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Outcomes of multiple sclerosis patients admitted with COVID-19 in a large veteran cohort

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ABSTRACT

Background: Given concerns over immune function, the decision whether to continue disease modifying therapy (DMT) in multiple sclerosis (MS) patients during the COVID-19 pandemic has been challenging, complicated by the risk of MS disease progression in the absence of treatment.

Methods: This retrospective analysis of patients treated for COVID-19 infection at veteran affairs healthcare systems across the United States, investigated 30-day all-cause mortality after first positive COVID-19 in patients with and without MS. We examined mortality risk impact of disease modifying therapy for MS, accounting for other relevant factors known to be associated with COVID-19 mortality. Patients were propensity score matched in a 1:20 fashion based on MS diagnosis.

Results: 49,737 COVID-19 inpatient cases were identified, of which 258 were diagnosed with MS. In the propensity score matched cohort, MS patients taking DMT (excluding those receiving anti-CD20 antibodies) had a lower odds of 30 day mortality (OR: 0.18 [95%CI: 0.00988-0.94] p = 0.041). Similarly, in the unmatched cohort, patients on DMT had a lower risk of death (OR: 0.16 [95%CI: 0.01-0.82] p = 0.023). There was no statistically significant difference in mortality between those with and without MS. In the propensity matched cohort, age over 65, heart failure, chronic kidney disease (CKD), and diabetes increased the risk of mortality while vaccination reduced the risk of mortality.

Conclusion: Veteran patients with MS hospitalized for COVID-19 were less likely to die when taking DMTs (excluding those receiving anti-CD20 antibodies), accounting for other relevant factors. Results suggest that, in relation to the COVID-19 pandemic, not only is it safe to continue most DMTs in people with MS, but it may be beneficial given the decreased risk of COVID-19 mortality and decreased risk of MS disease progression.

1. Introduction

Coronavirus, SARS-CoV-2, the origin of the COVID-19 pandemic, has resulted in over 5 million deaths worldwide as of November 2021. Many cases of COVID-19 result in only mild disease, however a portion result in hypoxic respiratory failure due to systemic inflammation. (Verity et al., 2020) This inflammation includes the release of interleukin (IL)-1, IL-6, and tumor necrosis factor alpha. (Del Valle et al., 2020)

Immunocompromised patients have been shown to be at increased risk for severe COVID-19 infection, and often have worse outcomes. (Haidar and Mellors, 2021) Much of the data focuses on patients with solid organ transplants, hematopoietic stem cell transplants, human immunodeficiency virus (HIV), solid tumors, and other primary immunodeficiencies. (Kates et al., 2020, Sharma et al., 2021, Fung and Babik, 2021, Tesoriero et al., 2021)

Patients with multiple sclerosis (MS), an inflammatory autoimmune disease of the central nervous system, are treated with a variety of immunocompromising or immunomodulating drugs to control the progression of the disease. In general, medications such as natalizumab, fingolimod, ocrelizumab, alemtuzumab, cladribine, and rituximab have
been shown to be associated with the highest risk of infections in patients with MS over time. (Chisari et al., 2021, Chisari et al., 2019) Disease modifying therapies (DMTs) with the lowest infection risk include interferon beta and glatiramer acetate. (Luna et al., 2020, Wijnands et al., 2018) This has made the decision to initiate or continue disease modifying treatment for MS throughout the COVID pandemic challenging. In the beginning of the pandemic, many MS patients were told to withhold their disease modifying therapy (DMT) for fear of poorer outcomes in patients on these medications. (Ciccarelli et al., 2020, Bsteh et al., 2021) The decision to withhold DMTs, however, is especially complicated given the known risk of MS disease progression in the absence of continued treatment with DMTs. (Jakimovski et al., 2021)

Some studies have suggested that patients with MS do not have an increased risk of COVID infection. (Sahraian et al., 2020, Evangelou et al., 2020, Zabalza et al., 2021) Robust data in these patients however, particularly regarding the effect of disease modifying and immunosuppressive therapies on risk of COVID and related morbidity and mortality, is lacking. The purpose of this study was to evaluate the risk of COVID-19 infection mortality in patients with MS and the factors which contribute to increased risk. This study aimed to determine if hospitalized patients with MS who are currently being treated with disease modifying or immunosuppressive therapies are at increased risk of death from COVID.

2. Methods

2.1. Patient selection

Data were retrospectively obtained via the Corporate Data Warehouse (CDW) and analyzed in the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI). (VINCI) VaClI 2008 Cases of COVID-19 were identified by the COVID-19 Shared Data Resource from March 3, 2020 through October 1, 2021 and included veteran patients treated at VA inpatient centers across the United States. (COVID-19: Shared Data Resource 2020) Patients were followed for 30 days after positive testing to ensure that the primary endpoint was met. COVID-19 positive cases were included as their first documented positive result. All cases were identified for the primary analysis and patients hospitalized in 125 healthcare systems nationwide were included for the multivariable analysis. The primary outcome was 30-day all-cause mortality after the first positive COVID-19 result in patients with and without MS. The secondary endpoint included morbidity and mortality of patients hospitalized for COVID-19 with and without MS examining the impact of DMT for MS. This study was deemed exempt by the Institutional Review and Board and was approved by the Research and Development committee of VA Western New York. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. (von Elm et al., 2007)

DMTs considered in our analysis included dimethyl fumarate, fingolimod, glatiramer, interferon 1A and 1B, natalizumab, siponimod, teriflunomide. Other DMTs were also considered, however if no person in the database was on a medication it was not included in the analysis. These medications were considered active if patients received a prescription within 90 days of diagnosis of COVID-19 or if an inpatient medication order was in place at the time of hospitalization with COVID-19. Due to reports of increased mortality in patients taking ocrelizumab specifically, anti-CD20 inhibitors were considered separately from DMTs of other mechanisms. (Cabeirra et al., 2021, Pesotti et al., 2021, Hughes et al., 2021) In our database, this included ocrelizumab and rituximab. However, no admitted MS patients were on either agent so these were not analyzed individually. COVID medications evaluated included baricitinib, tocilizumab and tofacitinib and were included as the use of these agents generally indicates severe disease. Dexamethasone was included in the propensity score matched analysis as a marker for disease severity. Similarly, because disease comorbidities are also associated with COVID-19 risk, we evaluated disease comorbidities using the Charlson comorbidity index for the propensity score match. They were independently evaluated in the multivariable analysis. (Zhou et al., 2020, Charlson et al., 1987) MS and comorbidities were defined via the COVID Shared resource using ICD 10 code and natural language processing, within two years of diagnosis of COVID-19. There were 42 patients which were excluded as their MS status was unknown.

Patients were considered fully vaccinated against COVID-19 if they received 1 dose of Johnson and Johnson, 2 doses of AstraZeneca, or 2 doses of MRNA Vaccine (Pfizer-biontech or Moderna) at least two weeks prior to date of COVID-19 testing.

2.2. Statistics

The MS patients were characterized relative to non-MS controls using Chi-squared tests for categorical data and Student’s t-test for continuous data.

To evaluate the degree to which MS diagnosis and DMT in hospitalized veterans affects 30-day mortality following infection with COVID-19, a multivariate logistic regression was performed accounting for factors commonly identified in the literature as associated with increased risk of COVID-19 mortality. (Yek et al., 2022) Odds ratios (OR) with 95% Confidence Intervals (CI) were produced to determine the odds of death at 30 days. Medians were presented with an interquartile range (IQR).

Propensity score matching was done in a 1:20 fashion between MS and no MS control. Variable ratio matching resulting in a 1:18 match for improved balance. Groups were propensity score matched to adjust for the following covariates: age, gender, race, Charlson comorbidity index (0-5 and 6-19), use of dexamethasone, and ventilator status. Dexamethasone was included in the match as hospitalized patients on oxygen and dexamethasone have decreased mortality from COVID-19 and the latter are recommended by guidelines for those in a cytokine storm. (Sahraian et al., 2020) We were originally going to match based on use of medications used to treat COVID-19, however, shortages during periods of surges would lead to unintentional bias. Age was matched as a continuous variable. The greedy or nearest neighbor was used for matching and the caliper size was 0.01. Balance of the propensity score matching algorithm was tested by the distribution of propensity scores and can be found in the supplementary appendix (Supplemental Table 1).

Sensitivity analyses were also planned to address the following question: Are the results observed in the primary analysis (effect of MS DMT on COVID-19 mortality) specific to isolated subsets within the data? For this question, the study examined whether the results were changed when considering subsets of patients who were fully vaccinated against COVID-19 versus those who were unvaccinated.

3. Results

In the whole cohort, 49,737 COVID-19 inpatient cases were identified, of which 258 were diagnosed with MS. In the propensity matched cohort, 4,628 patients without MS were matched to 255 patients with MS. Most of the population was composed of older males. Most of the population had a Charlson comorbidity index of 0-5. Table 1 shows the differences between those with and without MS in the Whole Model and Propensity Matched cohorts.

In the whole model, patients with MS were less likely to have CAD, heart failure, chronic kidney disease, CVD, diabetes, hypertension. MS patients were more likely to be vaccinated. In the propensity score matched cohort, the differences in comorbidities became less, however, MS patients were still less likely to have CAD, heart failure, CKD, CVD, and diabetes. Vaccination status did not statistically differ between groups in the propensity score matched cohort. (Table 1).

Unadjusted outcomes for patients admitted with COVID-19 to the VA included no difference in 30-day mortality in the whole model between
30,683 (62.01%) & 114 (44.19%) & <0.0001 & 2,167 (46.82%) & 113 (44.31%) & 0.43 \\
Age & 70 (60-76) & 64 (53-72) & <0.0001 & 64 (54-72) & 64 (53-72) & 0.59 \\
MS medication & 0 & 50 (19.38%) & <0.0001 & 0 & 49 (19.22%) & <0.0001 \\
Male & 46,700 (94.38%) & 206 (79.84%) & <0.0001 & 4,132 (89.28%) & 205 (80.39%) & <0.0001 \\
Race & 13,095 (26.47%) & 66 (25.58%) & 0.018 & 1,236 (26.71%) & 65 (24.94%) & 0.89 \\
African American & 31,871 (64.41%) & 181 (70.16%) & 3,181 (68.73%) & 179 (70.20%) & \\
White & 4,513 (9.12%) & 11 (4.26%) & 211 (4.56%) & 11 (4.31%) & \\
Other & & & & & \\
BMI & <0.35 & 38,239 (77.62%) & 200 (77.52%) & 3,693 (79.8%) & 213 (83.53%) & 0.041 \\
& >35 & 11,023 (22.38%) & 58 (22.48%) & 935 (20.2%) & 42 (16.47%) & 0.12 \\
BMI & 29 (25-34) & 29 (24-34) & 0.13 & 30 (26-34) & 29 (24-34) & 0.0007 \\
CCI & & & & & \\
0–5 & 32,340 (65.36%) & 151 (58.53%) & 2,738 (59.16%) & 150 (58.82%) & \\
6–22 & 17,139 (34.64%) & 107 (41.47%) & 1,890 (40.84%) & 105 (41.18%) & \\
CAD & 15,258 (30.84%) & 47 (18.22%) & <0.0001 & 1,419 (30.66%) & 46 (18.04%) & <0.0001 \\
Cancer & 12,925 (26.16%) & 56 (21.71%) & 0.11 & 1,245 (26.90%) & 54 (21.18%) & 0.044 \\
Cardiomyopathy & 3,320 (6.71%) & 10 (3.88%) & 0.069 & 331 (7.13%) & 10 (3.92%) & 0.049 \\
Cerebrovascular disease & 1,936 (3.91%) & 8 (3.16%) & 0.50 & 158 (3.41%) & 8 (3.16%) & 0.81 \\
CHF & 8,523 (17.23%) & 30 (11.62%) & 0.018 & 765 (16.53%) & 30 (11.76%) & 0.045 \\
Cirrhosis & 2,098 (4.42%) & 6 (2.33%) & 0.13 & 222 (4.89%) & 6 (2.35%) & 0.072 \\
CKD & 12,645 (25.56%) & 38 (14.73%) & <0.0001 & 1,153 (24.91%) & 38 (14.90%) & 0.0003 \\
COPD & 12,644 (25.55%) & 58 (22.48%) & 0.26 & 1,165 (25.17%) & 58 (22.75%) & 0.38 \\
CVD & 25,008 (50.54%) & 102 (39.53%) & 0.0004 & 2,249 (48.60%) & 101 (39.61%) & 0.0052 \\
Diabetes & 22,959 (46.40%) & 98 (37.98%) & 0.0008 & 2,167 (46.82%) & 95 (37.25%) & 0.0029 \\
HTN & 37,154 (75.09%) & 178 (68.99%) & 0.024 & 3,353 (72.45%) & 175 (68.63%) & 0.18 \\
COVID medication & 1,829 (3.70%) & 5 (1.94%) & 0.13 & 89 (1.92%) & 4 (1.57%) & 0.68 \\
Vaccinated (2 doses) & 7,955 (16.08%) & 58 (22.48%) & 0.0053 & 842 (18.19%) & 58 (22.75%) & 0.068 \\
Vaccine category (2 doses) & & & & & \\
J&J & 549 (1.11%) & 3 (1.16%) & & 70 (1.51%) & 3 (1.18%) & \\
MRNA & 7,398 (14.95%) & 55 (21.32%) & & 771 (16.66%) & 55 (21.57%) & \\
None & 14,532 (83.94%) & 200 (77.52%) & & 2,787 (61.83%) & 197 (77.25%) & \\
Readmission within 30 days & 5,933 (11.99%) & 33 (12.79%) & 0.69 & 292 (63.31%) & 33 (12.94%) & <0.0001 \\
ICU within 60 days & 15,939 (32.21%) & 68 (26.36%) & 0.045 & 1,053 (22.75%) & 68 (26.67%) & <0.0001 \\
Ventilator within 30 days & 5,617 (11.35%) & 27 (10.47%) & 0.65 & 384 (8.30%) & 27 (10.59%) & 0.20 \\
LOS & 5 (3-11) & 6 (3-13) & 0.070 & 2 (1-4) & 7 (3-13) & <0.0001 \\
LOS (ICU) & 5 (2-10) & 4 (2-7.5) & 0.022 & 2 (1-5) & 4 (2-7) & 0.23 \\
30-day mortality & 6,228 (12.59%) & 24 (9.3%) & 0.11 & 402 (8.69%) & 24 (9.41%) & 0.69 \\

| Whole Model | MS (N=49,479) | P value | Propensity Matched | MS (N=4,628) | P value |
|-------------|---------------|---------|-------------------|---------------|---------|
| Readmission within 30 days | 5,933 (11.99%) | 33 (12.79%) | 0.69 | 292 (63.31%) | 33 (12.94%) | <0.0001 |
| ICU within 60 days | 15,939 (32.21%) | 68 (26.36%) | 0.045 | 1,053 (22.75%) | 68 (26.67%) | <0.0001 |
| Ventilator within 30 days | 5,617 (11.35%) | 27 (10.47%) | 0.65 | 384 (8.30%) | 27 (10.59%) | 0.20 |
| LOS | 5 (3-11) | 6 (3-13) | 0.070 | 2 (1-4) | 7 (3-13) | <0.0001 |
| LOS (ICU) | 5 (2-10) | 4 (2-7.5) | 0.022 | 2 (1-5) | 4 (2-7) | 0.23 |
| 30-day mortality | 6,228 (12.59%) | 24 (9.3%) | 0.11 | 402 (8.69%) | 24 (9.41%) | 0.69 |

Table 1
Baseline Characteristics for Inpatients with COVID-19.

Table 2
Unadjusted Outcomes for Inpatients with COVID-19.
The controlled immunosuppression in MS patients on DMTs, other than anti-CD20 agents, were over 5 times less likely to die from COVID-19 infection, though rare, must be considered in patients with neurologic diseases, such as patients with MS. (Jewell et al., 2016)

DMTs are an important component of MS therapy as they help to prevent disease progression and related disability. (Hart and Bainbridge, 2016) Results of this study suggest that not only is it safe to initiate or continue DMTs in MS patients during the COVID-19 pandemic, but it is also beneficial in the MS population given the decreased risk of COVID-19 mortality in addition to the established decreased risk of MS disease progression attributed to these therapies. Nonetheless, we are hesitant to suggest these data support the use of MS therapies for COVID-19 treatment or prophylaxis in the general population given the known risks associated with long-term MS therapy. (Hartung et al., 2021)

In the overall study cohort as well as the propensity score matched cohort, vaccination was associated with a decreased risk of 30-day mortality, further validating continued support for vaccination programs. When comparing the two groups in the whole model, more patients in the MS group were vaccinated compared to the general population (22.48% vs 16.08%, p<0.0053), and patients with MS also had lower rates of ICU admission and length of ICU stay.

Subset sensitivity analysis shows that DMT use remained a statistically significant predictor of lower 30-day mortality relating to COVID-19 infection in the unvaccinated sub-group. These results suggest the main result may have been driven by effect of DMT use in the unvaccinated population. However, the samples for the non-vaccinated group were smaller, and lower statistical power for this group cannot be ruled out. As well, DMT use remained a statistically significant predictor of lower 30-day mortality in the analysis completed in the propensity-score matched database, suggesting the difference in mortality is less likely to result from systematic group differences between the MS and control samples.

Limitations of this study include the primarily older male veteran population, which may limit external validity. Another limitation is the retrospective nature and manner in which data was extracted, as high reliability was placed on accurate documentation and data reporting. Lastly, the lack of use of anti-CD20 agents in MS patients is a limitation, given certain DMTs may carry different risks of COVID-19 infection severity. (Zheng et al., 2020) In general, anti-CD20 medications have been shown to have the highest risk of infections in patients with MS over time. (Chisari et al., 2021, Chisari et al., 2019) Unfortunately, there was insufficient sample size of patients taking anti-CD20 agents to investigate this effect on mortality. A strength of this study was the large, diverse, and multi-centered nature, with data collected from 13 Veterans Affairs Hospitals to allow for a large number of patients included. Future research direction is to expand the population to examine the impact of immunomodulators in other groups, such as those with rheumatoid arthritis.

5. Conclusion

Hospitalized veteran patients with MS who were taking DMTs, excluding anti-CD20 inhibitors, were over 5 times less likely to die from complications relating to COVID-19 infection. MS patients in general...
also had less severe infection, evidenced by the lower rate of ICU admission as well as lower duration of ICU stay. Results of this study suggest that not only is it safe to continue most DMTs in people with MS, but it may be beneficial given the decreased risk of morbidity and mortality from COVID-19 and the decreased risk of MS disease progression. Our results raise questions regarding early guidance in the pandemic where MS patients were taken off their previously prescribed DMT. Current recommendations support patient discussion with their provider. Further research is warranted to confirm this important finding.

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Tom A. Fuchs: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. Bethany A. Wattengel: Conceptualization, Writing – original draft, Writing – review & editing. Michael T. Carter: Conceptualization, Data curation, Methodology, Writing – review & editing. Ali A. El-Sohl: Conceptualization, Methodology, Writing – review & editing. Alan J. Lesse: Conceptualization, Methodology, Writing – review & editing. Kari A. Mergenhagen: Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Writing – review & editing.

Declarations of Competing Interest

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Supplementary materials

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References

Bteh, G, Hegen, H, Kiedl, K, et al., 2021. Quantifying the risk of disease reactivation after interferon and glatiramer acetate discontinuation in multiple sclerosis: The VIAADISC score. Eur. J. Neurol. 28 (5), 1609–1616.
Calbirea, V, Albreu, P, Soares-Dos-Reis, R, Guimarães, J, Sá, MJ., 2021. Multiple sclerosis, disease-modifying therapies and COVID-19: a systematic review on immune response and vaccination recommendations. Vaccines 9 (7).
Charlson, ME, Pompei, P, Ales, KL, Mackenize, CR., 1987. A new method of classifying disability with long-term prognostic study. J. Chronic Dis. 40 (5), 373–383.
Chisari, CG, Toscano, S, D’Amico, E, et al., 2019. An update on the safety of treating relapsing-remitting multiple sclerosis. Expert Opin. Drug Saf. 18 (10), 925–948.
Ciccarelli, O, Cohen, JA, Thompson, A., 2020. Response of the multiple sclerosis community to COVID-19. Multiple Sclerosis J. 26 (10), 1134–1136.
COVID-19: Shared Data Resource. 2020; https://vhacdwdhweb1100.veh.med.va.gov/phenotype/index.php/COVID-19:Shared_Data_Resource#Acknowledgements.
Del Val, DM, Kim-Schulze, S, Huang, HH, et al., 2020. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat. Med. 26 (10), 1636–1643.
Evangelou, N, Garjani, A, dasNair, R, et al., 2020. Self-diagnosed COVID-19 in people with multiple sclerosis: a community-based cohort of the UK MS Register. J. Neurol. Neurosurg. Psychiatry 92 (1), 107–109.
Fung, M, Babik, JM., 2021. COVID-19 in Immunocompromised Hosts: What We Know So Far. Clin. infect. dis.: an official publication of the Infect. Society of Am. 72 (2), 240–254.
Haidar, G, Mellors, JW., 2021. Improving the outcomes of immunocompromised patients with coronavirus disease 2019. Clin. infect. dis.: an official publication of the Infect. Society of Am. 73 (6), e1397-e1401.
Hart, FM, Bainbridge, J., 2016. Current and emerging treatment of multiple sclerosis. The Am. J. Care 22 (6), s159–s170. Suppl.
Hartung, HP, Meuth, SG, Miller, DM, Comi, G., 2020. Stopping disease-modifying therapy in relapsing and progressive multiple sclerosis. Curr. Opin. Neurol. 34 (4), 598–603.
Hughes, R, Whiteley, L, Fitovski, K, et al., 2021. COVID-19 in ocrelizumab-treated people with multiple sclerosis. Mult. scler. related disorder. 49, 102725.
Jakimovski, D, Kavak, KS, Vaughan, CB, et al., 2021. Discontinuation of disease modifying therapies is associated with disability progression regardless of prior stable disease and age. Mult. Scler. Related Disorder. 57, 103406.
Jewell, P, Ansorge, O, Kuker, W, irani, SR, Zamboni, G., 2016. Tocilizumab-associated multifocal cerebral thrombotic microangiopathy. Neurol. Clin. Practice 6 (3), e24-e26.
Kates, OS, Haydel, BM, Florman, SS, et al., 2020. COVID-19 in solid organ transplant: a multi-center cohort study. Clin. infect. dis.: an official publication of the Infect. Society of Am.
Louapre, C, Collongues, N, Stankoff, B, et al., 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. 77 (9), 1079–1088.
Luna, G, Alping, P, Burnjan, J, et al., 2020. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol. 77 (2), 184–191.
Pedotti, R, Muros-Le Rouzic, E, Raposo, C, Schippings, S, Jessop, N, 2021. Understanding the impacts of COVID-19 pandemic in people with multiple sclerosis treated with ocrelizumab. Mult. Scler. Related Disorder. 55, 103203.
Rod, JE, Oviedo-Trespalacios, O, Cortes-Ramirez, J., 2020. A brief-review of the risk factors for covid-19 severity. Rev. Saude Publica 54, 66.
Sahraian, MA, Azimi, A, Naser Moghadasi, A., 2020. Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis. Mult. Scler. Related Disorder. 46, 102472.
Sharma, A, Bhatt, NS, St Martin, A, et al., 2021. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. The Lancet Haematol. 8 (3), e185-e193.
Tenforde, MW, Self, WH, Adams, K, et al., 2021. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 326 (20), 2043–2054.
Tesoriero, JM, Swain, CE, Pierce, JL, et al., 2021. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. JAMA Netw. Open 4 (12), e2037069.
Tuy Kuwadzana, RA, Henrina, J, Pranata, R, Anthonius Lim, M, Lawrensia, S, Sustikia, K, 2020. Charlon comorbidity index and a composite of poor outcomes in COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab. Syndr. 14 (6), 2103–2109.

(VINCI) ViCi, 2008. VA Informatics and Computing Infrastructure (VINCI). U.S. Department of Veterans Affairs, p. 2020. VA HSR RES 13-457. https://vaww.VINCI.med.va.gov. Accessed May 2020, 2020.
Verity, R, Okell, LC, Dorigatti, I, et al., 2020. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect. Dis. 20 (6), 669–677.
von Elm, E, Altman, DG, Egger, M, Pocock, SJ, Gotzsche, PC, Vandenbroucke, JP., 2007. The strengthening the reporting of observational studies in epidemiology (strobe) statement: guidelines for reporting observational studies. Lancet (London, England) 370 (9596), 1453–1457.
Wijndans, JMA, Zhu, F, Kingwell, E, et al., 2018. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. J. Neurol. Neurosurg. Psychiatry 89 (10), 1050–1056.
Yek, C, Warner, S, Wilte, JL, et al., 2022. Risk factors for severe COVID-19 outcomes among persons aged ≥18 years who completed a primary COVID-19 vaccination series - 465 health care facilities, United States, December 2020-October 2021. MMWR Morb. Mortal. Wkly. Rep. 71 (1), 19–25.
Zabalza, A, Gómez-Robleda, S, Tagliani, P, et al., 2021. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. 28 (10), 3384–3395.
Zheng, C, Kav, I, Chen, CK, et al., 2020. Multiple sclerosis disease-modifying therapy and the COVID-19 pandemic: implications on the risk of infection and future vaccination. CNS Drugs 34 (9), 879–896.
Zhou, F, Yu, T, Du, R, et al., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 395 (10229), 1054–1062.