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EMJ COVID-19 Monthly top five

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Title: EMJ COVID-19 monthly top five

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Abstract:

Following from the successful "RCEM weekly top five" series starting in April 2020, this is the second of a monthly format for EMJ readers.[1] We have undertaken a focussed search of the PubMed literature using a standardised COVID-19 search string. Our search between 1st November 2020 and 30th November 2020 came up with 216 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, we 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 a combined Emergency Medicine and Intensive Care group working at Salford Royal NHS Foundation Trust. We look forward to next month's instalment by our colleagues at the Centre for Urgent and Emergency Care Research (CURE), University of Sheffield.

1. Efficacy of tocilizumab in patients hospitalised with COVID-19

Topic: Intervention

Rating: Head Turner

The search for a magic bullet in COVID-19 continues. The end of 2020 saw publication of a trial on the IL-6 antagonist tocilizumab, one of many therapies already being 'compassionately' used off-label, with observational data suggesting benefit. [2-4]

This was a double-blinded, placebo-controlled randomised trial conducted across seven sites in the United States. Hospitalised patients with confirmed SARS-COV-2 infection, clinical inflammatory state and raised inflammatory biomarkers were eligible. Sicker patients with high oxygen requirements were excluded. No patients received dexamethasone therapy. The primary outcome was a composite of progression to invasive mechanical ventilation or death.

The trial recruited 243 patients; baseline characteristics were reasonably matched between intervention and control groups. Only 11.2% of patients achieved the primary outcome at 28-days with no significant difference between intervention and control groups. Regarding safety outcomes, more overall adverse events were seen in the placebo group, although rates of neutropenia were predictably higher with tocilizumab.

There are limitations to this work. The primary outcome event rate was overestimated at 30% in the sample size calculation, which could have led to a Type II error. There were also clear baseline group differences, despite randomisation. Generalizability is limited given recruitment in a single country. However, this is the best evidence to date on tocilizumab and good scientific progress, even though the results may not be what we wished for.

Bottom line:

Tocilizumab did not improve outcome for hospitalised patients with COVID-19 in this study. Further effectiveness trials in specific cohorts are ongoing and subsequent use of tocilizumab should ideally be conducted within a research context.

2. Post-exertion oxygen saturation as a prognostic factor for adverse outcome in patients attending the emergency department with suspected COVID-19: a substudy of the PRIEST observational cohort study

Topic: Prognosis

Rating: Head turner

The value of post-exertion oxygen saturation as a prognostic factor in suspected COVID-19 has been debated. To date, we have seen little scientific evaluation. Steve Goodacre and colleagues from Sheffield have grasped this nettle and report their subgroup findings within a large cohort study in this months EMJ.[5]

This paper presents data for 817 emergency department patients and describes performance of a ≥3% post-exertion oxygen desaturation for predicting adverse outcome (death or organ support within 28 days of Emergency Department attendance). The authors found a relatively poor discriminatory performance, with a c-statistic of 0.59 (95% CI 0.47 - 0.71). Positive and negative likelihood ratios (LRs) were 1.78 (1.25 - 2.53) and 0.67 (0.46 - 0.98), respectively. On multivariable analysis, post-exertion oxygen desaturation was not shown to be a significant predictor of adverse outcome (p=0.37). When patients in whom post-exertion oxygen saturation measurement appeared inappropriate were excluded (baseline oxygen dependency), the c-statistic improved to 0.70 (0.58 - 0.82) with LRs of 1.98 (1.26 - 3.10) and 0.61 (0.35 - 1.07). The former LR suggests a slight increase in the post test probability of an adverse outcome, following post-exertion desaturation. The latter is less useful given the confidence interval spans 1. Both these values are well outside the suggested threshold for a test which moderately affects the post-test probability of disease, at <0.2 (LR-ve) and >5 (LR+ve).[6] The authors suggest there was some evidence of additional prognostic value on multivariable analysis (p=0.02).

There are other limitations to this work. There was no comparison between patients with and without post-exertion desaturation and only 5% of 22,000 patients within the entire PRIEST cohort had this data recorded. However, this post hoc analysis evaluated approximately 10% of the eligible (discharged) study population (7,260).

Bottom line:

Post-exertion oxygen desaturation may provide modest prognostic information in the assessment of selected patients attending the emergency department with suspected COVID-19.

3. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study

Topic: Health worker occupational risk in COVID-19
Rating: Head turner

The potential increased risk to healthcare workers during this pandemic and the consequent impact on morale/mental health has been widely discussed. This paper aims to quantify some of this risk, using high quality routine data collection.

The authors link databases containing clinical information (virology for SARS-CoV-2, hospital admissions, critical care admissions and deaths) with healthcare workforce databases for all of Scotland.[7] They also identified people sharing a household with a healthcare worker. They subsequently compare these groups with the general population using data derived from an existing case-control study, in order to estimate the comparable risk of admission to hospital with COVID-19.[8]

The study included 158,445 healthcare workers and 229,905 household member contacts. The results are certainly head turning: healthcare workers and their household contacts comprise a staggering 17.2% of all hospital admissions for COVID-19 in the working age group (18 to 65), despite representing only 11.2% of this population and having access to personal protective equipment (PPE). The overall risk of admission to hospital with COVID-19 was 0.20% in patient-facing workers and 0.07% in non-patient facing roles. After adjustment for multiple factors, the increased admission risk for patient facing healthcare workers is summarised by a hazard ratio of 3.30 (95% CI 2.13 to 5.13).

This study was limited to working age people, reflected in the hospitalisation rates. That said, the results are an important reminder of the need for PPE vigilance, a topic recently highlighted by RCEM.[9]

Bottom line:

This study suggests patient facing healthcare workers and their household members have a significantly increased risk of hospitalisation with COVID-19 (despite current PPE precautions), compared to a matched cohort of non-patient facing healthcare workers.

4. Treatment of out-of-hospital cardiac arrest in the COVID-19 era: A 100 days experience from the Lombardy region

Topic: Epidemiology
Rating: Worth a peek

This observational analysis of out-of-hospital cardiac arrest (OOHCA) data in one of Italy's areas hardest hit regions during the early months of the pandemic provides interesting insight into the wider impact of COVID-19 on other healthcare conditions.

The authors compared 2020 data to the same 100-day period in 2019, looking principally at the first links in the chain of survival for OOHCA. [10] More arrests were seen in 2020 despite lockdown measures, with 694 events compared to the 520 in 2019.

More arrests occurred at home (90% vs 81% p<0.001) and sadly, they were more likely to be unwitnessed (50% vs. 42% p=0.002). Worse still, the rate of bystander CPR was also lower in 2020 (24.5% vs 35.7%, p <0.001) and the rate of attempted resuscitation by medical response team was significantly reduced (64.5% vs. 72% p=0.008). Not surprising therefore, the return of spontaneous circulation (ROSC) rate was lower in 2020 (11% vs. 20% p=0.001). Using medical records, the authors estimate that 20% of OOHCA patients had suspected or confirmed COVID-19 at the time of CPR. This did not appear to affect the delivery of resuscitation by medical teams and was not an independent predictor of ROSC on arrival at hospital.

The data stops there but the discussion highlights genuine fears about the peripheral impact of this pandemic on other reversible medical conditions. Principally, that a fear of contracting COVID-19 reduces bystander intervention and this is compounded by increased social isolation reducing the potential for early CPR.

Bottom line:

Despite higher rates of OOHCA during the initial wave of the COVID-19 pandemic, patients were less likely to receive bystander CPR and less likely to achieve ROSC.

5. A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia

Topic: Epidemiology

Rating: Worth a peek

Convalescent plasma has been used to treat infectious diseases previously and has face validity in COVID-19. Early reports and observational studies describe improved outcomes.[11] [12] However, healthy scepticism and patience for trial data are to be encouraged during this pandemic, for a variety of reasons.[13]

Fortunately, the PlasmAr study group have now conducted a randomised, double-blinded, placebo-controlled, multi-centre trial.[14] Hospitalised adult patients with COVID-19 and hypoxia (SpO2 <93% on room air) or an elevated SOFA score were randomised in a 2:1 ratio to convalescent plasma or placebo, with a total of 334 participants recruited. A single patient withdrew consent. The primary outcome focussed on clinical status at 30 days post intervention, measured using a 6 point ordinal scale.

Disappointingly, no significant difference was seen in the distribution of clinical outcomes between the convalescent plasma and placebo groups, in either the whole population or multiple pre-specified subgroups. The 30 day mortality was 10.96% and 11.43%, respectively. Antibody levels for SARS-CoV-2 were higher in the convalescent plasma group at day 2 but were equivalent between groups at days 7 and 14.

There were significant baseline differences that may have impacted on outcomes, such as gender and more respiratory comorbidity in the plasma group. The median onset time of hypoxia and inclusion criteria also mean these findings cannot be extrapolated to earlier diagnoses and milder cases. However, these results do not support on-going use outside a research context.

Bottom line:

The use of convalescent plasma in this trial did not show any significant benefit to patients with severe COVID-19.

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