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ORIGINAL ARTICLE

Immunosuppression as a risk factor for COVID-19: a meta-analysis

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Abstract

Background: While immunosuppression poses a theoretical increase in the risk of COVID-19, the nature of this relationship is yet to be ascertained.
Aims: To determine whether immunosuppressed patients are at higher risk of COVID-19 to help inform the management of patients receiving immunosuppressant therapies during the pandemic.
Methods: We performed a random-effects meta-analysis of data from studies that reported on the prevalence of immunosuppression among patient cohorts with COVID-19.
Results: Sixty full-text publications were identified. In total, six individual studies were included in the final analysis, contributing a total of 10 049 patients with COVID-19 disease. The prevalence of immunosuppressed patients among the study cohorts with COVID-19 ranged from 0.126% to 1.357%. In the pooled cohort a total of 64/10 049 (0.637%) patients with COVID-19 disease was immunosuppressed. Observed to expected ratios were used to compare the prevalence of immunosuppression in cohorts with confirmed COVID-19 disease to the background prevalence of immunosuppression in the general community. The observed to expected ratio of immunosuppression among patients with COVID-19 illness, relative to the general community, was 0.12 (95% confidence interval: 0.05–0.27).
Conclusions: Compared to the general population, immunosuppressed patients were not at significantly increased risk of COVID-19 infection. This finding provides support for current expert consensus statements, which have recommended the continuation of immunosuppressant therapy in the absence of COVID-19.

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by a novel coronavirus. Epidemiological studies examining patients with COVID-19 are fast emerging. To date, studies have demonstrated that the risk of severe disease is highest among those of advanced age and those with medical comorbidities.[1] In particular, the highest case fatality rates have been observed among the elderly and those with comorbid cardiovascular disease.[1–3]

Immunosuppression may lead to an increase in the rate of certain types of infection. While many conditions may involve the use of immunosuppressing treatments, typical recipients of immunosuppression include: cancer patients, organ transplant recipients and sufferers of chronic inflammatory diseases.[4–10] Although the exact global prevalence of immunosuppression is unknown, the increasing use of immunosuppressant therapies makes it likely that more members of the community are immunosuppressed at this time than in any past pandemic.[11]

Accordingly, bodies such as the Centers for Disease Control and Prevention (CDC) have warned

immunocompromised patients that they are at increased risk of severe COVID-19 illness.[12] Yet stopping immunosuppressant treatments in an attempt to reduce the risk of COVID-19 poses an obvious risk to the health of these patients also. Transplant rejection, relapses in malignancy or flares in the activity of inflammatory diseases are all possible complications of immunosuppressant withdrawal.[13,14] Moreover, the possible increase in hospitalisations from withholding clinically necessary immunosuppressant treatment may serve to increase patient exposure to the novel coronavirus responsible for COVID-19.

Expert consensus statements from various societies have been rapidly produced to guide the management of immunocompromised patients at this time.[15–17] At present, these statements support an increase in vigilance toward infection prevention measures and the continuation of immunosuppressant treatment in the absence of COVID-19. However, these recommendations are based mainly on expert opinion rather than real-world data from the current pandemic.

We conducted this meta-analysis to test the hypothesis that immunosuppression increases the risk of COVID-19. We achieve this by consolidating the current literature and comparing the prevalence of immunosuppression in cohorts with COVID-19 to the prevalence of immunosuppression expected in the general community. We aim to provide insight into the impact of immunosuppression on COVID-19 risk.

Methods

This review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[18]

Identification of relevant literature

Multiple search techniques were utilised to identify potentially relevant papers, based primarily on resources suggested by the World Health Organization.[19] Searches were performed manually by two authors and involved several sources, including high impact journals, preprint databases (MEDRXIV), online databases (MEDLINE and EMBASE), libraries (Elsevier ScienceDirect and Wiley) and the reference lists of expert consensus statements. Studies published between 1 November 2019 to 22 April 2020 were included.

Concerning the databases, MEDLINE and EMBASE, the following Medical Subject Headings (MeSH) and keywords were used alone or in combination: immunosuppression, immunosuppressive agents, immunomodulation, monoclonal antibodies, thiopurine,

azathioprine, mercaptopurine, methotrexate, infliximab, adalimumab, golimumab, vedolizumab, ustekinumb, coronavirus, coronavirus infections, COVID-19 and 2019-nCOV.

In addition, attempts were made to contact the authors of publications included in this meta-analysis to obtain further information on the patients designated as immunocompromised within their respective publications. However, at the time of writing, no additional information had been received.

Inclusion and exclusion criteria

Selection criteria were prespecified to reduce potential bias in study selection. Initial study selection was performed via title and abstract screening by one author with the full-text screening of shortlisted publications undertaken independently by two authors.

Inclusion criteria

All article types reporting on (i) cohorts of patients from the general community with (ii) laboratory-confirmed COVID-19 disease and (iii) data on the number of immunosuppressed patients were included in this analysis.

We considered immunosuppressed patients to be those patients explicitly designated by study authors as either immunosuppressed, immunocompromised or immunodeficient. Patients in these categories include those with primary or acquired immune deficiencies and those receiving immunosuppressive treatments. We also regarded patients actively undergoing chemotherapy or solid organ transplant recipients to be immunosuppressed and included these patients in this analysis.

Exclusion criteria

Publications in languages other than English were excluded. Studies reporting on the prevalence of immunosuppression among samples of patients from a specific disease population, rather than the general population, were excluded from the analysis. This was to avoid introducing bias associated with different risk profiles between the general population compared with cohorts which share a common disease.

Assessment of study quality

The study quality of publications included in this analysis was independently rated on a 5-point scale by two authors according to a modified rating scale from the Oxford Centre for Evidence-based Medicine (OCEBM).[20] These ratings are provided in the results section below (Table 1).

Table 1 Overview of studies reporting on the prevalence of immunosuppression in COVID-19 patient samples

Author	Title	Study design	Study quality (OCEBM)	Sample	Outcome of interest	Findings
Guan et al.[21]	Clinical characteristics of coronavirus disease 2019 in China	Retrospective cohort	3	1099 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	2/1099 COVID-19 patients designated as immunosuppressed by study authors
Jin et al.[22]	Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms	Retrospective cohort	3	651 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	1/651 COVID-19 patients designated as immunosuppressed by study authors
Lian et al.[23]	Analysis of epidemiological and clinical features in older patients with corona virus disease 2019 (COVID-19) out of Wuhan	Retrospective cohort	3	788 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	1/788 COVID-19 patients designated as immunosuppressed by study authors
Liang et al.[24]	Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China	Prospective cohort	3	1590 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	2/1590 COVID-19 patients were designated as currently receiving chemotherapy.
Richardson et al.[25]	Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalised with COVID-19 in the New York City area	Case series	4	5700 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	55/5700 COVID-19 patients were designated as solid organ transplant recipients by study authors
Zhang et al.[26]	Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China	Retrospective cohort	3	221 patients with COVID-19 disease	Number of immunosuppressed patients in cohort with COVID-19 disease	3/221 COVID-19 patients were designated as recipients of immunosuppressant therapy by study authors

Data collection and study outcomes

Data abstraction was performed by one author using standardised evidence tables developed for this review. Year of publication, first author, study title, study design, sample size and number of immunosuppressed patients among the COVID-19 disease cohort were abstracted. Any queries were resolved through discussion between the authors.

The primary study outcome examined was the prevalence of immunosuppression among patient cohorts with COVID-19 disease.

Statistical analysis

We computed the ratio of immunosuppressed patients in cohorts with COVID-19 to the number of immunocompromised patients expected in an equivalently sized sample from the general community. We used an estimate of the background prevalence of immunosuppression of 2.7% (95% confidence interval (CI) 2.4–2.9).[11] This estimate was based on the analysis of data on 34 426 adult respondents from the United States.[11]

It was assumed that the observed number of immunosuppressed patients followed a Poisson distribution, and 95% CIs were calculated using MS Excel 2016 via the = POISSON.DIST function, according to formulae described by Sahai and Khurshid.[27]

Using methods presented in sections 6.3.1-2 of the *Cochrane Handbook for Systematic Reviews of Interventions*[28] standard errors were then calculated for each effect measure, and the estimates entered into RevMan v5.3 for

meta-analysis. Studies were combined using a random-effects model to account for inter-study heterogeneity. A sensitivity analysis was then performed by varying the background immunosuppression prevalence from 2.4% to 2.9% to assess the effect on the significance of the estimates.

Results

Our searches identified over 3000 COVID-19 publications, which were each screened by title and abstract for relevance, leading to 60 publications suitable for full-text analysis. A total of six unique studies met our prespecified inclusion criteria and were included in this analysis.

Immunosuppression and the risk of COVID-19 disease

Six studies, contributing a combined 10 049 patients, were utilised to investigate the risk of developing COVID-19 disease in immunosuppressed patients (Table 1). Each of these studies examined cohorts of patients with laboratory-confirmed COVID-19 illness to explore the clinical and epidemiologic characteristics of the disease. These papers were distinguished from other observational studies published on COVID-19 because the prevalence of immunosuppression within the study cohorts was indicated or could be derived from data included in appendices.

The prevalence of immunosuppression among the COVID-19 cohorts from individual studies was: 0.127%,[23] 0.182%,[21] 1.357%,[26] 0.154%,[22] 0.96%[25] and 0.126%[24] (Table 2). We calculated the total prevalence of immunosuppression in the pooled cohort to be 0.637% (64/10 049).

Of the 64 immunosuppressed patients identified among 10 049 patients with COVID-19; 55/64 (85.9%) patients were organ transplant recipients,[25] 2/64 (3.13%) patients were recipients of chemotherapy,[24]

3/64 (4.69%) patients were recipients of an unspecified immunosuppressant treatment[26] and the remaining 4/64 (6.25%) patients were designated as immuno-suppressed with no cause specified.[21–23]

Based on a background immunosuppression prevalence of 2.7%,[11] we expected to observe 271 immunosuppressed patients among the 10 049 patients with COVID-19 disease. Instead, 64/10 049 (0.637%) were observed, leading to an observed to expected ratio (O/E) ratio of 0.12 (95% CI: 0.05–0.27). Sensitivity testing was conducted by varying the estimate for expected immunosuppression prevalence to assess the effect this would have on the computed O/E ratio. With an estimated background prevalence of immunosuppression of 2.4%, we found the O/E ratio to be 0.13 (95% CI: 0.05–0.30) while with the background prevalence set to 2.9% the O/E ratio was 0.11 (95% CI: 0.05–0.25). Subsequent testing demonstrated that if the background immunosuppression prevalence was set at any value above 0.67%, then the results of this analysis maintain statistical significance.

Discussion

This study suggests that the risk of developing COVID-19 is not significantly higher among immunosuppressed patients compared with the general community.

Based on the assessment of 10 049 patients with laboratory-confirmed COVID-19 illness from early observational studies,[21–26] we observed a lower than expected prevalence of immunosuppression among the COVID-19 cohorts (O/E ratio = 0.12, 95% CI: 0.05–0.27). Importantly, the significance of this finding was maintained under sensitivity analysis.

While in theory, immunosuppression would be a significant risk factor for the development COVID-19, the data available so far do not support this hypothesis. As a result, in the absence of suspected or confirmed COVID-19, the suspension of clinically indicated immunosuppressant

Table 2 Assessment of the prevalence of immunosuppression among COVID-19 infected patients (I^2 = 93%, $P < 0.00001$)

Author	Sample	Observed patients receiving immunosuppression	Expected patients receiving immunosuppression	The observed prevalence of immunosuppression (%)	Weight (%)	Observed to expected ratio (95% confidence interval)
Guan *et al.*[21]	1099	2	29.67	0.182 (2/1099)	16.3	0.07 (0.03–0.15)
Jin *et al.*[22]	651	1	17.58	0.154 (1/651)	16.0	0.06 (0.02–0.13)
Lian *et al.*[23]	788	1	21.28	0.127 (1/788)	15.5	0.05 (0.02–0.12)
Liang *et al.*[24]	1590	2	42.93	0.126 (2/1590)	15.4	0.05 (0.02–0.12)
Richardson *et al.*[25]	5700	55	153.90	0.96 (55/5700)	18.3	0.36 (0.26–0.50)
Zhang *et al.*[26]	221	3	5.97	1.357 (3/221)	18.5	0.5 (0.38–0.66)
Total	10 049	64	271.32	0.637 (64/10049)	100%	0.12 (0.05– 0.27)

therapy to prevent COVID-19 disease is not advisable and may actually lead to increased morbidity.

Our findings are consistent with current guidelines advising on the use of immunosuppressants during the COVID-19 pandemic. Overwhelmingly, the consensus among these recommendations is for treatment to be considered on an individual basis, with the default position to continue therapy in the absence of suspected or confirmed COVID-19.[15–17,29,30]

Investigation into the inflammatory response in COVID-19 disease highlights a possible therapeutic role for immunosuppression.[31] Immunosuppressants, through their ability to modulate mechanisms of inflammation, may ameliorate symptoms and limit complications of COVID-19 such as pneumonia.[32] Our analysis does not allow us to distinguish whether there is clinical improvement following administration of selected classes of immunosuppressants. Instead, it enables us to conclude that in general, immunosuppressed patients are not at elevated risk of developing COVID-19 disease.

Given the paucity of current evidence, we utilised an inclusive approach in the selection of publications to ensure that all relevant papers were incorporated into our analysis. We only specified the exclusion of non-English language studies after balancing the time delay involved in translation; however, no non-English language papers were identified in our searches. Therefore, we believe that the studies included in this analysis are an appropriate representation of the current evidence.

Each of the studies included in this analysis followed an observational, cohort-based or case-series study design and was rated as a 3–4/5 study quality according to OCEBM methods.[20] While we believe the overall risk of bias of the included studies to be low, some degree of publication bias is possible given that the study cohorts comprise hospitalised patients and therefore represent a certain level of disease severity. Furthermore, the evolving testing criteria, as the public health response develops, may lead to variability in the number and type of COVID-19 cases reported, and therefore, the cohorts included in this analysis. For instance, current CDC guidelines have suggested that the majority of infections with the novel coronavirus result in mild illness, which can be managed conservatively in the individual's home, and possibly without the need for formal diagnostic testing.[33] Therefore, large numbers of cases of mild or asymptomatic infection may have been omitted from the studies included in this analysis.

Similarly, the potential for immunosuppression to limit the severity of COVID-19 disease may lead to an under-identification of COVID-19 cases among those receiving immunosuppression. Furthermore, if immunosuppressed patients comprise a younger cohort overall,[11] the propensity of younger individuals to develop mild disease or asymptomatic infection may further contribute to an underestimation of the true impact of immunosuppression on COVID-19 risk.

In addition, the effects of selection bias, arising from the possibility that immunocompromised patients more strongly adhere to exposure-limiting precautions compared to the general population, cannot be excluded. However, the patient cohorts included in this study are primarily from earlier in the disease outbreak before extensive public health measures to increase COVID-19 awareness and precautions, which may somewhat reduce this effect.

A further limitation of this analysis is the sample size and composition of the immunosuppressed cohort studied. In particular, the small sample size of 64 immunosuppressed patients identified in this analysis, with solid organ transplant recipients over-represented (85.9%), may limit the generalisability of our findings to immunosuppressed patients in general. However, the relatively large subset of 10 049 COVID-19 cases captured by the studies in the analysis helps to limit this shortcoming.

While the small cohorts currently available from various observational studies limit the statistical power of this analysis, this is to be expected in the midst of the COVID-19 pandemic and possible underreporting from various countries. We were also unable to locate a reliable point estimate of the prevalence of immunosuppression in China. While the estimate used in this analysis was based on a comprehensive cross-sectional study of 34 426 adults from the United States,[11] we do acknowledge that the prevalence of immunosuppression between the Chinese and US populations may differ. However, our sensitivity analysis addresses this concern by demonstrating that immunosuppressed patients are not at significantly increased risk of COVID-19 disease, provided the rate of immunosuppression in China exceeds approximately 0.67%. This rate is considerably less than the best estimate of the prevalence immunosuppression available to us of 2.7%.[11]

Finally, there is insufficient detail available in the data to assess for an association between a specific class of immunosuppressant treatment and COVID-19 risk or any given cause for immunodeficiency and the risk of COVID-19. Instead, our findings provide a broad insight into the impact of immunosuppression on COVID-19 risk.

Conclusions

We did not identify immunosuppression to be a significant risk factor for the development of COVID-19 disease based on our finding of a lower than expected prevalence of immunosuppression in cohorts with COVID-19. This result, therefore, provides support for current guidelines

which recommend the continuation of clinically necessary immunosuppressant therapy in the absence of COVID-19. However, as more data become available, ongoing analysis of this key clinical question is recommended.

Acknowledgements

Data availability statement

Data sets may be obtained from the corresponding author at nik.ding@svha.org.au

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