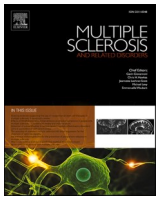
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 64 (2022) 103964

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



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

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ARTICLE INFO

Keywords:
Multiple sclerosis
COVID
Mortality

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

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https://doi.org/10.1016/j.msard.2022.103964
Received 19 April 2022; Received in revised form 3 June 2022; Accepted 10 June 2022
Available online 11 June 2022
2211-0348/Published by Elsevier B.V.

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) VIaCI 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 post positivity 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. (Cabreira et al., 2021, Pedotti 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 agent 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 resulted in a 1:18 match for an 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

Table 1
Baseline Characteristics for Inpatients with COVID-19.

	Whole Model			Propensity Matched		
	No MS(N=49,479)	MS(N=258)	P value	No MS(N=4,628)	MS(N=255)	P Value
Age >65	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 (25.49%)	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			0.97			0.15
<35	38,239 (77.62%)	200 (77.52%)		3,693 (79.8%)	213 (83.53%)	
>35	11,023 (22.38%)	58 (22.48%)		935 (20.2%)	42 (16.47%)	
BMI	29 (25-34)	29 (24-34)	0.13	30 (26-34)	29 (24-34)	0.0007
CCI			0.021			0.91
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 (7.15%)	10 (3.92%)	0.049
Cerebrovascular disease	1,936 (3.91%)	8 (3.10%)	0.50	158 (3.41%)	8 (3.14%)	0.81
CHF	8,523 (17.23%)	30 (11.63%)	0.018	765 (16.53%)	30 (11.76%)	0.045
Cirrhosis	2,098 (4.24%)	6 (2.33%)	0.13	222 (4.8%)	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%)	0.0068	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)			0.017			0.12
J&J	549(1.11%)	3 (1.16%)		70 (1.51%)	3 (1.18%0	
MRNA	7,398 (14.95%)	55 (21.32%)		771 (16.66%)	55 (21.57%)	
None	14,532 (83.94%)	200 (77.52%)		3,787 (81.83%)	197 (77.25%)	
Readmission within 30 days	5,933 (11.99%)	33 (12.79%)	0.69	292 (6.31%)	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%)	0.15
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

MS=multiple sclerosis, CCI-Charlson comorbidity index, BMI=body mass index, CAD=coronary artery disease, CHF=congestive heart failure, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, CVD=cardiovascular disease, HTN=hypertension, LOS=length of stay, ICU=intensive care unit

those with MS (9.3%) and those without (12.6%); p=0.11. In the propensity score analysis 30-day mortality was 8.7% for those without MS and 9.4% for those with MS; p=0.69. Readmission was similar in the whole model cohort but was greater in the propensity score matched group. (Table 2). Two of the MS patients received tocilizumab for inpatient COVID treatment, of which both survived within the window of observation.

In the multivariable logistic regression analysis, DMT for MS consistently reduced the odds of 30-day mortality. In the whole model, DMT medications have reduced risk of death at 30 days (OR: 0.16 [95% CI: 0.01-0.82] p=0.023). Vaccination also reduced the risk of death (OR: 0.41 [95%CI: 0.37-0.44] p<0.0001). Factors which increased the risk of death included the male race, older than age 65, heart failure, and cirrhosis (Table 3). In the propensity score matched cohort, MS meds also reduced the risk of death (OR: 0.18 [95%CI: 0.00988-0.94] p=0.041). Vaccination also reduced the odds of death (OR: 0.35 [95% CI: 0.25-0.48] p<0.0001). Age over 65, heart failure, CKD, and diabetes all increased the risk of death (Table 4).

The sensitivity analysis addressed the question of whether the results are changed when considering subsets of patients who were fully vaccinated against COVID-19 compared with those who were unvaccinated. In the unvaccinated cohort, DMT decreased the odds of death at 30 days (OR: 0.18 [95%CI: 0.0097-0.91] p=0.036) (Supplemental Table 2). In the vaccinated subgroup, there were not enough patients who received DMT to evaluate the results (Supplemental table 3)

Table 2
Unadjusted Outcomes for Inpatients with COVID-19.

	Whole Model			Propensity Matched		
	No MS (N=49,479)	MS (N=258)	P value	No MS (N=4,628)	MS (N=255)	P Value
Readmission within 30 days	5,933 (11.99%)	33 (12.79%)	0.69	292 (6.31%)	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%)	0.15
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

MS=multiple sclerosis, LOS=length of stay, ICU=intensive care unit

Table 3
Whole Model Multivariable Logistic Regression.

	OR	95% CI	p-value
Age >65	3.87	3.59-4.18	<0.0001
Male: female	1.70	1.43-2.04	<0.0001
CHF	1.25	1.16-1.34	<0.0001
Cirrhosis	1.23	1.08-1.39	0.0017
CKD	1.38	1.30-1.47	<0.0001
Diabetes	1.07	1.01-1.13	0.030
Race			
Other: black	1.23	1.11-1.37	0.0001
White: black	1.04	0.97-1.11	0.30
Other: white	1.19	1.08-1.31	0.0004
Vaccinated (2 doses)	0.41	0.37-0.44	<0.0001
BMI <35	1.09	1.01-1.17	0.024
MS	1.24	0.77-1.91	0.36
MS medications (excluding anti CD20)	0.16	0.01-0.82	0.023

CHF=congestive heart failure, CKD=chronic kidney disease, BMI=body mass index, MS=multiple sclerosis

Table 4
Multivariable Analysis of Propensity Score Matched Cohort.

Variable	OR	95% CI	p-value
Age over 65	5.93	4.56-7.83	<0.0001
MS medication	0.18	0.00988-0.94	0.041
Vaccination	0.35	0.25-0.48	<0.0001
CHF	1.96	1.54-2.49	<0.0001
CKD	1.56	1.24-1.96	0.0002
Diabetes	1.28	1.02-1.59	0.031
MS	1.53	0.93-2.42	0.089

MS=multiple sclerosis, CHF=congestive heart failure, CKD=chronic kidney disease

4. Discussion

Following hospitalization for COVID-19 infection, MS patients who were taking DMTs (excluding anti-CD20 inhibitors) were over 5 times less likely to die from complications relating to COVID-19 infection (OR 0.18), accounting for other relevant factors, such as age, vaccination status, and comorbidities. Immunocompromised patients in general 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, however, 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) Because of the variety of immunocompromising or immunomodulating drugs used in MS patients, concern has arisen that patients with MS may also be at increased risk of severe COVID-19 infection and death. In this study, however, this was not the case. In fact, as stated above, MS patients were less likely to die than those in the general population when taking DMTs. DMT therapy aside, rates of 30-day mortality between the two inpatient groups were comparable in both the whole model and the propensity matched cohort. In the whole model, hospitalized patients with MS had less severe infection compared to the general population evidenced by the lower rates of ICU admission (26.4% vs 32.2%, p=0.045) and shorter mean length of time in the ICU (4 days vs 5 days, p=0.022). Given the decreased risk of COVID-19 related severity and mortality in MS patients on DMTs, a clear distinction can be made between the controlled immunosuppression in MS patients on DMT vs the more significant immunosuppression in patients with transplants, HIV, solid tumors, or those receiving anti-CD20 agents.

Recently published literature suggests use of DMTs did not increase severity of COVID-19 infection. (Louapre et al., 2020) Results of this study are not only consistent with the literature but may even suggest a protective effect of DMTs, other than anti-CD20 agents, in hospitalized patients. Furthermore, all MS patients in this study treated with tocilizumab survived. Nonetheless, neurologic side effects of tocilizumab, 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 whole cohort, patients with MS were more likely to be younger, white, and have a higher Charlson Comorbidity Index compared to the general population. These factors, however, were controlled for in the main analyses. The majority of patients overall were male, however there were significantly more in the general population (79.8% in MS group vs 94.4% in general population, p<0.0001). In this study male gender and age > 65 years, were associated with increased risk for mortality. This is consistent with other studies which have also identified older age and male gender as independent risk factors for severe COVID infection and associated mortality. (Louapre et al., 2020, Rod et al., 2020, Tuty Kuswardhani et al., 2020)

Vaccination against COVID, particularly with MRNA vaccines, has been shown to decrease risk of COVID infection severity and mortality. (Tenforde et al., 2021) Vaccination was also found to be protective in this study. 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 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.

Disclosures

There is no conflict of interests to disclose concerning financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this article. The contents of this article do not reflect or represent the views of the Department of Veterans Affairs or the United States Government.

Funding

This study was completed without external funding.

CRediT authorship contribution statement

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-Solh:** 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

None.

Acknowledgements

We would like to acknowledge Dejan Jakimovski, MD, for his intellectual contributions to the present work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103964.

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