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RCEM COVID-19 CPD Journal club
Weekly top 5 papers
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Another week, another top 5! The team has sorted through thousands of papers, and here are the papers that deserve your attention. If you have the head space for ten more fantastic papers check out the Director's Cut. If an interactive live journal club captures your interest then checkout the webinar Tuesdays at 11:00 click here to register.

The following papers have been split into 3 categories that will allow you to focus on those 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 should change practice

Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients by Williamson et al [1]

Topic: Prognosis
Rating: Game changer
Scout: Dr Daniel Darbyshire

First a caveat, this study hasn't gone through peer-review. So, if you still believe that peer- review is the panacea to achieving quality you can wait until it passes this hurdle. This cohort study takes General Practice records for over 17 million patients (that's not a typo) in England linked with in-hospital COVID-19 death data. It therefore attempts to delineate the risk to the general population – as opposed to other studies looking at the risk to those diagnosed with COVID-19, admitted to hospital or intensive care.

The major limitations with the study are related to the quality of general practice data, which is generated over time and is sometimes lacking in demographic data. The in-hospital reporting of COVID-19 deaths is also a relatively new system, the wrinkles of which are still being ironed out. Despite any limitations this study is relevant on two levels. First is getting such a large study completed rapidly using open science principles. This type of study has been a pipe dream for many years, with every conceivable barrier being put in the way, all of which have been bulldozed due to the urgency of the pandemic.

There are too many findings to go into any detail; they can be summarised as: demographic features and medical history (associated with risk of future ill health) are associated with risk of death from COVID-19. Not surprising. Nor is the finding that being male is associated with increased risk – something that has been consistently found in other cohort studies. The finding that being black or Asian is associated with increased risk should give you pause for thought. This was despite controlling for all the factors they could measure, including a national deprivation metric. A lot of studies are looking for genetic factors to try and explain this racial disparity, and without denying that this may be a factor, we may need to look at factors we can't easily measure within society to explain at least some of the difference. The idea that risk of death from a novel pandemic virus is partly explained by racial bias within society, and within healthcare, is an uncomfortable possibility, especially given the demographics of the losses we have suffered working at the frontline of the pandemic.

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Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19 by Liang et al [2]

Topic: Prognosis
Rating: Head turner
Scout: Kirsty Challen

COVID-19 has left clinicians with a conundrum; we don't know who will remain 'happily' hypoxic and who will deteriorate. This retrospective cohort study sought to answer this question. Included were 1590 patients in 575 Chinese hospitals (derivation), & 710 patients (validation). Multivariable logistic regression was used to identify factors predicting critical illness (death, ICU admission, invasive ventilation). 10 variables made up the final model: CXR abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, bilirubin, to give an AUC of 0.88 (95% CI 0.85-0.91) in the development cohort & 0.88 (0.84-0.93) in the validation cohort (compare it with 0.75 for CURB-65).

This isn't a perfect paper - by traditional sample size methods there aren't enough outcomes of interest for the number of variables they assessed, and we can't be sure it will generalise to the UK population - for that we will need the PRIEST study. However in the meantime it gives us some insight into which patients we probably need to be more worried about.

A phased approach to unlocking during the COVID-19 pandemic – Lessons from trend analysis by Stedman et al [3]

Topic: Epidemiology
Rating: Head turner
Scout: Dr Anisa Jafar

The take home messages from this modelling study appear to suggest that the true number of UK people who have already been infected with COVID-19 is 29%; the R-value (number of people an infected person will infect) has moved from 2.8 to 0.8 (between 23rd March and mid April; and, music to our ears, the peak has passed and community immunity will see continuing reduction in cases. However, as much as this is what we want to read, we do need to read with caution. As with any modelling study, assumptions have been made. This study also only considers UK data and UK lockdown/testing data and does not incorporate more recent information from antibody testing. It points at locally tailored easing of lockdown with the implication that places of higher caseload could release quicker as there is less chance of significantly increasing the R-value there. It feels like a good news story, perhaps less for the micro-population of those shielded and at highest risk as their rates of historical infection are (or ought to be at least) lower, and so their release from lockdown poses a challenge. However the story up until mid-April is not the whole picture, reported case numbers are now much higher which will challenge the modelling assumptions. Chasing a moving target is a real issue with these "live" modelling studies. More problematic perhaps is the media reaction to hard numbers associated with a science which needs to be read with more than just a pinch of salt.

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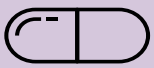
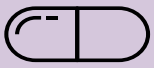
Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial by Hung et al [4]
Topic: Treatment
Rating: Worth a peek
Scout: Dr Anisa Jafar

Comparison of a 2-week course of lopinavir–ritonavir, ribavirin and interferon beta-1b and a control group who were given 2 weeks of lopinavir–ritonavir. The 127 patients were adults admitted to 6 Hong Kong hospitals with confirmed COVID-19, with symptoms for 14-days or less and NEWS2 of at least 1. The idea for the study came from a similar intervention in previous SARS patients. The methods need a bit of concentration to track exactly who got what and when depending how many days of symptoms, sample size was based on SARS mortality data and the control group had somewhat higher co-morbidity (but otherwise were reasonably well-matched). End-points seem to point to quicker reduction in NEWS2/SOFA scores to 0 and quicker time to negative nasopharyngeal swab in the intervention area. There are attempts to draw other conclusions by splitting out the sub-groups who started the treatment earlier and later in symptom history, which appears to increase the signal for negative viral swabs generally. No placebo here, no interferon given if treatment was being started 7 days after symptom-onset, powered for SARS, not tested in critically unwell patients and outcome measures of questionable clinical significance given the caveats… Again, hang fire on stockpiling the interferon, we need a bit more to go on than this relatively small, albeit well-designed but fragmented study.



COVID-19, Clinical Trials and QT-Prolonging Prophylactic Therapy in Healthy Subjects: First, Do No Harm by Gollob [5]
Topic: Treatment
Rating: Worth a peek
Scout: Dr Gaby Prager

The spread and death toll of COVID-19 has spurred the research community into finding potential life- saving treatments. There has been large investment in this, financially and logistically to expedite research. There has been a surge in trials looking at a broad range of patients and treatments. Whilst celebrating the huge amount of work done so far, this article explores the ethics of using known QT prolonging drugs in asymptomatic healthy individuals and discusses the risks and potential criteria that could be used to safeguard individuals moving forward, reminding us to "first do-no harm'.



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Game changer summary

Williamson et al should have our full attention; patients of black and asian ethnicity have a higher risk of death from COVID-19. [1]

In summary

Liang et al tentatively put forward a prediction model for disease severity [2]
Stedman et al tried to make us happy with an R less than 1 [3]
Hung et al tentatively pointed towards interferon being of benefit [4]
Gollob reminded us to be wary of the miracle cure [5]

References

1) Williamson, E., Walker, A.J., Bhaskaran, K.J., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P. and Cockburn, J., 2020. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv.

2) Liang, W., Liang, H., Ou, L., Chen, B., Chen, A., Li, C., Li, Y., Guan, W., Sang, L., Lu, J. and Xu, Y., Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Internal Medicine.

3) Stedman, M., Davies, M., Lunt, M., Verma, A., Anderson, S.G. and Heald, A.H., 2020. A phased approach to unlocking during the COVID-19 pandemic–Lessons from trend analysis. International Journal of Clinical Practice, p.e13528.

4) Hung, I.F.N., Lung, K.C., Tso, E.Y.K., Liu, R., Chung, T.W.H., Chu, M.Y., Ng, Y.Y., Lo, J., Chan, J., Tam, A.R. and Shum, H.P., 2020. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet.

5) Gollob, M.H., 2020. COVID-19, Clinical Trials and QT-Prolonging Prophylactic Therapy in Healthy Subjects: First, Do No Harm. Journal of the American College of Cardiology.