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Utilizing the National COVID Cohort Collaborative to Evaluate Risk of Serious Outcomes with COVID-19 Among Chronically Immunosuppressed Persons

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Disclosures

- **No direct funding was received for this work.**

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  - Dr. Garibaldi is a member of the Food and Drug Administration Pulmonary and Asthma Drug Advisory Committee and a consultant for Janssen Research and Development, LLC.
  - Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee.

There are plausible mechanisms by which chronic immunosuppressive drugs could affect COVID-19 outcomes while hospitalized.

Beneficial?

May prevent hyperinflammatory response

Harmful?

Consistently identified as risk factor for infection

Emerging evidence does not suggest strong association

- Others have reported nonsignificant effects or small hazardous effects.
- No increased risk noted in MERS or SARS (2003) coronavirus outbreaks.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Association Between Chronic Use of Immunosuppresive Drugs and Clinical Outcomes From Coronavirus Disease 2019 (COVID-19) Hospitalization: A Retrospective Cohort Study in a Large US Health System

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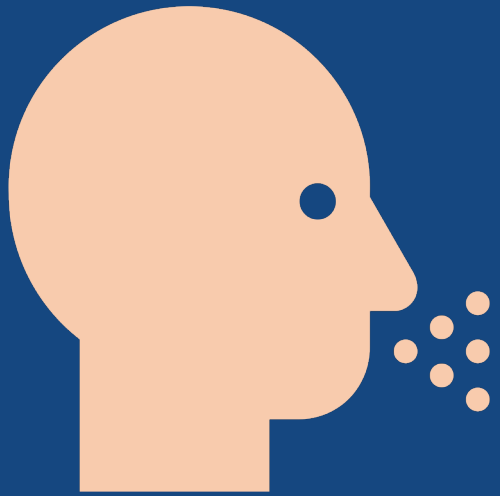
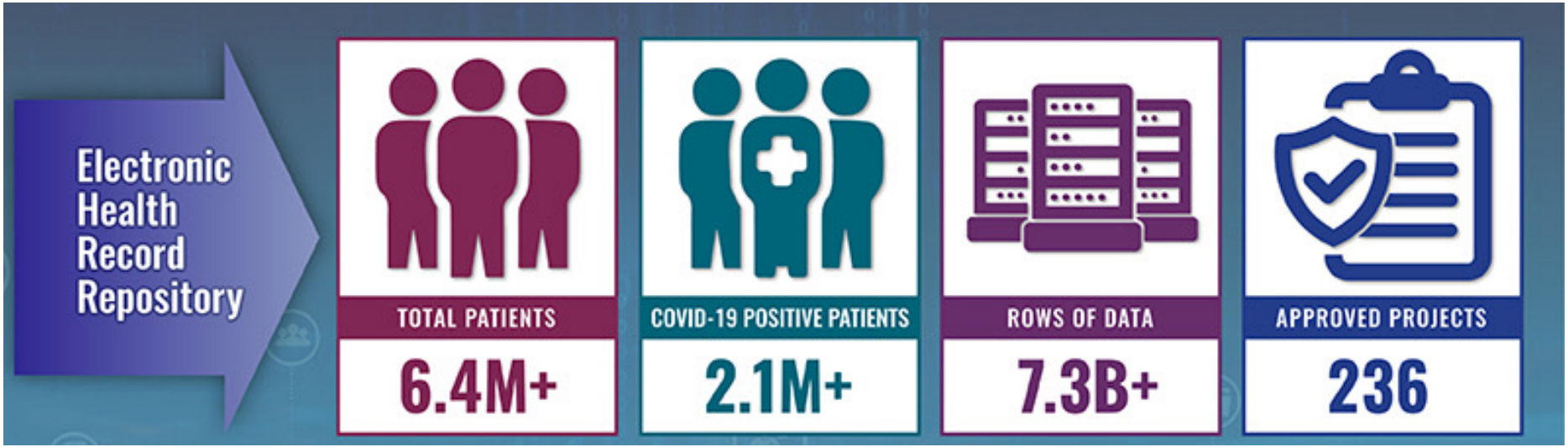


There is mixed evidence regarding the impact of immunosuppression and immunosuppressive medicines on COVID-19 outcomes.

It is further unclear whether associations vary by medication class.

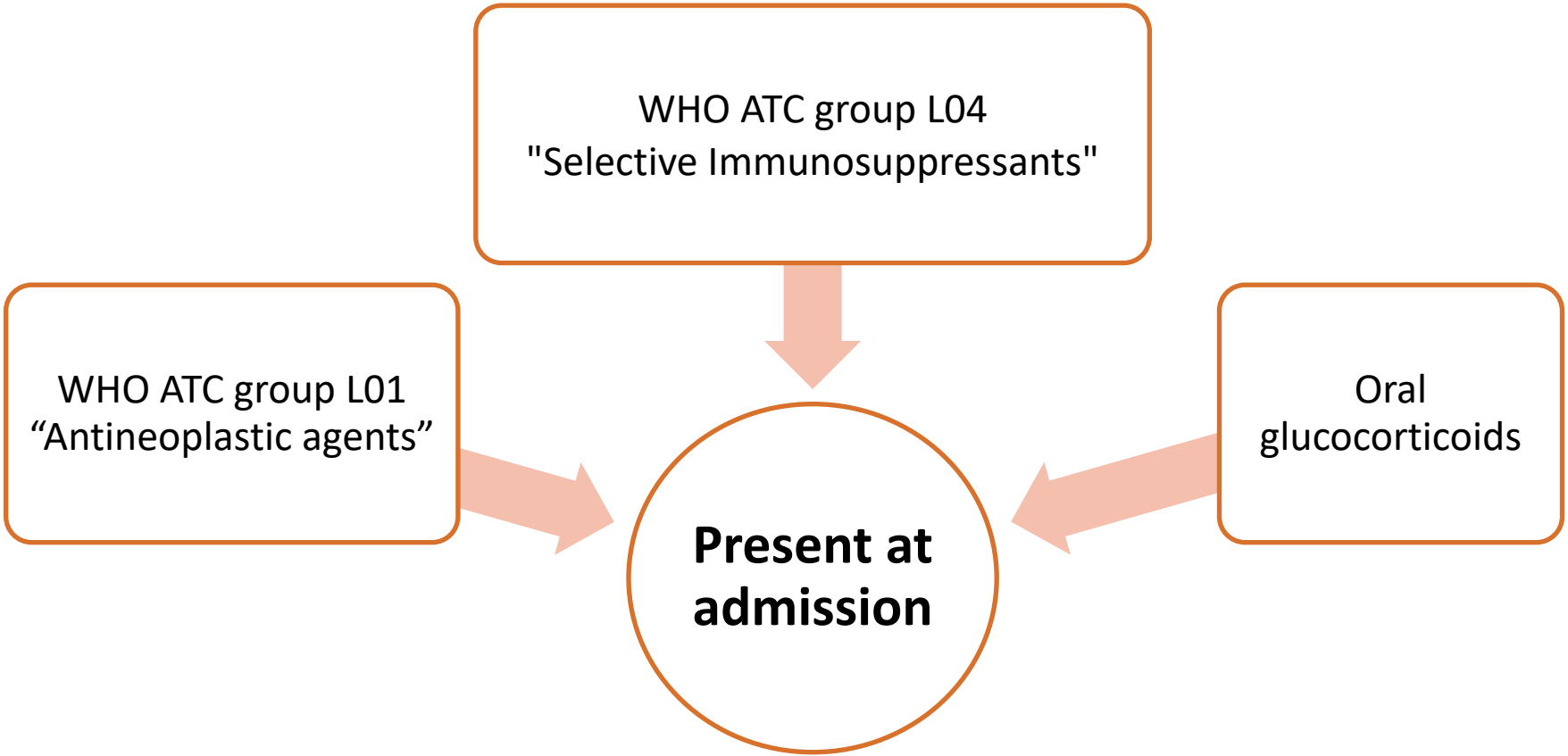
Study Design and Population

We conducted a retrospective cohort study using the National COVID Cohort Collaborative (N3C).



Our cohort was 222,575 adults hospitalized with COVID in 42 health systems in the United States from January 2020 – June 2021.

Exposure


WHO ATC group L04
"Selective Immunosuppressants"
WHO ATC group L01
“Antineoplastic agents”
Oral
glucocorticoids
Present at admission

Exposure - Pharmacologic subclasses

Select rheumatologic drugs

- Interleukin inhibitors
- Janus kinase inhibitors
- Tumor necrosis factor alpha inhibitors
- Others, like sirolimus and leflunomide

Antimetabolite drugs

- Azathioprine
- Calcineurin inhibitors
- Mycophenolic acid

Cancer therapies

- Anthracyclines
- Checkpoint inhibitors
- Cyclophosphamides
- Protein kinase inhibitors
- Targeted cancer therapies
- Others, like cisplatin and vincristine

Rituximab

- Rituximab with autoimmune diagnosis
- Rituximab with cancer diagnosis

Oral glucocorticoids

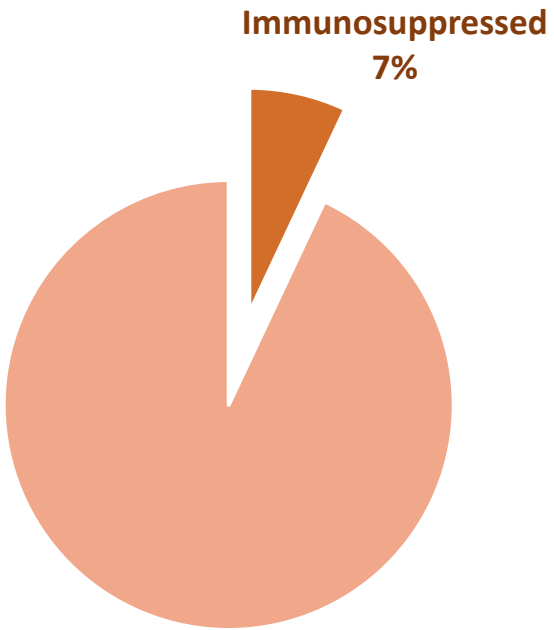
Outcomes

 Invasive mechanical ventilation	Fine and Gray's proportional subdistribution hazards models, with the competing risk of death
 In-hospital death	Cox proportional hazards models

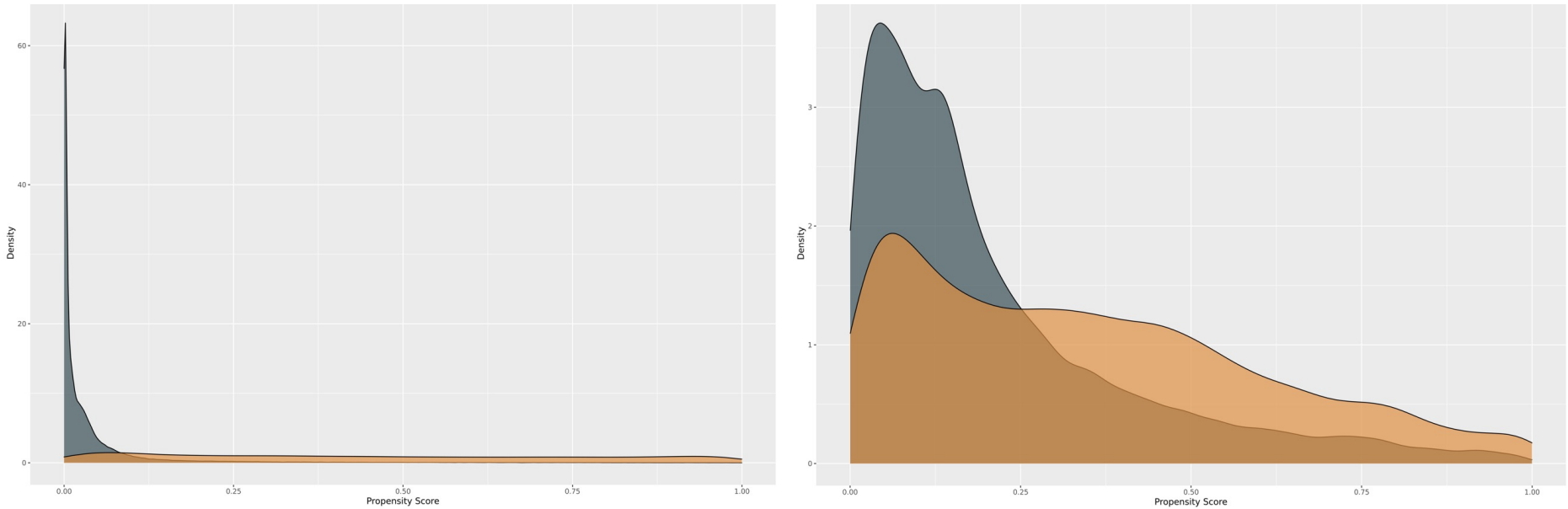
We truncated the 1st and 99th percentiles of the propensity score, and used 4:1 nearest neighbor matching with a tight caliper. We implemented doubly robust adjustment for remaining imbalances.

Descriptive statistics of immunosuppressed adults

- Most frequent: prednisone, tacrolimus, mycophenolate mofetil
- Comparatively older (mean age 61 vs 59 years)
- More often female (56% vs 49%)
- Less likely to be Hispanic or Latinx
- Greater prevalence of comorbidity



Propensity score distribution before and after matching



Overall effects of any immunosuppression

Reduced risk of mechanical ventilation

9% vs 6% in unadjusted analyses

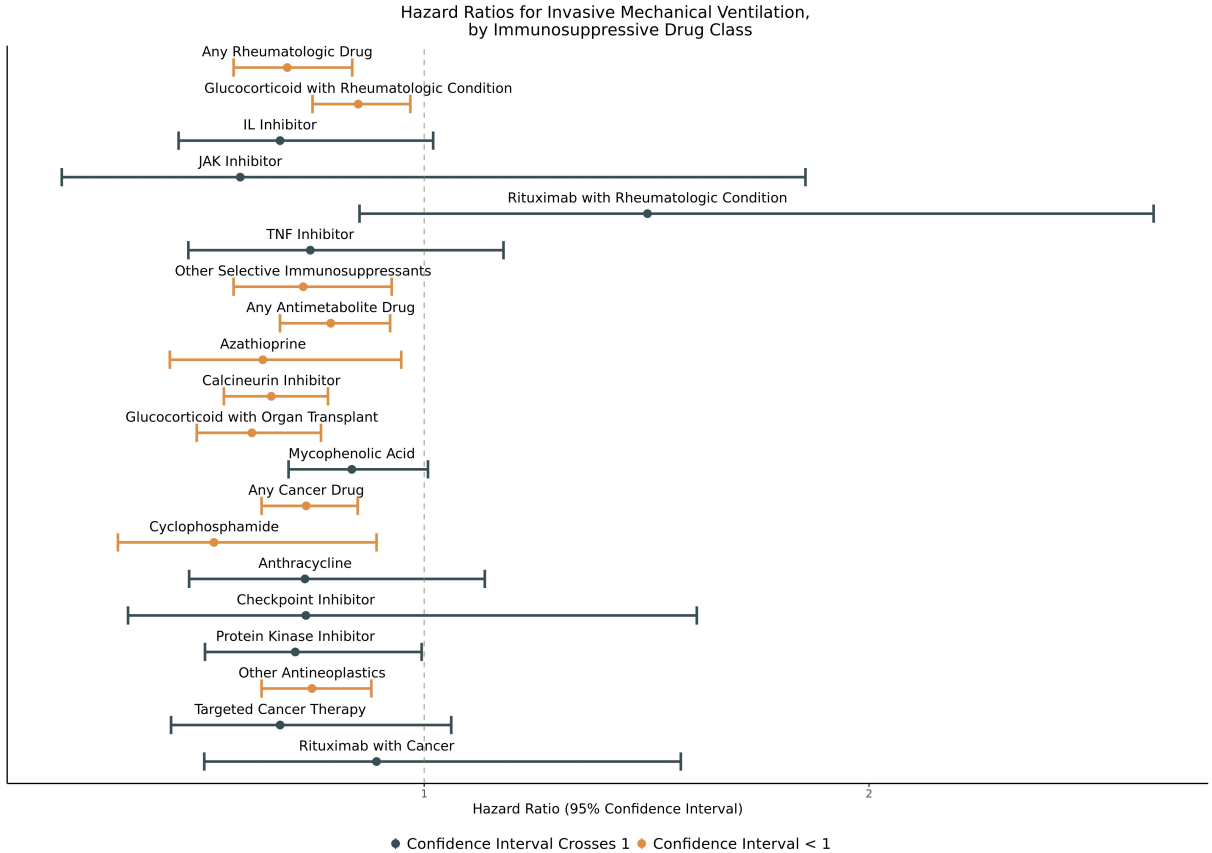
In matched cohort: **HR 0.89 (95% CI 0.83-0.96)**

No differences in risk of in-hospital death

14% vs 9% in unadjusted analyses

In matched cohort: HR 0.97 (95% CI 0.91-1.02)

Risk of mechanical ventilation



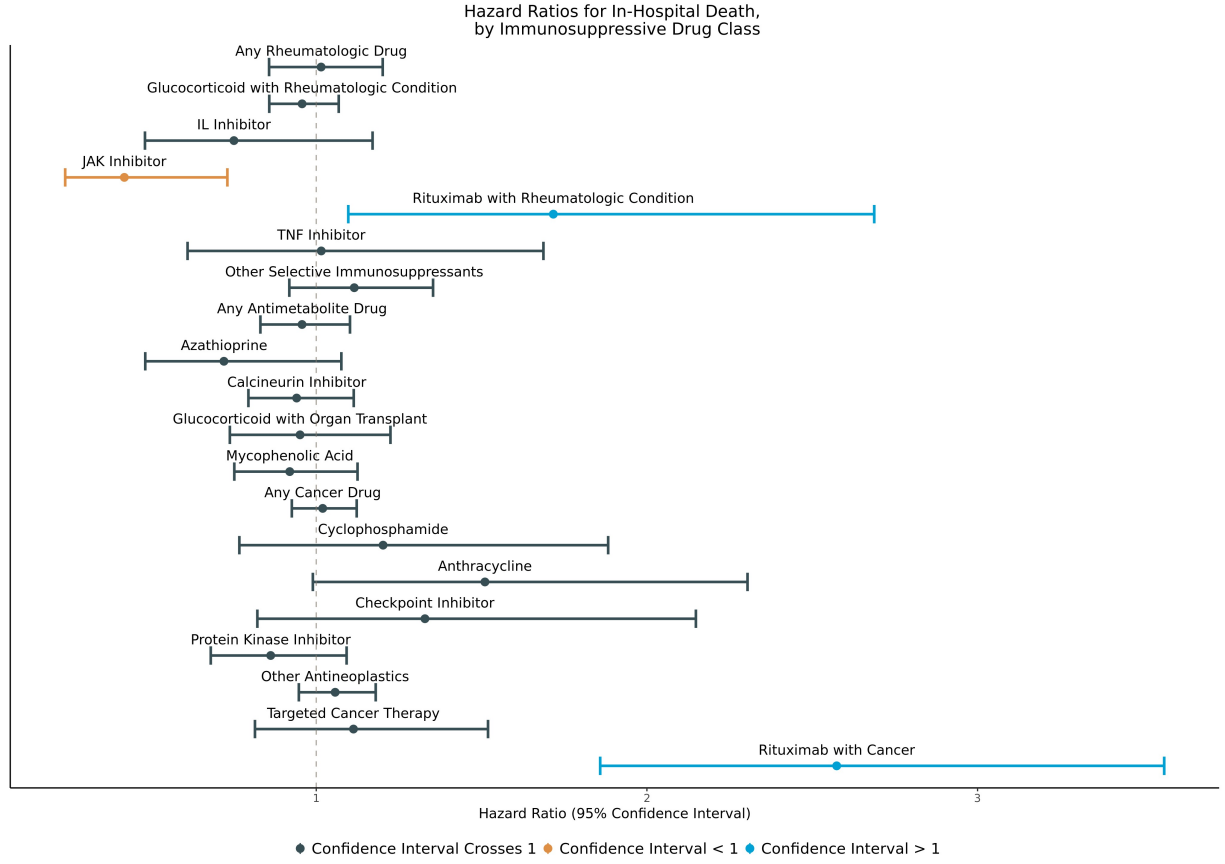
None of the classes were associated with an increased risk of invasive ventilation.

Several classes had non-significant effects.

Decreases noted with:

- **Glucocorticoids**
- **Calcineurin inhibitors**
- **Cyclophosphamide**
- **Some selective immunosuppressants and some antineoplastics**

Risk of death



Decreased risk of noted with janus kinase inhibitors.

Most classes had non-significant effects.

Rituximab was associated with large increase in risk of death.

Results of sensitivity analyses generally consistent

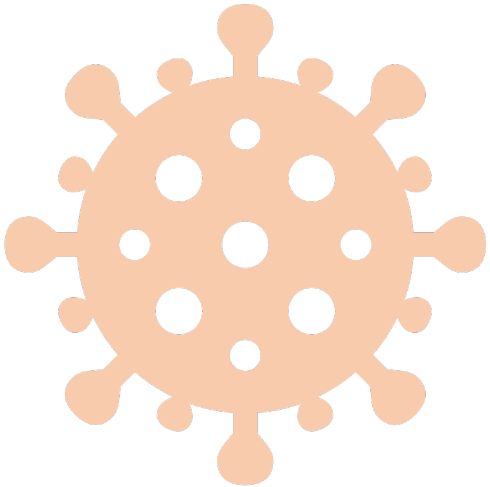
- Varied exposure definition
  - Restricting glucocorticoid definition to persons with dose information available
- Varied outcome ascertainment
  - Restricted cohort to persons with minimum 2 days length of stay
  - Varying ventilation onset definition
- Varied covariate assessment
  - Restricting cohort to persons with at least 1 prior encounter
  - Adding available zip code and socioeconomic variables
  - Adding laboratory measures and vital signs from day of admission

Discussion

- Our findings regarding immunosuppressive therapies extend the results of our earlier work and that of others examining the association between use of these medication classes and COVID-19 outcomes.

- Rituximab, a chimeric monoclonal antibody, powerfully interferes with antibody response to infection, and can lead to prolonged viral replication. **It is therefore not surprising that we found null effects for ventilation and an increased risk of death, given the impaired antiviral humoral response.**

Conclusion



- **Among this cohort, with the exception of rituximab, there was no increased risk in ventilation or death for the rheumatologic, antineoplastic or antimetabolite therapies examined.**
- Our sample size was large enough to consider separately a variety of drug classes with distinct molecular mechanisms of action including the targeting of B-cell versus T-cell mediated immunity.

Our results add to a growing body of evidence suggesting the overall safety of several products against the backdrop of continued COVID-related morbidity and mortality.

These findings are important because of how commonly these products are used, and ongoing questions regarding the degree to which they increase the risks of poor outcomes among individuals who are hospitalized with COVID-19.

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Questions?
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