vaccine (5807 participants) or 2 doses of the control vaccine (5829 participants). Protection against primary symptomatic COVID-19 >14 days after second dose was found to be 60%–65% (of note this was at the higher end in the Brazilian group whose second dose came at 6 weeks as compared with 12 weeks in the UK group although this was not found to be statistically significant).

Safety data were taken from all four trials with adverse event rate similar between the vaccinated and control groups. Two of three cases of transverse myelitis were reported in the vaccine group, and one of these was considered possibly related to the intervention. All four deaths in the study were considered unrelated to the study itself.

The four trials, while similar, were not the same and widespread criticism of this point has highlighted several aspects. There was variation in the dosing regime in one of the UK trials (included in the efficacy analysis), with some first doses at a lower than standard dose. There was also modification to the timing of the second vaccine dose in the Brazilian trial (again included in the efficacy analysis). Blinding within the four trials was not consistent, inclusion criteria meant limited data on those over 55 years of age and exclusion criteria (while perhaps pragmatic) controversially discouraged those without reliable transport from enrolling hence discriminating against lower socioeconomic groups.
One disappointing feature of this study is the complexity with which the findings are presented, mainly related to differences between the contributing studies, in particular in the varied dosing regimens and timescales. Furthermore, we cannot yet know the duration of effect of this vaccine or its capacity to prevent asymptomatic spread. However, the take home message is that the vaccine appears to confer a level of protection (>50%) to warrant its licencing and also appears to have a good safety profile. On a practical level the AstraZeneca vaccine can be stored at higher temperatures than some of the other vaccines which is welcome news for those in resource-limited settings.

**Bottom line**
The ChAdOx1 nCoV-19 (AstraZeneca) vaccine appears safe to join the armoury in prevention of COVID-19 and its true (and at present lower) effectiveness compared with others awaits further study data.

**Contributors** AJ performed the literature search, TC and ME assembled the team of authors. TC, SE, MH, AM, JoV and DR screened titles in provided literature search and long-listed articles. ME, SE and TC handsearched selected journals. ME sifted the long list and selected articles for inclusion. All authors contributed to writing and editing the final piece.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** JoV declares funding from the National Institute for Health Research (Doctoral Research Fellowship NIHR300901). JoV is an author of the third study reviewed here. Citation screening was collaborative among the whole team. JoV was not involved in the review, appraisal, or final selection of this study.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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Received 25 February 2021
Accepted 27 February 2021
Published Online First 11 March 2021

doi:10.1136/emermed-2021-211373

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