SHORT REPORT

Prevalence and clinical correlates of dementia among COVID-19-related deaths in Italy

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Abstract

Introduction: We aimed at exploring the proportion of patients dying with COVID-19 and concomitant dementia in Italy, as well as their clinical characteristics and trajectories of care.

Methods: The proportion of COVID-19-related deaths occurring in people with dementia and the clinical characteristics of deceased individuals according to their dementia status were explored by considering the medical charts of a representative sample of patients deceased in Italian hospitals (n = 2621).

Results: A total of 415 individuals with dementia were identified in the study population, accounting for 15.8% of overall COVID-19-related deaths. Patients with dementia less frequently presented with cough, had lower chance of receiving supportive therapies and intensive care approaches, and showed a faster clinical worsening as compared with individuals with intact cognition.

Discussion: Dementia confers a relevant risk of adverse outcomes in case of SARS-CoV-2 infection and influences the clinical presentation, course and management of affected individuals.

KEYWORDS
COVID-19, dementia, public health, SARS-CoV-2

1 | BACKGROUND

Infections represent common complications and life-threatening events in people living with dementia, especially in the advanced stages of the disease.[1] Specifically, lower respiratory tract infections are a major cause of hospitalization and death in people with dementia.[2,3]

Patients with dementia may be particularly vulnerable in the ongoing COVID-19 pandemic. The weaker defense mechanisms, the close physical contact with caregivers, and the poor adherence to safeguarding measures (eg, social distancing, wearing masks) and hygienic practices (eg, washing hands) expose them to a higher risk of infection by SARS-CoV-2.[4] The difficulty at reporting symptoms and the presentation with atypical and misleading manifestations (eg, sudden confusion and delirium, exacerbation of neuropsychiatric symptoms) can contribute to late diagnosis and management.[4] The effectiveness of some supportive interventions (eg, continuous positive airway pressure) might be limited by partial adherence and tolerability. A relevant proportion of people with dementia lives in long-term facilities where the highest fatality rates have been observed.[5] Based on these premises, it might be expected that a relevant number of COVID-19-related deaths occurs in patients with dementing illnesses.

Italy, one of the oldest nations in the World, has been severely hit by the SARS-CoV-2 outbreak and > 1 million people with dementia live in the country.[6] As of August 12th, 2020, > 250,000 COVID-19 cases and 35,215 related deaths have been registered nationally.[7] The present study aimed at exploring the proportion of patients dying with COVID-19 and concomitant dementia in Italy, as well as their clinical characteristics and trajectories of care.

2 | METHODS

At the outset of the COVID-19 outbreak, the Italian National Institute of Health (Istituto Superiore di Sanità–ISS) launched an integrated national surveillance system to collect information on all individuals with COVID-19 throughout the country.[8] All deaths occurring in patients with confirmed COVID-19 were tracked. COVID-19-related deaths were defined as those occurring in patients who tested positive for SARS-CoV-2 through reverse transcription polymerase chain reaction (RT-PCR), independently of pre-existing diseases that may have caused or contributed to death.

In the present analysis, the proportion of COVID-19-related deaths in people with dementia and the clinical characteristics of deceased individuals with and without dementia were explored by considering a random sample of RT-PCR-positive SARS-CoV-2 hospitalized patients, representative in terms of age, sex, and geographical distribution of overall COVID-19-related deaths in Italy between February 21st and April 29th, 2020.[9] Specifically, 2621 medical charts consecutively collected from the Italian regions and autonomous provinces by May 7th, 2020 were centrally analyzed at the ISS and considered for the present purposes.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the scientific literature on dementia and COVID-19. We found preliminary evidence that dementia confers a higher risk of adverse outcomes in case of SARS-CoV-2 infection and that patients with dementia may exhibit atypical presentations of COVID-19. No nationwide studies exploring the proportion of COVID-19-related deaths occurring in people with dementia and describing the clinical characteristics and trajectories of care patients dying with COVID-19 and concomitant dementia were found.

2. **Interpretation**: People with dementia are particularly vulnerable to COVID-19. The presence of dementia also influences the clinical presentation, course and management of affected individuals. Persons with impaired cognition have often atypical presentation, steeper clinical worsening, and limited access to supportive and intensive care.

3. **Future directions**: People with dementia must be protected to reduce the impact of the ongoing and future pandemics. Dementia must not be used as an exclusionary criterion for guiding medical choices in contingencies of limited resources.

The following data were extracted by the charts: demographics; comorbidities; symptoms at onset; in-hospital complications; treatments received; admission to intensive care unit; time from symptom onset to hospitalization, SARS-CoV-2 testing, and death; time from hospitalization to death. The diagnosis of dementia was retrospectively assigned based on the presence in the clinical chart of (i) a previous diagnosis of dementia and/or (ii) a concomitant treatment with antidementia drugs (ie, cholinesterase inhibitors and memantine).

The prevalence of dementia observed in the study population was compared, by means of chi-square test, with that (ie, 11.3%) documented in a large sample of Italian older people with similar age distribution dying in hospital before the outbreak of the COVID-19 epidemic, considered as a reference.[10]

The characteristics of individuals with and without dementia were compared by means of Student's t-test for normally distributed variables, non-parametric Mann–Whitney U-test for skewed variables, and chi-square test or Fisher's exact test for categorical variables, as appropriate. A logistic regression model was used to identify clinical factors (ie, demographics and comorbidities) and in-hospital phenotype associated with dementia. Variables that significantly differed at baseline between patients with and without dementia with a P-value ≤.05 were included in the final multivariate model. A two-sided P-value ≤.05 was considered as statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. On February 27th, 2020, the Italian Presidency of the

Council of Ministers authorized the collection and scientific dissemination of data concerning the COVID-19 epidemic by the ISS and other public health institutions.[11]

3 | RESULTS

A total of 415 individuals with dementia were identified in the study population, accounting for 15.8% of overall COVID-19-related deaths. Such dementia prevalence was higher than expected based on the considered reference data (15.8% vs 11.3%; $P < .001$).

Compared to individuals without dementia, people with dementia were significantly older (84.3, SD 8.1 years vs 77.0, SD 10.9 years; $P < .001$) and more frequently women (47.2% vs 29.6%; $P < .001$) (Table 1). They had a higher prevalence of atrial fibrillation (27.0% vs 21.4%; $P = .01$) and stroke (18.8% vs 9.0%; $P < .001$) relative to no dementia cases. Conversely, they exhibited a lower prevalence of diabetes (25.5% vs 32.1%; $P < .01$), active cancer (11.3% vs 16.9%; $P < .01$), and obesity (3.6% vs 12.4%; $P < .001$).

COVID-19 clinical presentation varied according to dementia status. Fever was the most common manifestation at the clinical onset in both groups of individuals, whereas other symptoms including dyspnea (68.8% vs 74.3%; $P = .03$) and cough (30.9% vs 40.3%; $P < .01$) were less frequently documented in patients with dementia. They also had a lower chance of receiving antivirals including chloroquine and hydroxychloroquine (41.6% vs 60.6%; $P < .001$), and steroids (31.4% vs 38.4%) as compared to cognitively intact individuals as wells a lower likelihood of admission to intensive care units (4.5% vs 23.2%; $P < .001$).

No significant differences were observed in terms of in-hospital complications (data not shown), with acute respiratory distress syndrome representing the life-threatening complication in > 95% of individuals in both groups. Times from clinical onset to SARS-CoV-2 testing, hospitalization and death, and from hospital admission to death were significantly shorter in patients with dementia (Table 1).

To disentangle the intersection of the clinical features of individuals dying from COVID-19 according to dementia, a multivariable analysis adjusted for age, sex, comorbidities, symptoms at onset, treatment received, and clinical course was performed (Table 2). Female sex, older age, and stroke resulted independently associated with dementia. Patients with dementia less frequently presented with cough, had reduced access to intensive care, and were hospitalized earlier after onset. Moreover, they less commonly received antivirals, chloroquine and hydroxychloroquine.

4 | DISCUSSION

The present study investigated the prevalence of dementia among individuals dying with COVID-19 and assessed the clinical peculiarities of deceased patients with concomitant dementia. Based on our findings, nearly one out of six COVID-19 related death events in Italian hospitals has occurred in people diagnosed with dementia. As already shown in recent studies conducted in single Italian provinces,[12] this condition,

affecting nearly 50 million people worldwide,[13] seems to actually confer a relevant risk of mortality in case of SARS-CoV-2 infection. Accordingly, a higher than expected prevalence of dementia was observed in our study population. The presence of dementia was also found to significantly influence the clinical presentation, course and management of affected individuals, regardless of age, sex, and comorbidities. Compared with cognitively normal patients, those with dementia have more often atypical clinical presentations, characterized by the absence (or non-detection due to cognitive problems) of COVID-19 core manifestations like cough. They also exhibited a steeper clinical worsening as suggested by the shorter times between clinical onset, hospitalization, and death. It can be assumed that dementia may hinder the timely detection of the first signs and symptoms of the SARS-CoV-2 infection, thus resulting in the late diagnosis of more advanced and severe illnesses that are less likely to benefit from intervention and more rapidly evolve towards death.[3] Moreover, patients with dementia had a limited access to supportive and off-label pharmacological treatments and were almost completely excluded from intensive care approaches. Unfortunately, even in this pandemic, dementia therefore emerges as a discriminatory criterion for orienting difficult clinical choices. In situations of limited resources (as observed in Italy during the first weeks of the epidemic), patients with dementia may not be treated in favor of healthier and/or younger people who are believed to have more chances of recovery.[14]

Overall, these results should inform healthcare professionals and policymakers about the urgent need of implementing and reinforcing targeted strategies to tackle the spread of the SARS-CoV-2 infection in people with dementia. Once infected, they are exposed to an extremely high risk of poorer outcomes with relevant implications in terms of mortality and healthcare expenditures. Patients and caregivers must actively be instructed on fundamental hygienic and safeguarding precautions. Simple tips may be provided to limit the forgetting of these practices and enhance adherence.[15] Caregivers must be informed on how to recognize both the most common and atypical presentations (eg, confusion, agitation, falls) of COVID-19 for the purpose of timely detection and treatment.[16] Moreover, they should receive clear instructions on what should be done in the suspect of contagion. These seemingly easy recommendations, which should be entrusted not only to healthcare providers but to the entire community, can save many lives and need to be further enhanced in anticipation of possible new waves of COVID-19.

In parallel, in light of the limited accessibility of patients with dementia to intensive care, access to appropriate end-of-life/palliative care must be enhanced. Helping patients and families to understand and decide, managing pain and symptoms, ensuring comfort in dying, and supporting families and providers become key priorities.[17]

The main limitation of the present study is the lack of information on diverse determinants (eg, severity of functional deficits, living conditions, nursing home residency, caregiving, nutritional status) that have already been shown to influence health outcomes in people with dementia[18] and may also influence the course of COVID-19. However, it should be noticed that the considered medical charts were often compiled in situations of clinical urgency/emergency, thus with limited

TABLE 1 Characteristics of individuals deceased with COVID-19 in Italy by dementia status

	No dementia (n = 2206)	Dementia (n = 415)	P
Demographics			
Age	77.0 ± 10.9	84.3 ± 8.1	<.001[a]
Female sex	654 (29.6)	196 (47.2)	<.001[c]
Comorbidities			
Ischemic heart disease	634 (28.7)	111 (26.7)	.44[c]
Atrial fibrillation	472 (21.4)	112 (27.0)	.01[c]
Heart failure	360 (16.3)	67 (16.1)	1.00[c]
Stroke	198 (9.0)	78 (18.8)	<.001[c]
Hypertension	1510 (68.4)	278 (67.0)	.57[c]
Type 2 diabetes	708 (32.1)	106 (25.5)	<.01[c]
Chronic obstructive pulmonary disease	373 (16.9)	62 (14.9)	.35[c]
Active cancer (last 5 years)	372 (16.9)	47 (11.3)	<.01[c]
Chronic liver disease	90 (4.1)	14 (3.4)	.58[c]
Chronic renal failure	445 (20.2)	88 (21.2)	.64[c]
HIV	6 (0.3)	0 (0.0)	.60[c]
Autoimmune disease	86 (3.9)	15 (3.6)	.89[c]
Obesity	273 (12.4)	15 (3.6)	<.001[c]
Symptoms			
Fever	1639 (76.3)	300 (77.3)	.70[c]
Dyspnea	1597 (74.3)	267 (68.8)	.03[c]
Cough	865 (40.3)	120 (30.9)	<.01[c]
Diarrhea	128 (6.0)	16 (4.1)	.19[c]
Hemoptysis	14 (0.7)	1 (0.3)	.72[c]
Treatments			
Antibiotics	1835 (86.2)	323 (82.4)	.06[c]
Antivirals, hydroxychloroquine, chloroquine	1291 (60.6)	163 (41.6)	<.001[c]
Steroids	817 (38.4)	123 (31.4)	<.01[c]
Clinical course			
Admission to intensive care unit	469 (23.2)	17 (4.5)	<.001[c]
Time from symptom onset to SARS-CoV-2 testing (days)	5 (3-9)	4 (2-7)	<.001[b]
Time from onset to hospitalization (days)	4 (2-7)	3 (1-6)	<.001[b]
Time from onset to death (days)	11 (7-16)	9 (6-13)	<.001[b]
Time from hospitalization to death (days)	6 (3-10)	5 (2-9)	.04[b]

Data are expressed as mean ± standard deviation, n (%), or median (IQR).
Missing data for the overall sample (n = 2621): symptoms n = 26 (1.0%); treatments n = 39 (1.5%); clinical course n = 494 (18.8%).
[a] Student's *T*-test;.
[b] Mann-Whitney *U*-test.
[c] chi-square test.

possibility of collecting detailed information on each comorbid illness. It may therefore be assumed that dementia might have been underreported based on the charts analysis.[12] Another shortcoming is the lack of information on specific dementia diagnoses that was available only in a minority of charts.

In conclusion, our study confirms that people with dementia are particularly vulnerable to COVID-19 and must be protected to reduce the human, social, and healthcare impact of the ongoing and future pandemics. Dementia must not be used as an exclusionary criterion for guiding medical choices in contingencies of limited resources.

TABLE 2 Adjusted multivariable model of clinical phenotype independently associated with being a person with dementia dying with COVID-19

	Adjusted OR	95% CI	P
Men (vs women)	0.71	0.53-0.95	.02
Age < 70 years (vs 70-79 years)	0.99	0.55-1.82	.99
Age 80-89 (vs 70-79 years)	2.08	1.19-3.66	.001
Age ≥90 (vs 70-79 years)	4.79	2.55-9.01	<.001
Atrial fibrillation	0.99	0.72-1.37	.97
Stroke	1.98	1.35-2.92	.001
Type 2 diabetes	1.07	0.79-1.45	.65
Active cancer	0.63	0.41-0.97	.04
Obesity	0.48	0.25-0.92	.03
Dyspnea	0.89	0.65-1.22	.47
Cough	0.74	0.55-0.99	.04
Antivirals, hydroxychloroquine, chloroquine	0.68	0.51-0.90	<.01
Steroids	0.81	0.60-1.10	.18
Admission to intensive care unit	0.31	0.17-0.59	<.001
Time from onset to hospitalization (days)	0.96	0.94-0.99	.01

Abbreviation: OR, odds ratio.

Conversely, every effort must be made to support the dignity and wellbeing of the more vulnerable members of our societies.

CONFLICTS OF INTEREST

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