Title: Association of multiple sclerosis-related mortality with COVID-19 and other common infections: a multiple causes of death analysis

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Abstract

Background

People with multiple sclerosis (MS) suffer from higher infection-related mortality compared to the general population; however, sparse data are available on the increased risk of death associated with COVID-19 and other common types of infections.

Methods

All mortality records and multiple-cause-of-death data in 2010-2021 of residents in Veneto region (Northeastern Italy) were extracted. Mention of specific infections was compared between death certificates reporting MS or not. Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated by conditional logistic regression matching by age, sex, and calendar year. The bimonthly averages of MS-related deaths in 2010-2019 were compared to those registered during the pandemic (2020-2021).

Results

Of 580,015 deaths through 2010-2021, MS was mentioned in 850 cases (0.15%), 59.3% women. Influenza and pneumonia were reported in 18.4% of MS-related compared to 11.0% non-MS-related deaths (OR: 2.72; 95% CI 2.28-3.25). The odds of mention of urinary tract infections was significantly greater in MS-related deaths in men (OR: 8.16; 95% CI 5.23-12.7) than women (OR: 3.03, 95% CI 1.82-5.02). Aspiration pneumonia, pressure ulcers/skin infections, and sepsis were also significantly associated to MS-related deaths. Reporting of COVID-19 as a cause of death did not significantly differ between deaths with and without mention of MS (approximately 11% of both). However, compared to 2010-2019, peaks in MS-related deaths were observed during the pandemic waves.

Conclusions

Infections continue to play a significant role in MS-related deaths, underlying the need to improve prevention and management strategies.

Introduction

Multiple sclerosis (MS) is an immune-mediated degenerative disease leading to disability and shorter life expectancy[Scalfari2013]. Previous studies have consistently demonstrated a higher risk of infection-related hospitalizations and mortality compared to the general population[Nelson2015,Smyrke2021]. Standard studies of cause-specific mortality risk are based on the underlying cause of death (UCOD), the single disease selected from all conditions reported on death certificates according to rules set by the World Health Organization[WHO2016]. Such studies have demonstrated an increased mortality risk from respiratory infections in patients with MS[Willumsen2022,Smyrke2021]. To properly investigate the role of other infections that can contribute to death but are less often identified as the underlying cause, analyses extended to all causes reported on death certificates (multiple causes of death, MCOD) are warranted. A simple approach is to analyze associations between all conditions listed on death certificates; however, few such studies are available for MS, and are limited to North America. Studies carried out in the US, in 1990-2001[Redelings2006] and British Columbia, Canada, in 1986-2013[Harding 2020] found that mention of MS on death certificates is associated with mention of respiratory infections, aspiration pneumonia, urinary tract infections, pressure ulcers, and sepsis, with some sex differences[Harding2020]. The present report aims at investigating such associations in mortality records of a region in Southern Europe (Veneto, Italy) through the last decade, and examining the role of COVID-19 in MS-related mortality during the first two years of the pandemic.

Methods

The mortality register of the Veneto region (4.9 million inhabitants) includes all conditions reported on death certificates coded according to the International Classification of Diseases, 10th Revision (ICD-10). All deaths between January 1, 2010, and December 31, 2021 of residents in Veneto were collected. Death records that included any mention of MS (ICD-10 code G35) as a cause of death were defined as MS-related deaths.

Records reporting any of the following infections as causes of death were identified: influenza and pneumonia (ICD-10 J09-J18), aspiration pneumonia (J69), urinary tract infections (N10-N12, N30, N34, N39.0), pressure ulcers/skin infections (A46, L00-L08, L89, L97, M72.6, R02), sepsis/septic shock (A02.1, A32.7, A40-A41, B37.7, R57.2, R65.1), and COVID-19 (U07.1, U07.2). We also summarized the most commonly reported non-infectious comorbid conditions among MS-related deaths in the region, for descriptive purposes.

The association of each type of infection with MS was assessed by separate conditional logistic regression models stratified by age, sex, and calendar year. By this method, MS-related deaths were compared to non-MS-related deaths. In order to test differences by sex, an interaction term between sex and mention of infection was introduced in each model. The analysis was also carried out separately by sex.

Lastly, patterns of MS-related deaths during the pandemic were described by comparing the bimonthly number of deaths observed through 2020-2021 with the corresponding average registered in 2010-2019.

Results

Of 580,018 deaths registered between 2010 and 2021, MS was mentioned in 850 (0.15%) cases; 346 men (0.13% of all male decedents) and 504 women (0.17% of all female decedents), with a median age at death of 67 years in men and 69 years in women. The most common non-infectious comorbid conditions that contributed to MS-related deaths were neoplasms (14.5%), diabetes (8.2%), ischemic heart diseases (7.2%) and cerebrovascular diseases (7.1%). Of all death certificates reporting MS, the disease was selected as the UCOD in 577 cases (68%).

Influenza and pneumonia were mentioned in 18.4% of 850 MS-related deaths, compared to 11.0% of non-MS-related deaths, corresponding to an age-sex-year matched OR of 2.72 (95% CI 2.28-3.25). The association could be observed in both sexes, but risk estimates were significantly higher in women (Table 1). A significant difference by sex was found also for the association with urinary tract infections, with a markedly higher risk in men (OR: 8.15, 95% CI 5.22-12.7) than in women (OR: 3.02, 95% CI 1.82-5.02). Compared to non-MS-related deaths, risks were significantly increased for aspiration pneumonia, pressure ulcers and skin infections, and sepsis (Table 1). The proportion of death certificates reporting COVID-19 did not significantly differ between MS-related deaths and those without mention of MS (approximately 11% of both), corresponding to an OR of 1.13 (95% CI 0.70-1.84).

When examining the trend in the bi-monthly number of deaths in 2020-2021, compared to the average figures derived from the equivalent months in 2010-2019 (Figure 1), peaks in MS-related deaths were observed in correspondence to the pandemic waves, and were especially elevated in November-December 2020.

Discussion

The results show that all common infections that we analyzed were significantly associated with MS-related mortality: respiratory, urinary tract, skin infections, and sepsis. These associations, previously assessed using an MCOD approach only in North America[Redelings2006;Harding 2020], are now confirmed by more recent data from Europe. The association with urinary infection was stronger in men, while that with influenza/pneumonia was stronger in women. This report is the first investigating the role of COVID-19 as a cause of death in MS-related mortality: mention of COVID-19 did not significantly differ between deaths with and without MS.

Through 2020-2021, MS-related deaths peaked in March-April 2020 (when the first COVID-19 epidemic wave hit Northern Italy), and again in late 2020, when the largest epidemic wave in the region caused the greatest excess mortality in the general population, before COVID-19 vaccines became available[Voci2022]. This pattern in MS-related deaths was similar to that observed not only for total mortality, but also for mortality related to other chronic neurological conditions, such as Parkinson's disease[Fedeli2022]. However, we did not observe a significant association between COVID-19 and MS on death certificates. The lack of statistical significance might be explained by limited power due to low numbers of MS-related deaths in analyses restricted to 2020-2021. Therefore, further investigations are warranted to quantify MS-related mortality during the pandemic. A recent pooled analysis of cohort studies on deaths attributed to COVID-19 in patients with MS found a 24% excess in adjusted case fatality with respect to the general population[Prosperini2022]. On the other hand, our findings concur with the evidence from a population-based cohort study conducted in Sweden showing that patients with MS experienced increased mortality during the pandemic compared to a pre-pandemic period, but relative risks versus population-based controls remained unchanged[Longinetti2022].

The MCOD approach is a strength of this study as it provides a more complete overview of MS-related mortality compared to analyses of the UCOD alone. Findings obtained by the analysis of the associations between conditions reported on death certificates are consistent with results of the few cohort studies that have accessed MCOD data to investigate cause-specific mortality risk in MS patients. In Sweden, subjects with MS were at increased risk of mortality related to infections, and specifically sepsis[Burkill2017]. Elevated risks of death related to infections were also reported among US veterans with MS[Capkun2015]. One cohort study investigated multiple sites of infection among MS patients; an increased mortality risk was observed for pneumonia/influenza, aspiration pneumonia, urinary tract infection, and sepsis[Kingwell2020]. Our findings from MCOD data in Italy

confirm the association between MS and pressure ulcers/skin infections previously reported in the US using the MCOD approach[Redelings2006]. The observed interaction with sex in mortality related to UTI and to pneumonia warrants further investigations. Interestingly, the relatively larger OR of UTI as a mentioned cause in MS-related deaths among men (compared to women) is consistent with findings from MCOD analyses carried out in Canada[Harding 2020] and from claims data among US veterans with MS [Capkun2015].

We did not have access to clinical data, and were therefore unable to address questions about the impact of immunological therapies or vaccines, on the risk of infection-related death and vaccine response, including COVID-19 vaccination [Winkelmann2016]. Underreporting of contributing causes of death could be a study limitation, possibly affecting the reporting of MS and infections. As a consequence of excess deaths during the pandemic, increased pressure on physicians might have further hindered the completion of death certificates. However, increased underreporting is unlikely differential among subjects with and without MS. An advantage of using a population-based mortality registry to compare risks of death due to infections is that it captures all decedents and can therefore minimize surveillance bias and selection bias. Furthermore, the use of MCOD captures all related causes of death including those for non-severe conditions (such as UTIs and skin ulcers/infections) that are unlikely to be listed as the UCOD.

In conclusion, this study confirms in contemporary data how infections continue to play a significant role and represent a deadly threat for people with MS. Therefore, more effective prevention approaches and management of infections in MS could potentially impact mortality risk in people with MS. To increase sensitivity, future studies on causes of death related to MS, including those examining the role of COVID-19, should use all causes of death listed on the death certificate, rather than just the underlying cause.

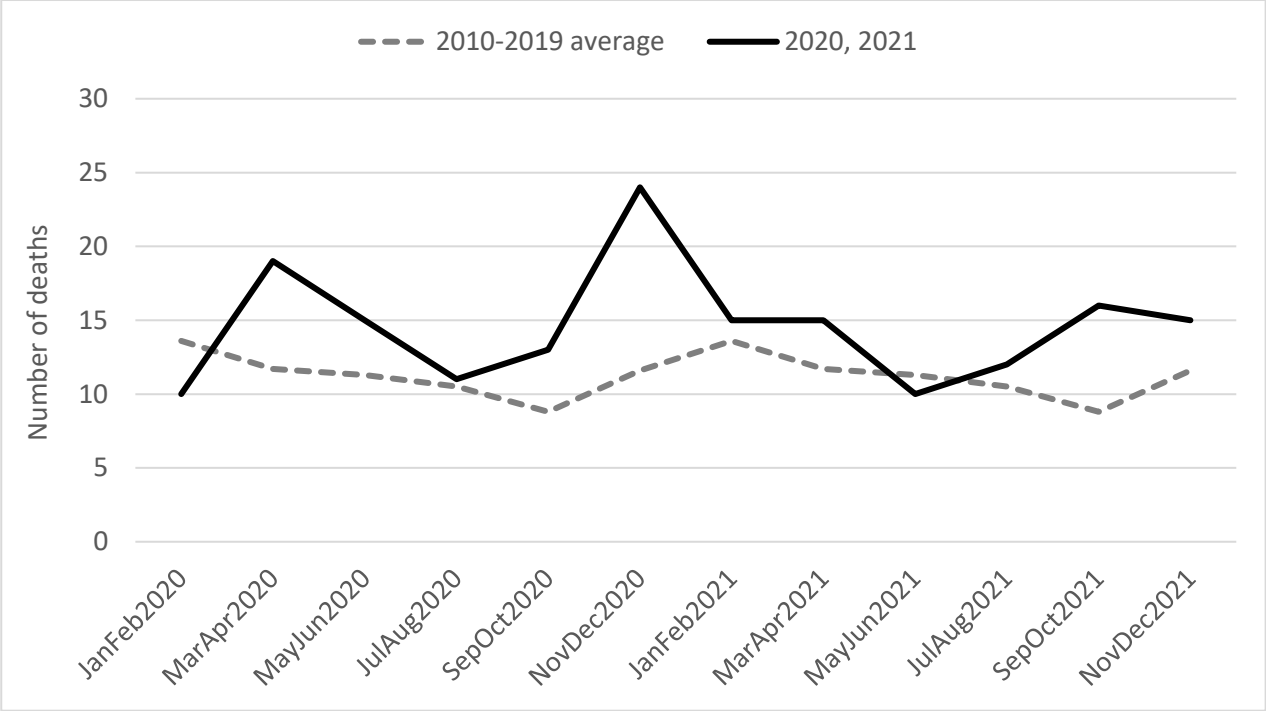
Table 1. Infectious diseases mentioned in multiple sclerosis-related deaths registered in the Veneto region (Italy) through 2010-2021 vs. all other deaths

	n reported in MS-related deaths (n=850)	Percentage of all deaths, MS-related vs non MS-related	OR (95% CI)	p
Influenza and pneumonia	156	18.4% vs. 11.0%	2.72 (2.28-3.25) *	<0.001
Aspiration pneumonia	81	9.5% vs. 3.1%	5.80 (4.58-7.35)	<0.001
Urinary tract infections	38	4.5% vs. 1.7%	4.79 (3.43-6.69) °	<0.001
Pressure ulcers/ skin infections	42	4.9% vs. 2.0%	3.95 (2.88-5.42)	<0.001
Sepsis / septic shock	139	16.4% vs. 8.9%	1.96 (1.63-2.36)	<0.001
COVID-19 (only 2020-2021)	19	10.9% vs. 11.5%	1.14 (0.70-1.84)	0.6

Interaction with sex: *p=0.006 (men OR 1.98, CI 1.47-2.67; women OR 3.35, CI 2.68-4.18); °p=0.004 (men OR 8.16, CI 5.23-12.7; women OR 3.03, CI 1.82-5.02)

Odds ratio (OR) with 95% Confidence Interval (CI) estimated for each infection type by separate conditional logistic regression models. MS-related and non-MS related deaths were matched by age, sex, and calendar year at death.

Figure 1. Bimonthly number of deaths with mention of multiple sclerosis in 2020-2021, compared with the average for corresponding months in 2010-2019. Veneto Region, Italy



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