COVID-19 Literature Review Newsletter Volume #37
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Articles:

Background:
- The clinical features and outcomes of COVID-19 in immunosuppressed patients are not well characterized.
- The immunocompromised population are at presumed risk for more severe disease
- However, perhaps the clinical state of immunosuppression may actually temper the inflammatory response associated with COVID-19 leading to less severe disease

Methods:
- Reviewed the existing literature on COVID-19 among immunocompromised populations ranging from cancer patients and solid organ transplant recipients to patients with HIV and those receiving immunomodulatory therapy for autoimmune disease

Results:
- Solid Organ Malignancy
  - High rates of comorbidities (hypertension, diabetes, heart disease, chronic kidney disease) known to be associated with severe disease
o Healthcare exposure was a significant risk factor for COVID-19 disease
o Increased risk for severe outcomes including intubation and death after adjusting for other COVID-19 risk factors
o Subgroups that had disproportionately high mortality from COVID-19: lung cancer (Case Fatality Rate (CFR) 18-55%) and hematologic malignancy (CFR 33-41%)
  o Recent active therapy for cancer (including immunotherapy and tyrosine kinase inhibitors) was associated with worse outcomes

- Hematologic Malignancy
  o Active malignancy and poor ECOG were independent predictors of mortality
  o The largest study included 35 hematologic patients (U.K.), 69% receiving active chemotherapy at the time of COVID-19 diagnosis and 40% died
  o Few SCT patients included, the overall CFR in the literature is 27%, observed to be lower than hematologic malignancy patients in general
  o Milder clinical courses after ibrutinib and pembrolizumab (based on a few case reports)
    ▪ Perhaps decreased Bruton’s tyrosine kinase Toll-like receptor and cytokine signaling may temper illness due to SARS-CoV-2.

- Solid Organ Transplant
  o Most existing literature consists of case series, case reports, and surveys from China, Spain, Italy, Netherlands, Iran, and the U.S
  o Comorbidities were highly prevalent.
  o High rates of complications (including mechanical ventilation), 39% in a New York City study and 75% in an Iran study (renal transplants)
  o Mortality ranged widely from 5-67%, potentially reflecting geographical differences in case number and available hospital resources
    ▪ Largest study of 90 SOT recipients (kidney, lung, liver, heart, heart kidney) from New York City reported a mortality rate of 18%.
  o Mainstay of treatment: decreased immunosuppression (range 43-100%)
    ▪ 90% held antimetabolite therapy and 70% held calcineurin inhibitor therapy

- Medications:
  o Biologics for IBD: based on 3 case series, not associated with worse outcomes or increased risk of COVID19
  o Biologics and JAK Inhibitors for Rheumatologic Disease: based on 6 large cross-sectional survey studies, associated with a lower odds of hospitalization (OR 0.46), largely driven by anti-TNF therapies
  o Anti-CD20 Ab: based on 5 case reports, no evidence of increased risk of severe COVID-19

- Primary Immunodeficiency: one small case series, more severe course in CVID vs agammaglobulinemia; perhaps related to the role of B cells in the inflammatory response
- HIV: multiple case series, most were well controlled (75-100% with CD4 >200 cells/µL, median CD4 305 to 1068 cells/µL), 25 to 100% of patients hospitalized and 11-56% required ICU care, mortality rate ranged between 0 and 28% in most studies

Conclusions:
- Immunocompromised patients seem to have typical clinical manifestations of COVID-19
- Cancer patients, and particularly those with lung cancer and hematologic malignancy, and SOT appear to be at higher risk for severe COVID-19 disease and mortality
  o A significant proportion of the patients in the literature had nosocomial acquisition
- Biologics may not be at higher risk for severe disease based on current data
- Inconclusive regarding whether HIV infection imparts a higher risk of severe disease.
- Further prospective, controlled studies are needed to determine the attributable risk of immunocompromising conditions and therapies on COVID-19 disease prognosis.

Limitations:
• Unclear inclusion/exclusion criteria for their methodology or number of articles reviewed
• Most of the literature to date consists of case reports, case series, and cohort studies, all of which have many potential sources for bias
• Did not evaluate for health care disparities or access to healthcare resources in determining outcomes

2. **Cruz et al.** Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study. *Antimicrobial Agents and Chemotherapy.* June 16th, 2020. [https://aac.asm.org/content/early/2020/06/16/AAC.01168-20](https://aac.asm.org/content/early/2020/06/16/AAC.01168-20)

**Background:**
• Use of steroids has been proposed in treatment regimens of COVID-19 to reduce mortality
• Insufficient evidence exists to support this claim and use is controversial.

**Methods:**
• Single center, retrospective, cohort study at a tertiary hospital in Madrid, Spain between March and April 2020.
• Inclusion: Adults with COVID-19 pneumonia with ARDS & hyperinflammatory syndrome
• Treatment groups: steroid treatment cohort (any steroid regimen) and control cohort.
  o Decision to use steroids or other COVID-19 therapies was determined by the treating physicians.
• Primary endpoint was in-hospital mortality, survival times compared using log-rank test
• Propensity score matching completed to reduce effect from selection bias. Another propensity score developed to adjust for choice of initial steroid regimen.

**Results:**
• 463 patients met inclusion criteria: 396 in steroid cohort, 67 in control cohort.
• Median time to use of steroids was 10 days.
  o 310 (78.3%) patients initially treated with 1mg/kg/day or equivalent of methylprednisolone while 86 (21.7%) received pulse steroids.
• Overall in-hospital mortality was 15.3%.
• Steroid use lowered in-hospital mortality compared to controls (13.9% vs 23.9%, HR 0.51 [0.27-0.96], p=0.044). After propensity matching, the difference persisted.
• No difference in in-hospital mortality in patients receiving 1 mg/kg/day of methylprednisolone vs steroid pulse regimens (13.5% vs 15.1%, OR 0.880 [0.449-1.725], p = 0.710)
• Older age, CKD, high LDH were independent risk factors for mortality. No difference in mortality between pulse dose and other group.

**Conclusion:**
• Steroid use may reduce mortality rates in patients with severe COVID disease
• Limitation: Single center study which may not provide external validation, selection bias and other confounders may play a significant role despite propensity matching and adverse effects of treatment were not studied.


**Background:**
• Long-term impact of COVID-19 in symptomatic individuals is unknown
• Aim: assess persistent symptoms in patients who were discharged from the hospital after recovery from COVID-19

**Methods:**
• Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy established an outpatient service for individuals discharged from the hospital after recovery
  o Conducted from April 21st- May 29th, 2020
Confirmed recovery was based on SARS-CoV-2 PCR negative

Clinical characteristics including symptoms and quality of life were assessed on included patients

Results:

179 eligible patients, 14 refused to participate, 22 had positive SARS-CoV-2 PCR test

- 143 patients were included in the analysis
- Mean age 56.5 years (range 19-84 years), 37% were women, 35% had hypertension and 10.5% active smokers, otherwise minimal co-morbidities
- Mean length of hospital stay 13.5 days
- 18 (12.6%) required ICU admission, 21 (15%) received non-invasive ventilation, 7 (5%) received invasive ventilation

Patients were assessed a mean 60.3 days after onset of first COVID-19 symptoms. At follow up:

- 18 (12.6%) were free of COVID-19-related symptoms
- Persistent reported symptoms: 53.1% fatigue, 43.4% dyspnea, 27.3% joint pain, 21.7% chest pain
- 44.1% reported worsened quality of life after hospitalization for COVID-19

Conclusions:

- At a mean 36 day follow up from hospitalization (60 days from onset of symptoms): 87.4% of patients reported persistent symptoms (mostly fatigue and dyspnea) suggesting long recovery times after COVID-19
- Limitations: small study, representing one region of the country, cases represented more mild-moderate disease (only 5% received invasive ventilation), short follow-up period.

Additional Resources:
3. 