



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Parkinson's disease related mortality: Long-term trends and impact of COVID-19 pandemic waves

Ugo Fedeli^a, Veronica Casotto^a, Claudio Barbiellini Amidei^a, Mario Saia^b, Silvia Netti Tiozzo^a, Cristina Basso^a, Elena Schievano^{a,*}

^a Epidemiological Department, Azienda Zero, Veneto Region, Italy

^b Clinical Governance Unit, Azienda Zero, Veneto Region, Italy

ABSTRACT

Introduction: Parkinson's disease (PD) mortality burden is increasing worldwide, but accurate estimates on the magnitude of the impact of the COVID-19 pandemic are missing. Mortality rates vary largely when considering PD as underlying cause of death (UCOD), or as one among multiple causes reported in death certificates (MCOD). The aim of this study is to assess COVID-19 impact on PD-related mortality trends using the UCOD and MCODE approach.

Methods: Mortality records between 01/2008-12/2020 of residents aged ≥ 45 years in Veneto Region (Northeastern Italy) with any mention of PD were collected. Age-standardized sex-specific mortality rates were estimated for PD-related deaths as UCOD and MCODE to assess time trends. The average annual percentage change in age-standardized rates (AAPC) was estimated by linear regression models. Monthly mortality in 2020, the first year of the pandemic, was plotted against the 2018–2019 average.

Results: Overall, 13,746 PD-related deaths (2.3% of all deaths) were identified, 52% males, median age 84 years. Proportional mortality increased from 1.9% (2008) to 2.8% (2020). AAPC through 2008–2019 was +5.2% for males and +5.3% for females in analyses of the UCOD, and +1.4% in both genders based on MCODE. Excess in PD-related mortality during 2020 corresponded to 19% for UCOD and 28% for MCODE, with the latter showing two peaks corresponding to the first (28%) and second (59%) pandemic waves.

Conclusion: Age-standardized PD-related mortality rates have steeply increased during COVID-19 pandemic, amplifying a pre-existing long-term trend. Hence, surveillance of mortality associated to PD is warranted in the forthcoming pandemic and post-pandemic years.

1. Introduction

Mortality from Parkinson's disease (PD) is increasing worldwide, including in many European countries [1] and the United States [2]. However, routinely collected mortality statistics based on the underlying cause of death (UCOD) suffer from changes in coding rules, such as the adoption of more recent versions of the International Classification of Diseases, 10th Revision (ICD-10). Analyses of all conditions mentioned in death certificates (the so-called multiple causes of death approach, MCODE) are robust to such changes and allow for a more complete estimate of the mortality burden associated to PD. Moreover, detailed analyses of all diseases reported in death certificates provide useful insights into conditions associated with or contributing to death due to COVID-19 [3]. In the United States, among death certificates listing COVID-19 as a cause of death in 2020, PD was not included among commonly co-occurring diseases [3], while in England, during the first pandemic wave, there was a large excess in PD-related deaths [4]. Nevertheless, accurate estimates on the magnitude of the impact of

COVID-19 pandemic are missing. The Veneto Region (Northeastern Italy, 4.9 million inhabitants) was one of the Italian regions hit the hardest by the COVID-19 pandemic. A previous report on MCODE in Veneto demonstrated an increase in PD-related mortality from 2008 to 2015, especially among males [5]. The aim of the study is to assess the impact of COVID-19 epidemic waves during 2020, the first year of pandemic, on long-term trends of PD-related mortality.

2. Methods

In the regional mortality register, causes of death are coded according to the ICD-10. Standard mortality statistics follow international rules that identify the UCOD from all conditions reported in the death certificate. Usually, the underlying cause chosen by the physician who fills in the certificate is confirmed, but in some cases a different UCOD may be selected if considered more appropriate according to rules set by the World Health Organization. To standardize the UCOD assignment, automated procedures are commonly used. In Veneto, the Automated

* Corresponding author. Epidemiological Department, Azienda Zero, Veneto Region, Via Jacopo Avanzo, 35, 35132, Padova, PD, Italy.

E-mail address: elena.schievano@azero.veneto.it (E. Schievano).

<https://doi.org/10.1016/j.parkreldis.2022.04.011>

Received 25 January 2022; Received in revised form 1 April 2022; Accepted 19 April 2022

Available online 25 April 2022

1353-8020/© 2022 Elsevier Ltd. All rights reserved.

Classification of Medical Entities (ACME) software was used until 2017, and the IRIS software, already adopted in most European countries, from 2018 onwards. The change in software corresponded to the adoption of slightly different rules for the selection of the UCOD based on the 2016 version of the ICD-10. All deaths of subjects aged ≥ 45 years with any mention of PD (ICD-10 code G20) were selected from January 1, 2008, to December 31, 2020. Data for the year 2020 are provisional, with an estimated coverage of 99% of all death certificates. Truncated age-standardized rates (direct standardization, 2013 European standard population), and the proportional mortality (% of total deaths) were calculated separately by sex for PD as the UCOD and as any mention in death certificates (MCOD). The average annual percentage change in age-standardized rates (AAPC) and the relative 95% confidence interval (CI) were obtained for the period preceding the pandemic (2008–2019) from linear regression models with the logarithm of age-standardized rates weighted by the inverse of their variance as the dependent variable and the corresponding year as the regressor.

PD-related mortality for the year 2020 was analyzed by two approaches. In a first descriptive analysis, the monthly number of PD-related deaths (based both on the UCOD and on MCODE) registered in 2020 was plotted against the monthly trends of the previous two years, when the same software for coding of mortality data was used. The ratio of deaths observed in 2020 to those expected (2018–2019 average) was computed with 95% CI based on the Poisson distribution both for the whole year, and separately for the two epidemic waves that occurred in Italy in March–May and October–December. Among deaths with mention of PD, those related to COVID-19 were identified by means of the codes U07.1 and U07.2.

Thereafter, a time-series approach was adopted to estimate more accurately the excess number of deaths observed in 2020. To this purpose, a Seasonal Autoregressive Integrated Moving Average model (SARIMA) was applied to monthly age-standardized mortality rates based on MCODE. By this method, the components of the time series (seasonality and trend), and the correlation between consecutive months and between the same month of consecutive years were taken into account. The model based on mortality rates registered in 2008–2019 was adopted to forecast mortality rates for the year 2020; the excess mortality was therefore estimated as the ratio between observed rates and those predicted by the model.

Data were analyzed using STATA software (Release 15) and R software (version 4.1.3).

3. Results

Overall, PD was mentioned in 13,746 death certificates in the study period, corresponding to 2.3% of all deaths registered among residents aged ≥ 45 years; the proportional mortality increased from 1.9% in 2008 to 2.8% in 2020 (from 1.8% to 3.2% and from 1.9% to 2.5% in males and females, respectively). Median age at death was 84 years (interquartile range 79–88), 52% of decedents were males. Out of all deaths with mention of the disease, PD was selected as the UCOD in 45% ($n = 6141$). Such percentage was 41% in 2008–2017, when UCOD selection was performed through the ACME software, and increased up to 55% in 2018–2020, when updated coding rules were applied by means of the IRIS software.

Age-standardized mortality rates increased in both sexes, with a larger increase when considering PD as the UCOD with respect to MCODE. The AAPC through the 2008–2019 period for mortality due to PD as the UCOD was +5.2% (CI 3.5–6.9%) and +5.3% (CI 3.3–7.5%) in males and females, respectively and the corresponding estimates for the MCODE analysis were +1.4% (CI 0.5–2.4%) and +1.4% (CI 0.2–2.6%). Fig. 1 shows that a sharp increase in rates based on the UCOD could be observed especially among males from 2017 to 2018, with the adoption of new rules to determine the UCOD. By contrast, the increase in mortality in 2020, the first year of the pandemic, was more evident for the MCODE analyses, regardless of sex.

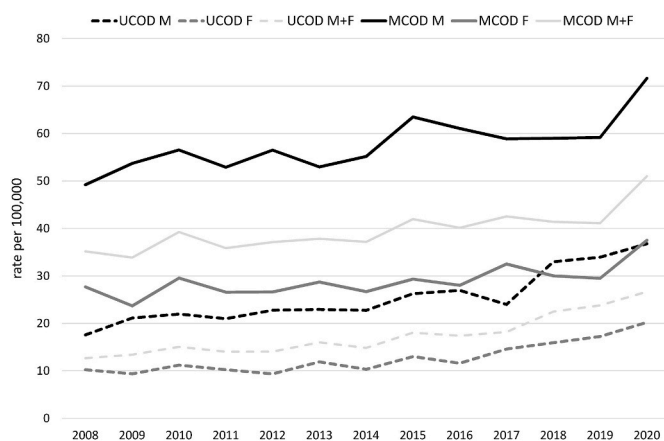


Fig. 1. Age-standardized PD-related mortality rates per 100,000 by sex and overall, based on the analysis of the underlying cause of death (UCOD) and on the multiple causes of death (MCOD) approach.

According to provisional data, in 2020 there were overall 56,412 deaths in the Veneto region. Among subjects aged ≥ 45 years, 810 deaths were registered with PD as the UCOD and 1554 deaths with any mention of PD (MCOD). The percentage increase with respect to the average number of deaths observed in 2018–2019 was 16% for all causes, 19% (CI 11–28%) for PD as the UCOD, while in the MCODE analysis PD-related deaths increased as high as 28% (22–35%).

Based on MCODE, overall 343 excess PD-related deaths were observed in 2020. Out of these, COVID-19 was mentioned in 57% of death certificates ($n = 197$), most of which were registered in November–December 2020. Fig. 2 clearly shows two distinct peaks of PD-related deaths, corresponding to the first minor COVID-19 epidemic wave in March–April, and to the second larger epidemic wave in October–December 2020. During the first pandemic wave the increase with respect to figures observed in the same months of the reference period (2018–2019) was 28% (CI 15–42%), whereas the excess in the second wave corresponded to 59% (CI 46–73%).

The time-series analysis applied to monthly age-standardized rates accounted for the ageing of the regional population and for the long-term growing trend in mortality from PD. A SARIMA (2,1,1)(2,0,0)₁₂ model was selected as the best model which minimized the value of the Akaike Information Criteria. The observed age-standardized rate in 2020 was higher than that predicted: $51.0 \times 100,000$ (CI 48.5–53.6) vs. 41.1, corresponding to a +24% of percentage change. This increase was mostly attributable to the first (March +26%, April +37%) and second

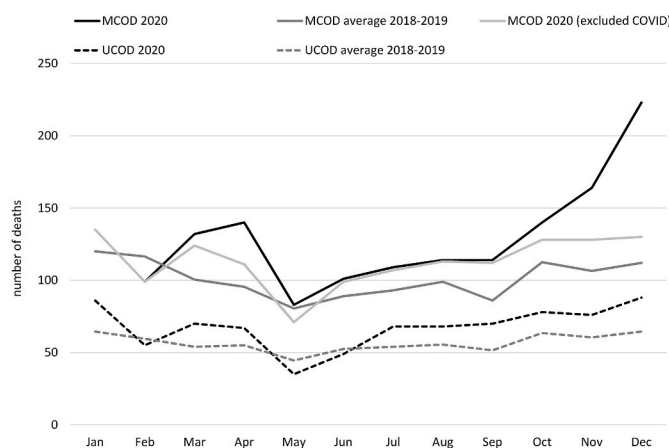


Fig. 2. Observed number of PD-related deaths by month in 2020 plotted against the average 2018–2019 trend, based on the analysis of the underlying cause of death (UCOD) and on the multiple causes of death (MCOD) approach.

pandemic wave (October +27%, November +49%, December +104%).

4. Discussion

The study confirms the long-term increasing trend in PD-related mortality in both sexes, and unveils the large impact of the pandemic, with an increase in PD-related deaths largely exceeding that observed for overall mortality. The study also demonstrates that time trends in mortality from PD based on the UCOD are likely overestimated also due to changes in internationally applied coding rules. By contrast, analyses limited to the UCOD might underestimate the burden of PD-related mortality during the pandemic due to competing causes of death (notably, deaths attributed to COVID-19 in subjects affected by PD). The MCODE approach, taking into account all diseases mentioned in the death certificates is more robust to such biases.

The pandemic has both directly and indirectly impacted the clinical status of people with PD. While the risk for individual patients to be infected by SARS-CoV-2 is predominantly dependent on functional autonomy, living environment, and number of social contacts, worse COVID-19 outcomes have been observed among PD patients both in hospital and in long-term care settings. Among hospitalized COVID-19 patients, those with PD were characterized by the presence of more risk factors for severe COVID-19 (old age, male sex, specific comorbidities) than non-PD patients [6]. Patients with PD are more likely to experience respiratory muscle rigidity, respiratory weakness, impaired cough reflex and dysphagia predisposing to pneumonia, which could lead to a greater severity of COVID-19. Furthermore, patients with PD may experience worsening of both motor and non-motor symptoms during the infection [7]. A pooled analysis showed that PD was associated with poor in-hospital outcomes, including severe disease (odds ratio 2.61, 95% CI 1.98–3.43) and mortality from COVID-19 (odds ratio 2.63, 95% CI 1.50–4.60), and the risk increased with age [7]. Furthermore, among Dutch nursing home residents affected by COVID-19, those with PD had a strongly increased risk of death compared to those without PD [8]. People with PD have also experienced indirect consequences of the pandemic. The introduction of lockdown restrictions and social disruption contributed to compromise the overall wellbeing of subjects with PD, including negative effects on their motor status and mental health compared to pre-pandemic conditions [9]. Furthermore, patients may have experienced barriers in the access to care (delays in routine clinical visits and elective surgical procedures).

Nonetheless, sparse data are available about the impact of the pandemic on PD-related mortality at the population level. During 2020 in Sweden there was an increase in the years of potential life lost from PD, limited to the first wave of the COVID-19 pandemic [10]. In England a 26% excess deaths from PD was observed between March and June 2020, mostly accounted by deaths without mention of COVID-19. The present time-series analysis based on MCODE found a 24% increase in PD-related mortality in 2020, with two peaks corresponding to the epidemic waves. In December 2020 the mortality rate exceeded that expected by over 100%. Death certificates reporting COVID-19 accounted for the majority of the increase in mortality associated to PD. As regards the remaining excess of PD-related deaths, it is difficult to disentangle the role of underdiagnosed COVID-19, especially in the early phases of the pandemic (first wave), from an increased mortality that could be attributed to indirect consequences of COVID-19, such as compromised healthcare support, with reduced or delayed access to

hospital-based services and social isolation.

Among the strengths of this study is the standardized methodology for coding MCODE data, limiting the influence of changes and inconsistencies in coding practices. Furthermore, population-based analyses spanning over twelve years prior to the pandemic, allowed for a more solid comparison and a more accurate estimate of the impact of COVID-19. Nonetheless, there are limits inherent to the accuracy of mortality records. In the Veneto Region between 2008 and 2015, PD was mentioned in only 60% of death certificates of patients with a previous diagnosis of PD [5]; such sensitivity is within the range reported from older reports and recent UK studies: 53% in North Wales [11], and 68% in Scotland [12].

Among neurological disorders, PD was the fastest growing in prevalence, disability, and deaths through the past decades [1]. Ageing of the population and the growing prevalence of neurodegenerative disorders, improved diagnostic approaches, declining mortality from competing causes (e.g. cancer and circulatory diseases), occupational and environmental exposures are among the main reasons for the increase in deaths from PD observed globally [1,2,5]. The current evidence has shown a further increase in PD-related mortality during COVID-19 pandemic waves, which has strongly amplified the pre-existing long-term trend. Therefore, in spite of possible limits inherent to this approach, surveillance of trends in PD-related mortality should become a priority in the forthcoming pandemic and post-pandemic years.

References

- [1] V.L. Feigin, et al., Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, *Lancet Neurol.* 18 (2019) 459–480.
- [2] S. Rong, G. Xu, B. Liu, Y. Sun, L.G. Snetselaar, R.B. Wallace, B. Li, J. Liao, W. Bao, Trends in mortality from Parkinson disease in the United States, 1999–2019, *Neurology* 97 (2021) e1986–e1993.
- [3] A.V. Gundlapalli, Death certificate–based ICD-10 diagnosis codes for COVID-19 mortality surveillance — United States, January–December 2020, *MMWR Morb. Mortal. Wkly. Rep.* 70 (2021).
- [4] J. Wu, M. Mafham, M.A. Mamas, M. Rashid, E. Kontopantelis, J.E. Deanfield, M. A. de Belder, C.P. Gale, Place and underlying cause of death during the COVID-19 pandemic: retrospective cohort study of 3.5 million deaths in England and Wales, 2014 to 2020, *Mayo Clin. Proc.* 96 (2021) 952–963.
- [5] U. Fedeli, E. Schievano, Increase in Parkinson's disease-related mortality among males in Northern Italy, *Park. Relat. Disord.* 40 (2017) 47–50.
- [6] R. Scherbaum, E.H. Kwon, D. Richter, D. Bartig, R. Gold, C. Krogias, L. Tönges, Clinical profiles and mortality of COVID-19 inpatients with Parkinson's disease in Germany, *Mov. Disord.* (2021) 1049–1057.
- [7] C. Putri, T.I. Hariyanto, J.E. Hananto, K. Christian, R.F.V. Situmeang, A. Kurniawan, Parkinson's disease may worsen outcomes from coronavirus disease 2019 (COVID-19) pneumonia in hospitalized patients: a systematic review, meta-analysis, and meta-regression, *Park. Relat. Disord.* 87 (2021) 155–161.
- [8] J.J.S. Rutten, J. van Kooten, A.M. van Loon, L.W. van Buul, K.J. Joling, M. Smalbrugge, C.M.P.M. Hertogh, Dementia and Parkinson's disease: risk factors for 30-Day mortality in nursing home residents with COVID-19, *J Alzheimers Dis* 84 (2021) 1173–1181.
- [9] S.A. Schneider, A. Hennig, D. Martino, Relationship between COVID-19 and movement disorders: a narrative review, *Eur. J. Neurol.* 29 (4) (2022) 1243–1253, <https://doi.org/10.1111/ene.15217>.
- [10] M. Axenhus, S. Schedin-Weiss, B. Winblad, A. Wimo, Changes in mortality trends amongst common diseases during the COVID-19 pandemic in Sweden, *Scand. J. Publ. Health* (2021), <https://doi.org/10.1177/14034948211064656>.
- [11] P. Hobson, J. Meara, Mortality and quality of death certification in a cohort of patients with Parkinson's disease and matched controls in North Wales, UK at 18 years: a community-based cohort study, *BMJ Open* 8 (2018), e018969.
- [12] H. Shi, C. Counsell, Accuracy of death certificates for recording parkinsonian syndromes and associated dementia, *J. Neurol.* 268 (2021) 140–146.