PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Association between immunosuppressive medications and COVID-19 hospitalization and death: a retrospective cohort study

Authors

Sechrist, Samantha J.; Tang, Emily; Arnold, Benjamin; Acharya, Nisha

---

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Lai, Quirino**
Affiliation	**Catholic Univ Louvain**
Date	**07-May-2024**
COI	**No competing interests**

Association between Immunosuppressive Medications and COVID-19 Hospitalization and Death (bmjopen-2024-087467)

This is a retrospective study based on a large population (N=10,109,596) aimed to identify the incidence rate ratios and hazard ratios for COVID-19 hospitalization and death in patients receiving immunosuppressive drugs.

The study is of great interest, underlying the negative role of steroids in favoring the COVID-19 infection. The study is well written and statistically solid.

I have no further comments. The study deserves publication in the present form.

Reviewer	**2**
Name	**Rotundo, Salvatore**
Affiliation	**Università Magna Graecia**
Date	**23-Jun-2024**
COI	**None**

The study by Sechrist SJ et al. aimed to evaluate the association between the use of systemic corticosteroids (SC) and COVID-19 hospitalization and death among immunosuppressed patients, focusing on the dose and duration of SC use. Utilizing a retrospective cohort design, data were collected from the Optum Labs Data Warehouse (OLDW) from July 1, 2021, to June 30, 2022.

Findings revealed a significant association between SC use and increased risk of COVID-19 hospitalization and death. Higher doses and longer durations of SC use correlated with greater risks. Specifically, a clear dose-response relationship was observed, with higher doses of SC leading to increased rates of hospitalization and mortality. Short-term, high-dose SC use was particularly linked to these adverse COVID-19 outcomes. The study also examined the effects of concurrent use of other immunosuppressive medications, such as disease-modifying anti-rheumatic drugs (DMARDs) and tumor necrosis factor-alpha (TNF-alpha) inhibitors. Patients using these additional immunosuppressants alongside corticosteroids exhibited even higher risks of severe COVID-19 outcomes. The impact of prior COVID-19 infection and vaccination was considered in the analysis. While vaccination appeared to mitigate some of the risks associated with corticosteroid use, the increased risk persisted.

The methodology appears well-suited for addressing the study's objectives. The use of a large, comprehensive dataset is a significant strength. The authors identified receiving at least one dose of a SARS-CoV-2 vaccine as a cut-off, acknowledging that this could be a primary limitation. The English language is both clear and accurate.

I have only a few comments:

- I partially disagree with your statement: “Receipt of outpatient and inpatient COVID-19 treatments was associated with an increased risk of both outcomes, likely indicating that these treatments were given to individuals with more severe infections and therefore may have been at risk for worse outcomes.” While this could be true for inpatients who likely receive treatments too late, once the disease is already severe, the situation for outpatients is different. The decision to treat outpatients with antivirals and/or monoclonal antibodies against SARS-CoV-2 is based on their risk of developing severe COVID-19 rather than the severity of their condition at the time of clinical consultation. This decision includes factors such as vaccination status, comorbidities, immunosuppressive treatments, and the time of symptom onset, as COVID-19 outpatient treatment is effective if prescribed as soon as possible. However, the true effectiveness of COVID-19 treatment in immunocompromised patients is still debated, as these patients were underrepresented in clinical trials. Therefore, the increased risk of in-hospital mortality in immunocompromised outpatients who have received COVID-19 drugs could be due to a delay in starting therapy or the ineffectiveness of conventional therapies with monoclonal or antiviral antibodies.

Consider these minor suggestions to improve clarity:

• Abstract:

o There were 10,109,596 eligible patients enrolled during the risk period, each with at least 365 days of continuous enrollment prior to July 1, 2021.

o Among individuals exposed to corticosteroids without a record of COVID-19 vaccination, risks for COVID-19 hospitalization and death increased by 3- and 14.5-fold.

o Page 4: COVID-19 vaccinations may be under-captured.

• Introduction: Due to impaired immune defenses from both underlying disease and immunosuppressive treatments, these patients are at higher risk of infection and severe COVID-19 outcomes.

• Methods: Patients enrolled in OLDW between July 1, 2021, and June 30, 2022, were included. Each patient had at least 365 days of continuous enrollment with medical and pharmacy coverage before July 1, 2021, to capture baseline comorbidities.

Reviewer	**3**
Name	**Tsheten, Tsheten**
Affiliation	**Australian National University College of Health and Medicine**
Date	**11-Oct-2024**
COI	**None**

Background

Line 15 – 17. It is recommended that authors expand their explanation on how the immunosuppressive therapies increases the risk of infection and the severity of disease. Authors may also explain about immunosuppressive drugs and their indications. The current length of introduction is quite short and do not provide adequate justification for conducting the study.

Methods

This section could be improved with appropriate sub-headings. This section may start with study design, study setting (location), and then followed by other sub-headings that's currently included in the manuscript. This would improve the clarity of the message that authors is trying to convey.

Line 22. What does medical and pharmacy coverage mean here? Can you please elaborate this.

Also, can you expand this statement "The risk period and the Delta variant period started on July 1, 2021". I found it quite hard to understand without any supporting information.

Line 33 – 35. Did you mean that you calculated incidence rate for each immunosuppressant and COVID-19 vaccination? Its not clear when you say exposed and non-exposed, can you be more explicit?

Results

Line 45. I suggest that you begin your sentence with some texts, not with number.

For both Table 1 and Table 2, I suggest removing the percentage symbols (%) from the cells and including them in the table titles. This adjustment will help declutter your currently overcrowded tables.

Line 25. As there will be layperson who may not understand the meaning of HR, I would suggest that you interpret what it means when this term appears for the first time. In the subsequent lines, you don't need to explain it.

Discussion

Line 54 – 57. The sentences "Our study evaluated time-updated SC exposures …..the attributable risk for the overall population" is your method and not the findings. I suggest removing this.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1's comments and author response:

Reviewer 1: Dr. Quirino Lai, Catholic Univ Louvain, Sapienza University of Rome
Comments to the Author:
Association between Immunosuppressive Medications and COVID-19 Hospitalization and Death (bmjopen-2024-087467)

This is a retrospective study based on a large population (N=10,109,596) aimed to identify the incidence rate ratios and hazard ratios for COVID-19 hospitalization and death in patients receiving immunosuppressive drugs.

The study is of great interest, underlying the negative role of steroids in favoring the COVID-19 infection. The study is well written and statistically solid.

I have no further comments. The study deserves publication in the present form.
RESPONSE: We thank the reviewer for their positive comments and careful review.

Reviewer 2's comments and author response:

Reviewer 2: Dr. Salvatore Rotundo, Università Magna Graecia
Comments to the Author:
The study by Sechrist SJ et al. aimed to evaluate the association between the use of systemic corticosteroids (SC) and COVID-19 hospitalization and death among immunosuppressed patients, focusing on the dose and duration of SC use. Utilizing a retrospective cohort design, data were collected from the Optum Labs Data Warehouse (OLDW) from July 1, 2021, to June 30, 2022. Findings revealed a significant association between SC use and increased risk of COVID-19 hospitalization and death. Higher doses and longer durations of SC use correlated with greater risks. Specifically, a clear dose-response relationship was observed, with higher doses of SC leading to

increased rates of hospitalization and mortality. Short-term, high-dose SC use was particularly linked to these adverse COVID-19 outcomes. The study also examined the effects of concurrent use of other immunosuppressive medications, such as disease-modifying anti-rheumatic drugs (DMARDs) and tumor necrosis factor-alpha (TNF-alpha) inhibitors. Patients using these additional immunosuppressants alongside corticosteroids exhibited even higher risks of severe COVID-19 outcomes. The impact of prior COVID-19 infection and vaccination was considered in the analysis. While vaccination appeared to mitigate some of the risks associated with corticosteroid use, the increased risk persisted.
The methodology appears well-suited for addressing the study's objectives. The use of a large, comprehensive dataset is a significant strength. The authors identified receiving at least one dose of a SARS-CoV-2 vaccine as a cut-off, acknowledging that this could be a primary limitation. The English language is both clear and accurate.
RESPONSE: We thank the reviewer for their encouraging and constructive comments.

I have only a few comments:
- I partially disagree with your statement: “Receipt of outpatient and inpatient COVID-19 treatments was associated with an increased risk of both outcomes, likely indicating that these treatments were given to individuals with more severe infections and therefore may have been at risk for worse outcomes.” While this could be true for inpatients who likely receive treatments too late, once the disease is already severe, the situation for outpatients is different. The decision to treat outpatients with antivirals and/or monoclonal antibodies against SARS-CoV-2 is based on their risk of developing severe COVID-19 rather than the severity of their condition at the time of clinical consultation. This decision includes factors such as vaccination status, comorbidities, immunosuppressive treatments, and the time of symptom onset, as COVID-19 outpatient treatment is effective if prescribed as soon as possible. However, the true effectiveness of COVID-19 treatment in immunocompromised patients is still debated, as these patients were underrepresented in clinical trials. Therefore, the increased risk of in-hospital mortality in immunocompromised outpatients who have received COVID-19 drugs could be due to a delay in starting therapy or the ineffectiveness of conventional therapies with monoclonal or antiviral antibodies.
RESPONSE: We thank the reviewer for their insight on outpatient and inpatient COVID-19 treatments and their associated risks with COVID-19-related mortality. We added an additional statement to address this concern: “Furthermore, delays in initiating therapy or reduced effectiveness of conventional treatments such as monoclonal antibodies or antiviral medications in immunocompromised patients, may have contributed to these results.” (Page 28, Lines 22-27)

Consider these minor suggestions to improve clarity:
• Abstract:
o There were 10,109,596 eligible patients enrolled during the risk period, each with at least 365 days of continuous enrollment prior to July 1, 202
o Among individuals exposed to corticosteroids without a record of COVID-19 vaccination, risks for COVID-19 hospitalization and death increased by 3- and 14.5-fold.
o Page 4: COVID-19 vaccinations may be under-captured.
• Introduction: Due to impaired immune defenses from both underlying disease and immunosuppressive treatments, these patients are at higher risk of infection and severe COVID-19 outcomes.
• Methods: Patients enrolled in OLDW between July 1, 2021, and June 30, 2022, were included. Each patient had at least 365 days of continuous enrollment with medical and pharmacy coverage before July 1, 2021, to capture baseline comorbidities.
RESPONSE: We thank the reviewer for these detailed suggestions and have made the edits accordingly.

Reviewer 3’s comments and author response:
Reviewer 3: Dr. Tsheten Tsheten, Australian National University College of Health and Medicine, Royal Centre for Disease Control
Comments to the Author:

Background

Line 15 – 17. It is recommended that authors expand their explanation on how the immunosuppressive therapies increases the risk of infection and the severity of disease. Authors may also explain about immunosuppressive drugs and their indications. The current length of introduction is quite short and do not provide adequate justification for conducting the study.

RESPONSE: Thank you for the suggestion. We expanded our explanation on immunosuppressive therapies and how they might increase the risk of infection and disease severity in the introduction: "Patients who are taking corticosteroids and other immunosuppressive therapies for chronic immune-mediated conditions are immunocompromised because of their treatments and may face higher risks of infections and potentially worse COVID-19 outcomes. Rituximab, an anti-CD20 monoclonal antibody, has been associated with increased odds of COVID-19-related death compared to methotrexate monotherapy in patients with rheumatic diseases likely due to B-cell depletion and compromised immunity against viruses, including less development of SARS-CoV-2 antibodies. As COVID-19 variants evolve, understanding the role of immunosuppressants on outcomes remains critical, yet there is limited information about their effect in the general population." (Page 12, Lines 28-47)

Methods

This section could be improved with appropriate sub-headings. This section may start with study design, study setting (location), and then followed by other sub-headings that's currently included in the manuscript. This would improve the clarity of the message that authors is trying to convey.

RESPONSE: We adjusted the first subheading in the Methods to be: "Study design and setting" to introduce the study design and setting, followed by the data source. (Page 13, Lines 12)

Line 22. What does medical and pharmacy coverage mean here? Can you please elaborate this.

RESPONSE: We added an explanation for medical and pharmacy coverage: "Medical and pharmacy coverage refers to health insurance benefits that provide access to healthcare services such as physician visits, hospital care, medical treatments (medical coverage), as well as prescription medications or vaccinations (pharmacy coverage)." (Page 13, Lines 50-56)

Also, can you expand this statement "The risk period and the Delta variant period started on July 1, 2021". I found it quite hard to understand without any supporting information.

RESPONSE: From The Centers for Disease Control and Prevention (CDC), the Delta variant dominant period started on July 1, 2021. *"Taylor CA, Whitaker M, Anglin O, et al. COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:466–473. DOI: http://dx.doi.org/10.15585/mmwr.mm7112e2".*

We have appended the statement "The risk period started on July 1, 2021, which is the date designated by the US Centers for Disease Control as the start of the Delta variant dominant period." to lines 56, 1-5 on pages 13, 14, respectively.

Line 33 – 35. Did you mean that you calculated incidence rate for each immunosuppressant and COVID-19 vaccination? Its not clear when you say exposed and non-exposed, can you be more explicit?

RESPONSE: We understand that "exposed and non-exposed" can be confusing to the reader. This has been changed to state, "Incidence rates of COVID-19 outcomes (hospitalization, in-hospital death) were calculated based on immunosuppressant categories (exposed vs. non-exposed to a medication in that category) and COVID-19 vaccination status." (Page 15, Lines 16-22)

Results

Line 45. I suggest that you begin your sentence with some texts, not with number.

RESPONSE: We have adjusted the wording to start with text and not the number in the results: "There were 10,109,596 patients included in the cohort." (Page 16, Lines 37).

For both Table 1 and Table 2, I suggest removing the percentage symbols (%) from the cells and including them in the table titles. This adjustment will help declutter your currently overcrowded tables.
RESPONSE: Thank you for this suggestion. We have removed the percentage symbols in Tables 1 and 2.

Line 25. As there will be layperson who may not understand the meaning of HR, I would suggest that you interpret what it means when this term appears for the first time. In the subsequent lines, you don't need to explain it.
RESPONSE: We thank the reviewer for this suggestion and have added a layperson's meaning for a hazard ratio in the Results: "The hazard ratio compares the likelihood of an event (e.g., COVID-19 death) occurring at any given time in the treatment group versus the control group (e.g., SC exposed versus SC unexposed)." (Page 21, Lines 46-52)

Discussion
Line 54 – 57. The sentences "Our study evaluated time-updated SC exposures …..the attributable risk for the overall population" is your method and not the findings. I suggest removing this.
RESPONSE: We have removed the following sentences from the discussion.

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Rotundo, Salvatore**
Affiliation	**Università Magna Graecia**
Date	**12-Nov-2024**
COI	

My comments have been adequately addressed.

Reviewer	**3**
Name	**Tsheten, Tsheten**
Affiliation	**Australian National University College of Health and Medicine**
Date	**17-Nov-2024**
COI	

Congratulations to the team for producing this important work!

One minor comment I have is in line 5.

You should specify which CDC you are referring to, as there are many CDCs worldwide. I believe you might be referring to the US CDC.