PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Severe COVID-19 outcomes among patients with autoimmune rheumatic diseases or transplantation: a population-based matched cohort study
AUTHORS	Marozoff, Shelby; Lu, Na; Loree, Jonathan; Xie, Hui; Lacaille, Diane; Kopec, Jacek; Esdaile, John; Aviña-Zubieta, J. Antonio

VERSION 1 – REVIEW

REVIEWER	Szekanecz, Zoltan University of Debrecen, Faculty of Medicine, Department of Rheumatology
REVIEW RETURNED	22-May-2022

GENERAL COMMENTS	This is a very important and interesting study assessing the severity and outcome of COVID-19 in more than 6500 patients with ARD and transplantation. Risk of hospitalization, ICU admission and mortality were adequately addressed. I only have a few minor comments 1. It is interesting that in addition to transplat patients, AS patients had high ICU admission risk and moratlity. Why? There were also SLE and SSc patients with systemic organ involvement. Was there any association with AS activity and severity (BASDAI), chest expansion (leading to limoited respiratory capacity)? Axial vs peripheral? HLA-B27 status? 2. After ICU submission, outcome highly depends on the need for NIV vs IV ventillation. Did the underlying disease affect the need for IV? 3. How many patients developed MIS/cytokine storm? What was their treatment and outcome in comparison to patients not reaching MIS?

REVIEWER	Lee, Eun Bong Seoul National University College of Medicine, Internal Medicine
REVIEW RETURNED	25-Jun-2022

GENERAL COMMENTS	The authors investigated the impact of ARD on the outcome of the Covid infection, using a large database in Canada. The results of the study is consistent with previous studies and very convincing. Considering the impact of Covid nowdays, the current study is important. Followings are several concerns related to this study. Abstract. Conclusions. The current study does not prove direct evidence that “booster vaccination, prompt diagnosis or early intervention” improves the outcome of the risk group found in this study. Method

	The authors defined the Covid-related ICU admission as an admission within one month of the diagnosis. Is there any reference to choose one-month as a criterion? The performance of the hospitals may contribute to the treatment outcomes of the results. Is the distribution of the caring hospitals balanced? Results The poorest outcome in transplantation suggests that more immunosuppressive agents may be the cause of the poor outcome in the study population. Is it impossible to add the data on the use of immunosuppressive medications to table 1? Throughout the manuscript, the definitions of “all ARD, ARD and SARD” may confuse the readers. For example, “all ARD” seems to represent “ARD” +”SARD” in table 1. But “ARD” throughout the manuscript seems to mean “all ARD”. Table 1 What does “Covid tests, n(%)” in table 1 represent. As far as I understand, all the population in this table is Covid-infected patients (ie, Covid-tested).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Zoltan Szekanecz, University of Debrecen, Faculty of Medicine
Comments to the Author:
This is a very important and interesting study assessing the severity and outcome of COVID-19 in more than 6500 patients with ARD and transplantation. Risk of hospitalization, ICU admission and mortality were adequately addressed. I only have a few minor comments

1. It is interesting that in addition to transplat patients, AS patients had high ICU admission risk and moratlity. Why? There were also SLE and SSc patients with systemic organ involvement. Was there any association with AS activity and severity (BASDAI), chest expansion (leading to limoited respiratory capacity)? Axial vs peripheral? HLA-B27 status?
Response: Thank you for this comment. We also find the ankylosing spondylitis (AS) results interesting. Unfortunately, for this study, we only had access to provincial administrative health data and not to laboratory or clinical data. Meaning, we have no data on disease severity (e.g., BASDAI), chest expansion, disease classification (e.g., axial vs. peripheral), or HLA-B27 status in this cohort. With regards to why patients with AS were at increased risk of most severe COVID-19 outcomes, we had previously written in the discussion section on Page 15, line 23 – Page 16, line 2 “We found an increased risk of mortality among patients with AS, which could be due to persistent chest immobility and associated impaired respiratory function[25,26]. Further research on severe COVID-19 outcomes in patients with AS is required.”

2. After ICU submission, outcome highly depends on the need for NIV vs IV ventillation. Did the underlying disease affect the need for IV?
Response: Thank you for this question. In this sample, of all individuals who were hospitalized, ≤5 received non-invasive ventilation. The following Canadian Classification of Health Interventions codes were used to identify these individuals: 1.GZ.31.CBND; 1.GZ.31.JANC; 1.GZ.31.CBEP; 1.GZ.31.JAMD; 1.GZ.31.JAPK. Based on the small cell size policy from Population Data BC, the providers of this data, we cannot report further on these results.
However, we were able to assess the risk of invasive ventilation for autoimmune rheumatic disease and transplant patients relative to matched comparators. As specified on Page 7, lines 18-21, “The

following Canadian Classification of Health Intervention codes were used to identify invasive ventilation: 1.GZ.31.CAND; 1.GZ.31.CAEP; 1.GZ.31.CAPK; 1.GZ.31.CRND; 1.GZ.31.GPND in hospitalized patients. Both short-term (<96 hours) and long-term (≥96 hours) invasive ventilation were included within 30 days of a positive SARS-CoV-2 test." The results of these analyses are presented from Page 13, line 21 to Page 14, line 10 "A total of 1.6% of patients with ARDs received invasive ventilation relative to 0.9% of matched comparators (Figure 1; Supplementary Table 2). The overall risk of invasive ventilation was increased for patients with ARDs versus comparators (aOR: 1.60 (95% CI: 1.27-2.01)). Relative to those without an ARD, the risk of invasive ventilation was also increased for those with RA (aOR: 1.56 (95% CI: 1.11-2.21)), AS (aOR: 2.63 (95% CI: 1.14-6.06)), and overall SARDs (aOR: 2.57 (95% CI: 1.51-4.36)). Overall 8.6% of transplant recipients received invasive ventilation compared to 1.3% of comparators (Figure 2; Supplementary Table 3). The risk of invasive ventilation was significantly increased for transplant recipients relative to comparators (aOR: 8.64 (95% CI: 3.81-19.61))." We also made changes in the following sections of the abstract and manuscript body to specify details about invasive ventilation: Page 2, line 3 and line 13; Page 3, line 1-4; Page 4, line 4; Page 5, line 4 and line 23; Page 7, line 7; Page 15, lines 10-12; Page 18, line 5; Supplementary Tables 2 and 3; Figures 1 and 2.

3. How many patients developed MIS/cytokine storm? What was their treatment and outcome in comparison to patients not reaching MIS?
Response: We are unable to assess the number of patients who developed multisystem inflammatory syndrome/cytokine storm using this administrative dataset as those variables are not included in the provincial administrative data.

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Reviewer: 2
Dr. Eun Bong Lee, Seoul National University College of Medicine
Comments to the Author:
The authors investigated the impact of ARD on the outcome of the Covid infection, using a large database in Canada. The results of the study is consistent with previous studies and very convincing. Considering the impact of Covid nowdays, the current study is important. Followings are several concerns related to this study.

1. Abstract. Conclusions.
The current study does not prove direct evidence that "booster vaccination, prompt diagnosis or early intervention" improves the outcome of the risk group found in this study.
Response: Thank you for this comment. The full sentence included in our abstract (Page 3, lines 4-6) and conclusion (Page 17, lines 21-23) is "Strategies to mitigate risk, such as booster vaccination, prompt diagnosis, and early intervention with available therapies should be prioritized in these groups according to risk." Given that the risk of the severe COVID-19 outcomes assessed in our study varies according to diagnosis (many patients groups were at no increased risk of severe COVID-19 outcomes, whereas the risk was greatly increased for other groups), we argue that strategies to mitigate risk should be prioritized in the groups at increased risk. The following papers have highlighted the utility of risk-mitigation strategies for individuals with various rheumatic diseases and have been added as references 41-43 on Page 18, line 11. For these reasons, we would like to keep this sentence in the abstract and conclusion.

I. Fragoulis GE, Karamanakos A, Arida A, et al. Clinical outcomes of breakthrough COVID-19 after booster vaccination in patients with systemic rheumatic diseases. RMD Open. 2022;8:e002279. doi: 10.1136/rmdopen-2022-002279.
II. Widdifield J, Kwong JC, Chen S, et al. Vaccine effectiveness against SARS-CoV-2 infection and severe outcomes among individuals with immune-mediated inflammatory diseases tested

between March 1 and Nov 22, 2021, in Ontario, Canada: a population-based analysis. Lancet Rheumatol. 2022 Jun;4(6):e440. doi:10.1016/S2665-9913(22)00096-0.

III. Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol. 2022 Apr;18(4):191-204. doi: 10.1038/s41584-022-00755-x.

2. Method

The authors defined the Covid-related ICU admission as an admission within one month of the diagnosis. Is there any reference to choose one-month as a criterion?

The performance of the hospitals may contribute to the treatment outcomes of the results. Is the distribution of the caring hospitals balanced?

Response: 30 days is a common time period for assessing COVID-19 outcomes in the literature. Outside of this time period, it is unlikely that these outcomes of hospitalization, intensive care unit admission, invasive ventilation, or mortality are due to COVID-19. Below are five papers that also used this time period for assessing severe COVID-19 admissions in patients with rheumatic diseases or transplantations:

I. D'Silva KM, Jorge A, Cohen A, et al. COVID-19 Outcomes in Patients With Systemic Autoimmune Rheumatic Diseases Compared to the General Population: A US Multicenter, Comparative Cohort Study. Arthritis Rheumatol. 2021 Jun;73(6):914-920. doi: 10.1002/art.41619.

II. Jorge A, D'Silva KM, Cohen A, et al. Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study. Lancet Rheumatol. 2021 Feb;3(2):e131-e137. doi: 10.1016/S2665-9913(20)30422-7.

III. Raiker R, DeYoung C, Pakhchanian H, et al. Outcomes of COVID-19 in patients with rheumatoid arthritis: A multicenter research network study in the United States. Semin Arthritis Rheum. 2021 Oct;51(5):1057-1066. doi: 10.1016/j.semarthrit.2021.08.010.

IV. Dumortier J, Duvoux C, Roux O, et al. Covid-19 in liver transplant recipients: the French SOT COVID registry. Clin Res Hepatol Gastroenterol. 2021 Jul;45(4):101639. doi: 10.1016/j.clinre.2021.101639.

V. Hadi YB, Naqvi SFZ, Kupec JT, Sofka S, Sarwari A. Outcomes of COVID-19 in Solid Organ Transplant Recipients: A Propensity-matched Analysis of a Large Research Network. Transplantation. 2021 Jun 1;105(6):1365-1371. doi: 10.1097/TP.0000000000003670.

We have cited these 5 papers on Page 7, line 19, as references 24-28.

Unfortunately, we are unable to access data on individual hospitals, as this information is masked by Population Data BC, the data providers for the provincial administrative data. We were able to assess hospital and intensive care unit visits in each health authority in BC and we matched on this variable (please see Page 7, line 12) to address variation in exposure and care in the different health authorities.

3. Results

The poorest outcome in transplantation suggests that more immunosuppressive agents may be the cause of the poor outcome in the study population. Is it impossible to add the data on the use of immunosuppressive medications to table 1?

Throughout the manuscript, the definitions of “all ARD, ARD and SARD” may confuse the readers.

For example, “all ARD” seems to represent “ARD” +”SARD” in table 1. But “ARD” throughout the manuscript seems to mean “all ARD”.
Response: We have conducted a separate analysis on the risk of severe COVID-19 outcomes according to immunosuppressive agents and are publishing these results in a separate paper. As a result, we cannot include this data in the Table 1 of this paper.
ARD refers to all autoimmune rheumatic diseases, including the SARDs. Specifically the term “all ARD” includes rheumatoid arthritis, psoriasis/psoriatic arthritis, ankylosing spondylitis, and any systemic autoimmune rheumatic diseases, as defined on Page 6, Lines 18-21.
We have added a footnote to Table 1 that specifies that “All ARDs includes rheumatoid arthritis, psoriasis/psoriatic arthritis, ankylosing spondylitis, and any systemic autoimmune rheumatic diseases (SARDs)”.

4. Table 1
What does “Covid tests, n(%)” in table 1 represent. As far as I understand, all the population in this table is Covid-infected patients (ie, Covid-tested).
Response: Thank you for this comment. We have renamed the column in Table 1 to “Previous COVID-19 tests, n (%)”. This column indicates the number of COVID-19 PCR tests that individuals took before the index date. As we included participants from the first positive COVID-19 PCR test, this column essentially indicates the number of negative COVID-19 tests before the first positive one.

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Additionally, we have had to remove three values from Table 1 (the percentage of participants who live in rural locations among those with systemic sclerosis, myositis, and the adult systemic vasculitides). Population Data BC has a policy where small cell sizes ≤5 must be suppressed in order to protect the privacy of participants. The three percentages were removed because they identified counts ≤5.
We also added in the volume, issue, and page numbers from references that were missing them.
Finally, with the addition of the invasive ventilation results to the abstract, we had to make some changes to phrasing in order to fit within the 300 word limit.
Again, we appreciate the editor and two reviewers’ comments for our manuscript. We look forward to hearing your decision on our manuscript.

VERSION 2 – REVIEW

REVIEWER	Szekanecz, Zoltan University of Debrecen, Faculty of Medicine, Department of Rheumatology
REVIEW RETURNED	22-Jul-2022

GENERAL COMMENTS	I have no further comments.

REVIEWER	Lee, Eun Bong Seoul National University College of Medicine, Internal Medicine
REVIEW RETURNED	21-Jul-2022

GENERAL COMMENTS	My comments are well addressed.