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EMJ COVID-19 monthly top five

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Following from the successful "RCEM weekly top five" series starting in April 2020, this is the first of a monthly format for EMJ readers. We have undertaken a focussed search of the PubMed literature using a standardised COVID-19 search string. Our search between 17th September and 31st October 2020 came up with 3,841 papers limited to human subjects and English language.

Our team have narrowed down the most interesting, relevant and important of the papers and provided a critical snapshot of 5 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, have created an accessible window into pertinent research findings for our busy colleagues during this fast-paced and ever-changing COVID-19 landscape.

The papers are ranked in one of 3 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 "RCEM weekly top five" founders in Manchester and we look forward to next month's instalment by our colleagues and neighbours in Salford.

Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies[1]

Topic: Outcome
Rating: Worth a peek

Arguably the greatest anxiety around the COVID-19 pandemic was ICU capacity for the sickest patients. This welcome meta-analysis including 24 observational cohort studies across Asia (mostly China), 6 countries from Europe and North America looked at outcomes for 10,150 patients.

Overall ICU mortality was 41.6% (95% CI, 34.0-49.7) with the largest dataset (8826) coming from the UK's Intensive Care National Audit & Research Centre. There was a progressive reduction in mortality over time, possibly reflecting the development of nascent expertise, new therapies, and expansion of capacity. Outcomes remained consistent after a sensitivity analyses, even after removing the UK data, a reassuring fact for the international medical community.

There are inevitably shortcomings; uncompleted episodes for a condition with long lengths of stay means incomplete data. Morbidity data is also lacking for survival beyond ICU. Heterogeneity is significant; included papers vary from single centre to national registry data. Most conspicuously absent are references to the antipodean data where an ICU mortality of 22.2% was reported this likely pertains to systems stress but warrants exploration.[2]

We must remember that a summary statistic on overall ICU mortality is highly dependent on what defines ICU care combined with whatever real or perceived barriers to entering higher level care exist in different health economies. Despite this limitation the finding that ICU outcomes improved over time is reassuring.

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Bottom line: ICU mortality rate appears consistent worldwide and as the pandemic progresses, this meta-analysis suggests that it could also be reducing.

Lung ultrasound for the diagnosis of SARS-CoV-2 pneumonia in the Emergency Department [3]

Topic: Diagnosis
Rating: Head turner

This paper from Emanuele et al. offers evidence for using lung ultrasound in the context of COVID-19. The authors conducted a prospective cohort study of patients presenting to the emergency department of an Italian academic hospital. Taking the premise that initial tests for COVID-19 (SARS–CoV-2 reverse transcription polymerase chain reaction, RT-PCR) have an important proportion of false-negative results, the authors sought to assess if combining lung ultrasound with clinical evaluation could facilitate the identification of false-negative RT-PCR results. In the absence of a true gold-standard test initial false negatives were determined by a positive result from a second RT-PCR performed within 72-hours of initial assessment.

They enrolled 228 patients and found that clinical assessment with lung ultrasound had better sensitivity (94.4% vs. 80.4%) and negative predictive values (95% vs 85.2%) than first RT-PCR. They considered positive findings to include: presence of focal/diffuse interstitial syndrome associated with spared areas, subpleural consolidations and irregular/thickened pleural line

The authors argue that the presence or absence of changes consistent with COVID-19 (showing here a higher sensitivity than first RT-PCR) not only influences the care of the patient themselves, but also impact healthcare systems by influencing treatment, infection control measures and quarantine of close contacts.

However, in addition to the lack of a true gold standard test, this study may have overestimated diagnostic accuracy as patients were assessed in an area where those with possible COVID-19 symptoms were cohorted; operators were experienced at lung ultrasound; and non-pre-specified diagnostic criteria were used.

Bottom Line – A patient with an initial negative RT-PCR for COVID-19 with clinical and ultrasound features suggestive of the disease should be considered positive and managed as such.

Risk stratification of patients admitted to hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score [4]

Topic: Prognosis
Rating: Game changer

Knight et al seek to answer the question of what might predict death from COVID-19. The authors derived and internally validated a model to predict mortality in COVID-19 patients admitted to hospital. They used the UK's ISARIC dataset, using data from 57,824 patients admitted to hospitals with COVID-19.[5] The authors utilised logistic regression and machine learning (ML) techniques to derive an algorithm. The logistic regression model was converted into a simplified integer 4C score that can be easily calculated (available at

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https://isaric4c.net/risk/), and the ML model was used as a comparator. Both models deliver a predicted mortality (expressed as a percentage) for an individual patient.

The 4C score performs almost as well as a discriminator as compared to the ML model with an area under the curve of 0.767 (0.760 to 0.773) vs 0.779 (0.772 to 0.785). Whilst the ML model was marginally better, the more usable, simpler 4C score is almost as good as the complicated, difficult-to-deploy ML version.

The authors suggest that the model could be used when making the decision to admit patients. However as it was not derived in a group where patients were considered for admission but rather were already admitted, this means that it may not perform as well in a mixed in/out patient cohort.

Clinical algorithms are typically finally evaluated through external validation studies, which would be good to see, although the pace and scale of the pandemic means that we may see this score entering practice before this final stage.

Bottom line: The 4C score is derived from one of the largest COVID-19 datasets and given the unknown accuracy of clinician gestalt it may be the best predictive algorithm at this stage.

Measuring geographical disparities in England at the time of COVID-19: results using a composite indicator of population vulnerability[6]

Topic: Epidemiology
Rating: Worth a peek

Nicodemo et al created an index to highlight communities in England likely to be more exposed and vulnerable in a pandemic. They used clinical commissioning groups (CCGs) as their geographical level. To build their index of vulnerability, they applied evidence from previous approaches in the literature to identify 15 variables that look at demand and supply-side factors influencing healthcare in a pandemic. They found that 80% of the most vulnerable CCGs are located in the North of England and that there was positive spatial correlation (Moran's I, I=0.155, p=0.00) i.e. bordering CCGs have similar vulnerability scores. There was a positive correlation between their vulnerability index and COVID-19 deaths. Notably however there is no mention of the COVID-19 incidence and thus we cannot comment on whether these death rates are disproportionate to case load.

A limitation of this index is that variables were equally weighted and dichotomised at the mean to create the score. As such, much of the information from the continuous data is lost, although the investigators found similar results when dividing the variables into quartiles. COVID-19 test data was available by hospital and therefore might not always represent the patient's CCG of residence, introducing some inaccuracy.

Nonetheless this paper presents a relevant scoring system which identifies areas at particular risk. Alongside other indicators such a score may guide pandemic preparedness and response and healthcare system strengthening.

Bottom line: This index of vulnerability highlights areas at risk of the effects of the COVID-19 pandemic, helping policymakers identify and target their support during further pandemic waves

Remdesivir for the Treatment of Covid-19 — Final Report[7]

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Topic: Treatment
Rating: Game Changer

The preliminary report on Remdesivir was published in May 2020, showing a reduced recovery time with its use, and resulted in an emergency use authorisation. Whilst never overwhelming, the evidence was deemed enough to add Remdesivir to the COVID-19 treatment box.

We now have the final report of this double-blind randomised placebo-controlled trial of hospitalised COVID-19 patients. 1062 patients were randomised to Remdesivir or placebo. Those receiving Remdesivir had a shorter median recovery time (10 versus 15 days) with a rate-ratio for recovery of 1.29 (95% CI, 1.12 to 1.49) i.e. those using Remdesivir had 1.29 times the rate of recovery as compared to placebo. The authors highlighted a "trend" toward survival benefit with Remdesivir at 29 days however the study does not demonstrate statistical significance.

Controversial aspects to this study included: the repurposing of a phase two to a phase three trial; varying the placebo used across sites; potential crossover in the severity categorisation and a change in the trial's primary outcome measure of mortality at 15 days to 29 days. Most criticism however points at the decision to stop the trial early, denying us more definitive evidence.

Of course, tides do turn, although perhaps never with such speed as we have seen in this pandemic. The coming weeks may see the WHO SOLIDARITY trial halt Remdesivir in its tracks with its own emerging evidence suggesting no evidence of benefit in COVID-19.[8] Pending this full publication, at the time of this writing, WHO have just made a conditional recommendation against the use of Remdesivir in COVID patients[9].

Bottom line: This trial demonstrated some evidence for Remdesivir utility in reducing time to recovery treating hospitalised COVID-19 patients but failed to significantly demonstrate survival benefit

References

1. Armstrong, R.A., Kane, A.D. and Cook, T.M. (2020), Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia, 75: 1340-1349. https://doi.org/10.1111/anae.15201
2. Burrell AJ, Pellegrini B, Salimi F, Begum H, Broadley T, Campbell LT, Cheng AC, Cheung W, Cooper DJ, Earnest A, Erickson SJ. Outcomes of COVID-19 patients admitted to Australian intensive care units during the early phase of the pandemic. *Med J Aust*. 2020 Sep 16;1.
3. Emanuele P, Alberto G, Maria T, *et al.* Lung ultrasound for the diagnosis of SARS-CoV-2 pneumonia in the Emergency Department. *Annals of Emergency Medicine* 2020;**0**. doi:10.1016/j.annemergmed.2020.10.008
4. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, Dunning J, Fairfield CJ, Gamble C, Green CA, Gupta R. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ*. 2020 Sep 9;370.
5. Docherty Annemarie B, Harrison Ewen M, Green Christopher A, Hardwick Hayley E, Pius Riinu, Norman Lisa et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study *BMJ* 2020; 369 :m1985

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6. Nicodemo C, Barzin S, Cavalli N*, et al* Measuring geographical disparities in England at the time of COVID-19: results using a composite indicator of population vulnerability *BMJ Open* 2020;**10:**e039749. doi: 10.1136/bmjopen-2020-039749
7. ACTT-1 Study Group Members, Wulff Madsen L. Remdesivir for the Treatment of Covid-19 - Final Report. *The New England Journal of Medicine*. 2020 Oct 8. https://doi.org/10.1056/NEJMoa2007764.
8. Pan H, Peto R, Karim QA, Alejandria M, Restrepo AM, García CH, Kieny MP, Malekzadeh R, Murthy S, Preziosi MP, Reddy S. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. *MedRxiv*. 2020 Jan 1.doi: https://doi.org/10.1101/2020.10.15.20209817
9. WHO (2020). *WHO recommends against the use of remdesivir in COVID-19 patients*. Available at: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients#:~:text=WHO%20recommends%20against%20the%20use%20of%20remdesivir%20in%20COVID%2D19%20patients,-20%20November%202020&text=WHO%20has%20issued%20a%20conditional,other%20outcomes%20in%20these%20patients. Accessed 23 November 2020

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