Diagnosis, Assessment
& Disease Monitoring

Impact of COVID-19 pandemic on mortality rate in memory clinic patients

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Abstract

INTRODUCTION: We investigated whether mortality in memory clinic patients changed due to coronavirus disease 2019 (COVID-19) pandemic.

METHODS: We included patients from the Amsterdam Dementia Cohort: (1) $n = 923$ pandemic patients (baseline visit: 2017–2018, follow-up: until 2021), and (2) $n = 830$ historical control patients (baseline visit: 2015–2016, follow-up: until 2019). Groups were well-balanced. We compared mortality during pandemic with historical control patients using Cox regression. Differences in cause of death between groups were explored using Fisher's exact test.

RESULTS: Pandemic patients had a higher risk of mortality than historical control patients (hazard ratio [HR] [95% confidence interval {CI}] = 1.34 [1.05–1.70]). Stratified for syndrome diagnosis, the effect remained significant in dementia patients (HR [95% CI] = 1.35 [1.03–1.78]). Excluding patients who died of COVID-19-infection, the higher mortality risk in pandemic patients attenuated (HR [95% CI] = 1.24 [0.97–1.58]). Only the difference in cause of death between pandemic patients and historical control patients for death to COVID-19-infection ($p = 0.001$) was observed.

CONCLUSION: Memory clinic patients had increased mortality risk during COVID-19 compared to historical control patients, attributable to dementia patients.

KEYWORDS
cause of death, COVID-19, dementia, infection, MCI, mortality, pandemic, subjective cognitive decline

Highlights

- We investigated if mortality rates in memory clinic patients changed due to COVID-19 pandemic.
- We included patients along the cognitive continuum, including SCD, MCI, and dementia.
- We used a well-balanced historical control group.

- Memory clinic patients had higher risk for mortality during COVID-19 lockdown.
- Our results indicate that excess mortality is mainly caused by death to COVID-19 infection.

1 | INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, high rates of mortality were reported worldwide, with elderly being particularly at risk of mortality.[1,2] People with cognitive impairment or dementia generally have higher mortality risk than people without cognitive impairment or dementia, and were also at risk for a severe COVID-19 infection.[3–7] Previous studies showed that dementia was an important risk factor for in-hospital deaths of COVID-19 infected patients, and the 6-month mortality risk in dementia patients with a COVID-19 infection was over 20%.[6,8]

Not only the COVID-19 infection itself, but also the restrictive measures due to COVID-19 may have affected people with cognitive impairment or dementia. The COVID-19 regulations caused disruption in many healthcare and support systems for this vulnerable group, having major consequences on patients' daily routine, which may have led to faster progression of the disease.[9–12] Both patients and caregivers reported worries for faster cognitive decline during COVID-19 lockdown.[9,10] In addition, there is objective evidence indicating that memory clinic patients showed faster cognitive decline during COVID-19 lockdown than before.[13–15]

It is conceivable that the combination of (1) high risk for a severe COVID-19 infection, (2) faster disease progression due to the restrictive measures, but also (3) worse access to healthcare and support during lockdowns and postponed healthcare led to excess mortality in people with cognitive impairment or dementia during the pandemic.[16] Previous studies investigating the impact of COVID-19 pandemic on mortality in people with cognitive impairment or dementia focused mainly on patients with a COVID-19 infection, and not on the general impact of the COVID-19 restrictions on mortality.[7,8] Furthermore, other studies investigating the impact of the COVID-19 pandemic on mortality are still limited if a balanced control group is considered, the same implies for including predementia stages.[3,7,8,17] Therefore, we aimed to investigate the effect of COVID-19 pandemic on mortality rate in a mixed memory clinic population, including people with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and dementia, compared to a balanced historical control patient group.

2 | METHODS

2.1 | Participants

In this case-control study, we included patients from the Amsterdam Dementia Cohort (ADC).[18,19] We selected two groups of patients: (1)

Pandemic patients: patients with a baseline visit at the memory clinic between January 2017 and December 2018, with 3–4 years of follow-up until December 31, 2021—that is, follow-up up to and including the restrictive COVID-19 measures in the Netherlands. The pandemic group consisted of n = 1022 patients with a diagnosis SCD (n = 254 (25%)), MCI (n = 133 (13%)), dementia (n = 426 (42%); for different types of dementia see Table S1 in the Supplemental Material), and other diagnosis (n = 209 (20%); for example, a neurological, psychiatric, or uncertain diagnosis). (2) Historical control patients: patients with a baseline visit between January 2015 and December 2016, with 3–4 years of follow-up until December 31, 2019, that is, follow-up ended before the COVID-19 pandemic. In total, n = 930 patients were identified as historical control patients, n = 195 (21%) SCD, n = 137 (15%) MCI, n = 421 (45%) dementia, n = 177 (19%) other diagnosis. Patients were included if data on age, sex, education level, diagnosis, MMSE (Mini-Mental State Examination) score, and comorbidity were complete.

All patients underwent cognitive screening at Alzheimer Center Amsterdam. The baseline diagnostic work-up consisted of neurological, physical, and neuropsychological evaluation, magnetic resonance imaging (MRI), laboratory tests and lumbar puncture for cerebrospinal fluid (CSF) measurement. Diagnosis was established during a multidisciplinary consensus meeting and followed conventional diagnostic guidelines.[20–26]

The study was approved by the local Medical Ethical Committee. All patients provided written informed consent for their clinical data to be used for research purposes. Consent was obtained according to the Declaration of Helsinki.

2.2 | Mortality

Mortality follow-up data were retrieved from Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek; i.e., cause of death). Data on date of death were available for the entire cohort, as described above. For data on cause of death, 90% of ADC data could be linked to Statistics Netherlands (n = 923 pandemic patients and n = 830 historical control patients). Statistics Netherlands collects data of all persons registered in the Netherlands. All included patients of the ADC were linked to data of Statistics Netherlands by a unique combination of four variables: sex, date of birth, postal code, and house number. The causes of death were coded according to the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) of the World Health Organization (WHO).[27] With regard to the cause of death due to COVID-19 infection, new codes have been issued for

COVID-19 according to ICD-10. Statistics Netherlands is responsible for the cause of death validation. Results regarding cause of death were based on calculations by the authors of this paper using nonpublic microdata from Statistics Netherlands.[28]

We used mortality as an outcome measure. In order to align the follow-up period between groups and to exclude a COVID-19 effect in the historical control group, we artificially limited the follow-up time window for the historical control patients until December 31, 2019, and for the pandemic patients until December 31, 2021. Time to death was measured in years from the diagnosis at baseline appointment in the memory clinic to the date of death. Information on excess mortality can be found in Supplemental Text 1 and Figure S1.

2.3 | Balanced groups

First, we assessed whether the pandemic patients and historical control patients were well balanced on demographic characteristics and comorbidity. We selected the following covariates: age, sex, diagnosis, MMSE score, education level, and comorbidity. The covariates were inspected on completeness and similarity of distribution between the pandemic and historical control group. The balance between groups was assessed based on absolute standardized mean difference. As the absolute standardized mean differences were under 0.1 for all selected covariates (Figure 1), groups were considered adequately balanced. This implicated that there was no need to perform a matching analysis, and that adjusting for the selected covariates in the following model was sufficient. The analyses for assessing the balance between pandemic patients and historical control patients were carried out in R Studio 4.0.3, with package MatchIt.[29]

2.4 | Statistical analyses

First, we performed Cox regression analyses to compare the all-cause mortality rate during COVID-19 pandemic with historical control patients (univariate and multivariate model). In the multivariate model, age, sex, diagnosis, MMSE score, education level, and comorbidity were added as covariates to the model. Education level was assessed using Verhage scale: ranging from 1 (none or low educational level) to 7 (high educational level: university degree).[30] Comorbidities were determined using the Charlson Comorbidity Index (CCI), which was composed based on medical history and medication use (CCI score ranges from 0 (low comorbidity) to 37 (high comorbidity)).[31] In addition, we performed the Cox regression analyses stratified by syndrome diagnosis: SCD, MCI, dementia, and other diagnosis. Kaplan-Meier curves were made stratified by syndrome diagnosis. Furthermore, we did a sensitivity analysis in which we excluded patients who died of COVID-19 infection. Subsequently, we examined whether the following variables modified the observed effect of pandemic patients versus historical control patients on mortality rate: sex, depressive feelings (Geriatric Depression Scale (GDS)) at baseline, comorbidity, education level, MMSE at baseline, syndrome diagnosis, and amyloid status

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed literature using traditional sources (e.g., Pubmed). Previous studies showed that dementia was an important risk factor for death to coronavirus disease 2019 (COVID-19) infection. They focused mainly on patients with COVID-19 infection, and not on the general impact of COVID-19 restrictions on mortality. Additionally, data are still limited if a balanced control group and pre-dementia stages are considered.

2. **Interpretation**: Memory clinic patients had increased risk of mortality during COVID-19 pandemic compared to historical control patients, mostly attributable to dementia patients. The results indicate that excess mortality is mainly caused by death to COVID-19 infection, and less likely as indirect effect of lockdown.

3. **Future directions**: Our results could inform governments and policy makers on the impact of lockdown-restrictions in memory clinic patients. The results of this study indicate that it is important that good quality healthcare continues for memory clinic patients during lockdown to diminish the effect of postponed care and undertreatment, and risk for mortality.

(measured with CSF). Finally, difference in causes of death between pandemic patients and historical control patients was explored by using Fisher's exact test. Fisher's exact test and cox regression analyses were carried out in SPSS Statistics version 25. p-Value of < 0.05 was considered significant.

3 | RESULTS

3.1 | Descriptive statistics

Demographic and clinical characteristics of pandemic patients and historical control patients, after linking to Statistics Netherlands, are summarized in Table 1. Mean age of the pandemic patients was 63 ± 9 years, $n = 378$ (41%) were female and mean MMSE score was 24 ± 5. The mean age of the historical control patients was 63 ± 9 years, $n = 360$ (43%) were female and MMSE score was 24 ± 5. Demographic and clinical characteristics of patients before linking to Statistics Netherlands can be found in the supplemental material (Table S1).

3.2 | Mortality in pandemic patients and historical control patients

In the pandemic patient group, $n = 165$ (18%) patients died during the 3–4 years of follow-up time. Among the historical control patients,
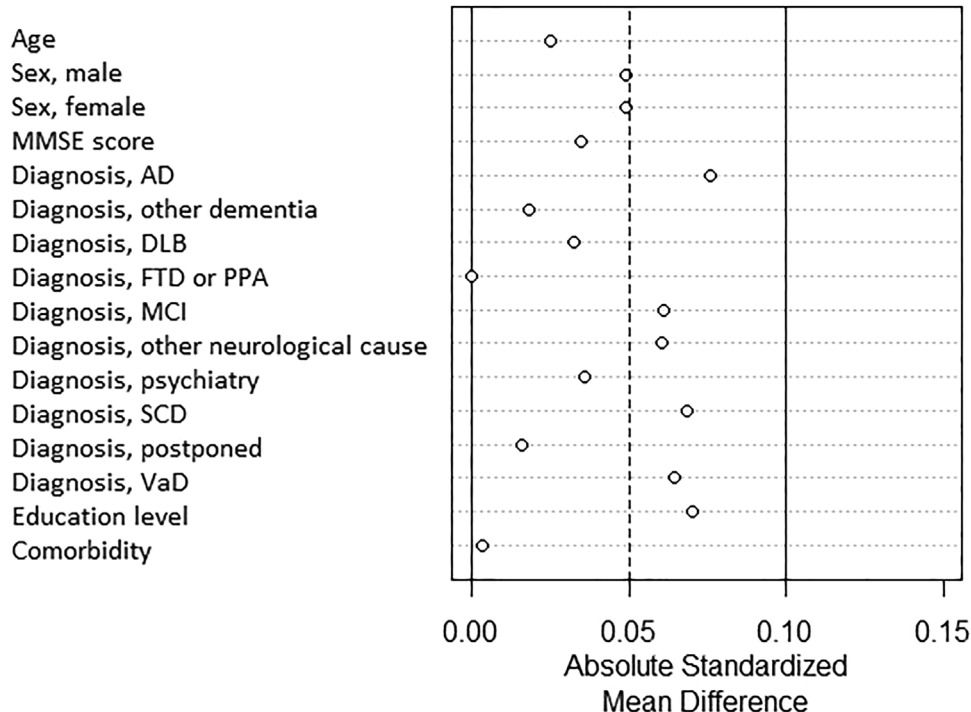
FIGURE 1 Absolute standardized mean differences between pandemic patients and historical control patients for the covariates age, sex, MMSE, diagnosis, education level, and comorbidity. AD, Alzheimer's dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PPA, primary progressive aphasia; SCD, subjective cognitive decline; VaD, vascular dementia.

TABLE 1 Demographic characteristics.

Parameter	Pandemic patients $n = 923$ (100%)	Historical control patients $n = 830$ (100%)
Age at baseline, mean ± SD	63 ± 9	63 ± 9
Sex, female n (%)	n = 378 (41%)	n = 360 (43%)
Education level (Verhage code),		
mean ± SD	5 ± 1	5 ± 1
MMSE at baseline, mean ± SD	24 ± 5	24 ± 5
Diagnosis at baseline, n (%)		
SCD	n = 231 (25%)	n = 183 (22%)
MCI	n = 118 (13%)	n = 123 (15%)
Dementia	n = 379 (41%)	n = 367 (44%)
Other	n = 195 (21%)	n = 157 (19%)
CCI score at baseline, mean ± SD	2.9 ± 1.7	2.9 ± 1.6
GDS score at baseline, mean ± SD	4.0 ± 3.4	3.9 ± 3.2
Amyloid status available (CSF), n (%)	n = 679 (74%)	n = 603 (73%)
Amyloid positive, n (%)	n = 353 (52%)	n = 296 (49%)

Abbreviations: CCI, Charlson Comorbidity Index; CSF, cerebrospinal fluid; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SCD, subjective cognitive decline; SD, standard deviation.

TABLE 2 Cox regression models for all-cause mortality in pandemic patients and historical control patients.

Parameter	Model 1 HR [95% CI]	Model 2 HR [95% CI]
All diagnoses	1.26 [0.995–1.593]	1.34* [1.051–1.697]
SCD	0.98 [0.264–3.656]	0.59 [0.138–2.494]
MCI	1.84 [0.770–4.376]	1.83 [0.756–4.410]
Dementia	1.33* [1.011–1.737]	1.35* [1.025–1.784]
Other diagnosis	1.37 [0.721–2.595]	1.25 [0.648–2.401]

Note: Model 1: group (pandemic patients and historical control patients). Model 2: group, adjusted for age, sex, education level, MMSE, diagnosis, CCI score.

Abbreviations: HR, hazard ratio; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

*$p < 0.05$.

$n = 120$ (14.5%) patients died. Table 2 shows that pandemic patients had increased risk of all-cause mortality compared to historical control patients after adjusting for the covariates age, sex, education level, MMSE score, diagnosis, and CCI score (HR [95% CI] = 1.34 [1.05–1.70]). When we stratified by syndrome diagnosis, we found that the effect on mortality was only significant in the dementia patients, although effect sizes in MCI and other diagnoses were rather similar (Table 2; Figure 2). In the sensitivity analysis, excluding the patients who died of COVID-19 infection, the effect attenuated (multivariate model: HR [95% CI] = 1.24 [0.97–1.58]). Furthermore, we investigated effect modification on the following covariates: sex, depressive feelings, comorbidity, education level, MMSE at baseline, syndrome diagnosis, and amyloid status. None of these variables was identified as effect modifier (see Table S2 in Supplemental Material).

Finally, when comparing causes of death between pandemic patients and historical control patients, we see a higher mortality rate in pandemic patients for death caused by COVID-19 infection and other causes of death (i.e., external cause of death). A lower mortality rate in pandemic patients is observed for death caused by neoplasmata and heart and vascular diseases. Only the difference between pandemic patients and historical control patients for death caused by COVID-19 infection is significant, not for other causes of death (see Table 3).

4 | DISCUSSION

In the current study, we showed that memory clinic patients had an increased risk of mortality during COVID-19 pandemic than memory clinic patients before the pandemic. This increased risk was mostly attributable to patients with dementia. Sex, depressive feelings, comorbidity, education level, cognition at baseline, syndrome diagnosis, and amyloid status did not influence the effect during the pandemic. When looking into causes of death, the higher mortality rate was mostly attributable to death due to COVID-19 infection. When patients who died of COVID-19 infection were excluded from the analysis, the increased risk of mortality during COVID-19 pandemic attenuated compared to historical control patients, although a nonsignificantly increased risk remained.

Previous studies have already found evidence that dementia is an important risk factor for death after a COVID-19 infection.[6–8,17] However, these studies focused only on a COVID-19 infection in relation to mortality, and not the COVID-19 restrictions and other factors that could be involved in mortality (e.g., comorbidity). Furthermore, there was no adequate balance between the pandemic-exposed group and historical control group. In addition, pre-dementia stages were not taken into account in this previous study, and cause of mortality was not addressed. Our results, comparing the pandemic patients to a well-balanced historical control patient group, confirm that there is indeed an increased risk of mortality in memory clinic patients during pandemic. When patients who died of COVID-19 infection were excluded from the analysis, the increased risk of mortality during COVID-19 pandemic attenuated compared to historical control patients. Therefore, we have not proven that excess mortality is due to the restrictions, as hypothesized in the introduction, but mainly due to COVID-19 infection itself. There are other studies that prove that restrictions do affect this patient population.[9,10,15] However, we do not know whether these observed effects, such as worsened cognition, are also present in the long term, and whether this leads to increased mortality. We think that for observing increased mortality due to COVID-19 restrictions, our time window in the current study was too short.

In the current study, we found a higher risk of mortality during COVID-19 pandemic mostly attributable for patients with dementia, and less for pre-dementia patients. It is possible that patients with dementia are more vulnerable for getting a COVID-19 infection, as they might not understand the restrictive measures that well. Additionally, dementia patients are possibly more vulnerable for developing more severe symptoms of the infection, compared to patients without dementia.[6–8,17] Furthermore, patients with dementia generally have more comorbidities than patients without dementia.[32,33] As healthcare was disrupted in times of lockdown, much healthcare was postponed. This might have resulted in undertreatment of comorbidities and, therefore, higher risk for mortality (e.g., due to COVID-19 infection). Indications of the effect of postponed healthcare and undertreatment are cautiously shown in this study, as a (nonsignificantly) smaller number of people died due to neoplasmata or heart and vascular diseases during the pandemic; due to postponed healthcare, a diagnosis of neoplasmata or heart and vascular diseases may also been postponed during the pandemic or even been unnoticed, resulting in worse health and higher risk of mortality. If this were true, then rate of death due to these conditions should increase in the years to come. Of note, a (nonsignificantly) larger number of people seem to have died of other cause of death (including, but not limited to external cause of death, infectious diseases, diseases of the digestive system, etc.) during the pandemic. For example, people who badly fell in their own home may have been found too late by a healthcare provider due to the COVID-19 restrictions. Previous studies show that people living with dementia (at home) have increased risk of mortality when good quality healthcare is limited.[34,35] Especially in the first year of the pandemic, with
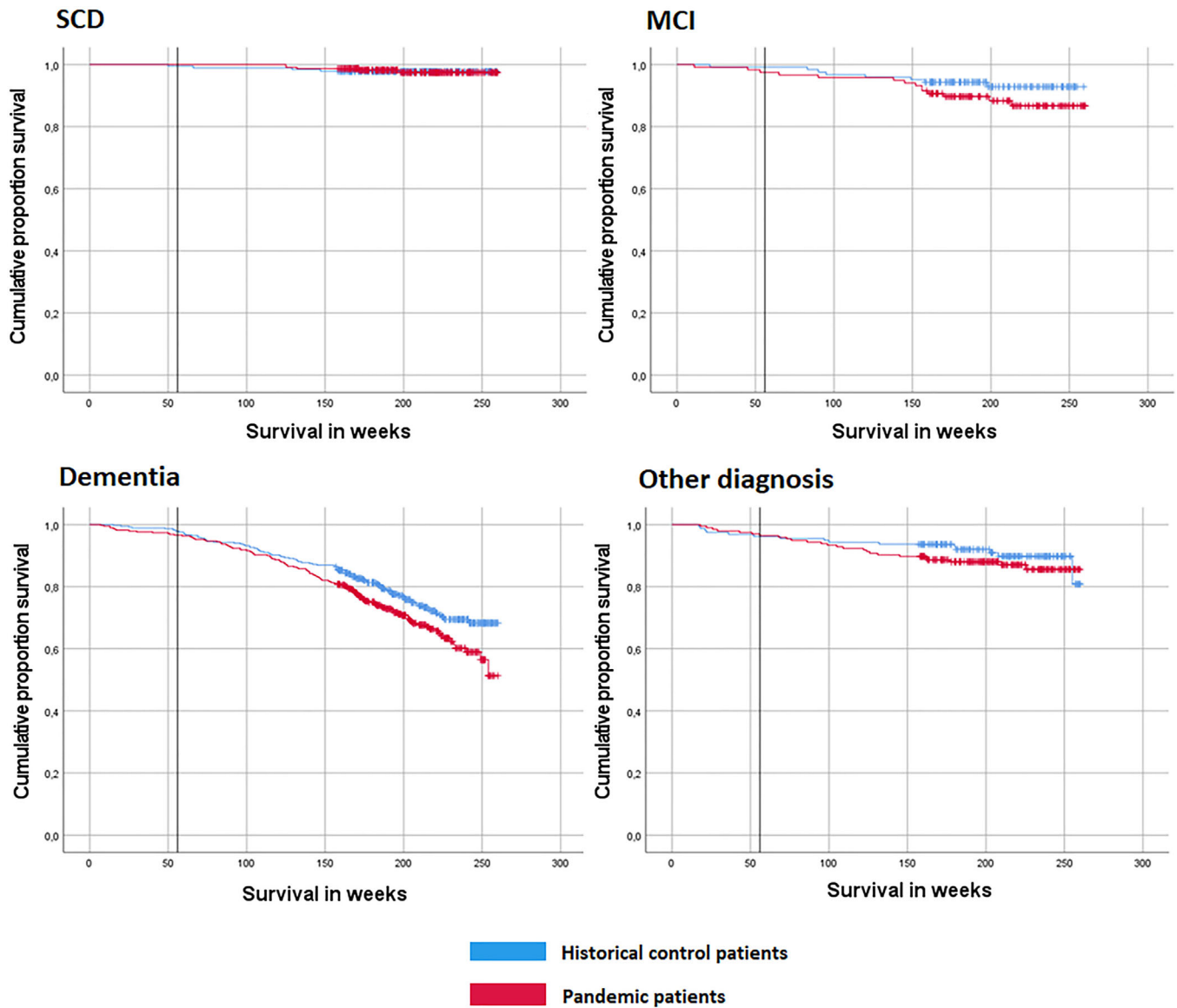
FIGURE 2 Kaplan-Meier curves in pandemic patients and historical control patients, stratified by syndrome diagnosis: subjective cognitive decline (SCD), mild cognitive impairment (MCI), dementia, and other diagnosis. The vertical line indicates the start of the coronavirus disease 2019 (COVID-19) pandemic for the first pandemic patient.

TABLE 3 Causes of death.

	Pandemic patients 1 n = 165 (100%)	Historical control patients n = 120 (100%)	p-Value (2-sided)
Neoplasmata	11 (7%)	15 (13%)	0.326
Organic and psychological disorders, and diseases of the nervous system	93 (56%)	69 (58%)	0.216
Dementia	54 (58%)	38 (55%)	0.240
Heart and vascular diseases	20 (12%)	19 (16%)	0.873
COVID-19	11 (7%)	0	0.001
Other cause of death [a]	30 (18%)	17 (14%)	0.139

Abbreviation: COVID-19, coronavirus disease 2019.

[a] I.e., infectious diseases, endocrine diseases, diseases of the respiratory system, diseases of the digestive system, diseases of bone and skin tisssue, diseases of genitourinary system, abnormal lab results, external cause of death.

the introduction of the strictest COVID-19 measures, good quality healthcare was definitely worse and lots of healthcare was postponed. Due to this postponed and worse quality healthcare, people living with dementia should have increased risk of mortality. Finally, it is possible that the follow-up time in the current study was too short for observing a higher mortality rate in pre-dementia patients. We previously showed faster cognitive decline in memory clinic patients during pandemic compared to historical control patients, especially in pre-dementia patients.[15] The findings of this study suggest an acceleration in disease progression, especially in pre-dementia patients, yet time to mortality may still be beyond the window of follow-up in the current study.

Among the limitations of the current study is that patients were included in a tertiary memory clinic, this might diminish the generalizability of the study's results (e.g., young patient population). However, we included SCD, MCI, and dementia patients in this study, representing the full cognitive continuum. Moreover, the included patients were relatively young. This may have influenced the observed effect in the current study, as the effect may even have been larger in an older cohort. Despite the relative young age, we still found an effect of increased risk of mortality during the pandemic. Another potential limitation is that we could not link all our ADC patients to Statistics Netherlands. Due to privacy reasons, probabilistic linkage procedures are used, which resulted in a considerable proportion of 90% successful linkage, still keeping two large groups of over 800 patients each. Furthermore, regarding to causes of death, Statistics Netherlands only allowed us to report groups larger than 10 persons, due to the potential risk of tracing back to the person and losing patient's anonymity. This led to a category "other cause of death" with a wide range of death causes which may be of particular relevance, yet do not allow analysis on an individual basis. Last, it is important to be aware of the fact that COVID-19 lockdowns, regulations and healthcare accessibility differed across countries worldwide. When comparing study results regarding mortality rates across countries, it must be done with caution.

Among the strengths of this study, is our methodological rigor, where we used a historical control patient group that was well-balanced and, hence, comparable to the pandemic group at baseline. In addition, we were able to link our clinical data to big registries for receiving date of death and cause of death, adding valuable information to the study. Furthermore, we stratified for syndrome diagnosis, investigating the effect of COVID-19 pandemic on mortality rate along the full cognitive continuum.

In conclusion, memory clinic patients, particularly patients with dementia, had increased risk of mortality during times of COVID-19 pandemic than before. This excess mortality was largely caused by COVID-19 infection, rather than by COVID-19 pandemic and corresponding restrictive measures.

AUTHOR CONTRIBUTIONS

Els D. Bakker, Ingrid S. van Maurik, and Wiesje M. van der Flier designed the study. Els D. Bakker and Ingrid S. van Maurik analyzed the data. Els D. Bakker, Ingrid S. van Maurik, and Wiesje M. van der Flier interpreted the data and wrote the manuscript. Els D. Bakker, Ingrid S. van Maurik, Marissa D. Zwan, Freek Gillissen, Pieter J. van der Veere, Femke H. Bouwman, Yolande A.L. Pijnenburg, and Wiesje M. van der Flier revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST STATEMENT

Research programs of W.M.F. have been funded by ZonMW, NWO, EU-FP7, EU-JPND, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Pasman Stichting, Biogen MA Inc, Boehringer Ingelheim, Life-MI, AVID, Roche BV, Fujifilm, Combinostics. W.M.F. is consultant to Oxford Health Policy Forum CIC, Roche, and Biogen MA Inc. W.M.F. has been an invited speaker at Boehringer Ingelheim, Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape). All funding is paid to her institution. W.M.F. participated in an advisory board of Biogen MA Inc. W.M.F. is associate editor at Brain. I.S.M. received a consultancy fee (paid to the university) from Roche. F.H.B. received Optina diagnostics payments and roche, biogen payments to her institution. Y.A.L.P. has received funding from the Dutch Brain Foundation and the Mooiste Contact Fonds (both paid to her institution). The other authors report no financial disclosures or conflicts of interest. The sponsors had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.