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Incidence and Outcomes of SARS-CoV-2 Infection in Older Adults Living with Dementia: A Population-Based Cohort Study

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Abstract.
Background: The identification of risk factors for SARS-CoV-2 infection and mortality in patients with dementia is a key aspect to support clinical decisions and public health interventions.
Objective: To assess the incidence of SARS-CoV-2 infection and COVID-19 related death in a cohort of patients with dementia residing in the Lazio region and to investigate predicting factors for both infection and mortality.
Methods: This population-based study used information from administrative databases and the SARS-CoV-2 infection surveillance system. Patients with dementia (age ≥65) were enrolled as of December 31, 2019 and followed-up until February 28, 2021. Cumulative risk of infection and death within 60 days of infection onset, and age-standardized incidence (SIR) and mortality (SMR) ratios were calculated. Logistic regression models were applied to identify factors associated with infection and mortality.
Results: Among 37,729 dementia patients, 2,548 had a diagnosis of SARS-CoV-2 infection. The crude risk of infection was 6.7%. An increase in risk of infection was observed both in women (SIR 1.72; 95% CI 1.64–1.80) and men (SIR 1.43; 95% CI 1.33–1.54). Pneumonia, cerebrovascular and blood diseases, femur fracture, anxiety, antipsychotic and antithrombotic use were associated with an increased risk of infection. The crude risk of death was 31.0%, the SMRs 2.32 (95% CI 2.05–2.65) for men, and 2.82 (95% CI 2.55–3.11) for women. Factors associated with mortality included: male gender, age ≥85, symptoms at the diagnosis, antipsychotic and systemic antibiotics treatment.
Conclusion: These findings emphasize the need of close and tailored monitoring of dementia patients to reduce the impact of COVID-19 on this fragile population.

Keywords: Administrative databases, Alzheimer's disease, cohort study, COVID-19, dementia, prognostic factors, SARS-CoV-2 infection

INTRODUCTION

The novel coronavirus SARS-CoV-2, identified in China on December 31, 2019, has spread worldwide in a short span of time, producing over 5 million deaths and causing dramatic public health issues. Italy is one of the oldest nations in the world, and one of countries most violently affected by the COVID-19 pandemic [1, 2]. A first pandemic wave was observed between February and May 2020, mainly affecting the Northern regions and a second one from October to December with a more homogeneous impact

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throughout the country [1, 3]. It quickly became apparent that older adults represent a population group particularly vulnerable to serious illness and complications, especially those living in long-term care facilities [4–6]. The cognitive impairment due to dementia exposes elderly subjects to a greater risk of becoming infected and to suffer worse outcomes as demonstrated by several studies that have identified dementia as an important risk factor for SARS-CoV-2 infection and COVID-19 mortality [7–11].

The worldwide prevalence of dementia has increased dramatically over the past three decades and its burden is expected to increase in the near future to the point that the World Health Organization defined dementia as a "global pandemic" [12]. In Italy, more than 1 million people are currently living with dementia, with a particularly higher prevalence of patients in long-term care facilities [13]. Available evidence suggests that the number of deaths for COVID-19 among those living in nursing and care homes was extremely high during the first year of the pandemic, due to infection quick spread and the age-related high lethality [14].

Strong risk factors for cognitive decline and dementia include cardiovascular diseases, diabetes, obesity, and hypertension [15]. Many of these common comorbidities in patients with dementia are also demonstrated as risk factors for COVID-19 and are associated with worse clinical outcomes [11, 16–18]. Several pandemic-related circumstances correlate with the severity of the impact of COVID-19 on these patients. Lockdowns and social distancing measures have made the social support and healthcare systems less accessible and even unavailable for people with dementia [19]. Moreover, patients with dementia may be unable to follow the recommendations from public health authorities to reduce the transmission of COVID-19: hand hygiene; covering one's mouth and nose when coughing; maintaining physical distance from others and self-isolating by remaining alone at home [20]. The restrictive measures, necessary to avoid or limit the spreading of the infection, also resulted in an increase in the occurrence of psychological and behavioral disorders in patients with dementia during the pandemic period [21, 22]. The identification of the contributing factors to both the infection and mortality is a very important issue to enable risk stratification and guide clinical and social interventions as well as public health recommendations. Actually, there is still little knowledge regarding the risk factors for SARS-CoV-2 infection and outcomes in individuals with dementia. The purposes of this study were to assess incidence of SARS-CoV-2 infection and 60-days mortality and to investigate predicting factors for infection and death in a population-based cohort of patients with dementia.

METHODS

Study design and sources of data

In this retrospective population-based cohort study, we considered older adults with dementia residing in the Lazio region (central Italy, including Rome, and with about 6,000,000 inhabitants). The study was conducted using health administrative databases, providing a comprehensive regional coverage and including high quality data. We used the Regional Health Assistance file, which includes all individuals registered with a general practitioner or who have ever had a contact with the regional health system; the Hospital Discharge Registry (HDR), which collects demographic and clinical data on all inpatients and day-case admissions in regional hospitals; the Drug Claims Registry (PHARM), including individual records for each drug prescription dispensed from public and private pharmacies in the outpatient setting, and reimbursed by the healthcare system; and, the Ticket Exemption Registry, including all residents who are entitled to co-pay fee exemptions for chronic diseases, low income, or old age. We also accessed the Integrated Surveillance System of SARS-CoV-2 infections, established in the Lazio Region during the pandemic period, which collects individual data on all patients that received a test for SARS-CoV-2 in public services. Information was available on sociodemographic characteristics, date of SARS-CoV-2 infection diagnosis, date of symptoms onset, clinical status at the diagnosis, COVID-19-related outcomes. Mortality was retrieved from the Regional Mortality Registry, which uses the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) to code causes of death. Record linkage procedures were based on a unique anonymous patient identifier.

Study population and outcomes

The cohort was defined as all individuals with dementia residing in the Lazio Region as of December 31, 2019 (enrolment date), aged 65 years or over. Patients were identified using a validated algorithm

based on data from the regional health administrative databases [23, 24]. We excluded individuals who were not residing or not covered by the Regional Health Service at the enrolment date. Dementia patients were linked with the database of SARS-CoV-2 infection in order to identify a positive reverse transcription (RT)-PCR test in nasopharyngeal swab during the follow-up period. Among those infected by the end of December 2020, we estimated the mortality rates within 60 days from the date of infection.

Follow-up period

Each patient was followed-up in the period between January 1, 2020 and February 28, 2021 to assess both the incidence of SARS-CoV-2 infection and mortality. SARS-CoV-2 infection was considered as the exposure variable to estimate the mortality rate at 60 days from the date of testing.

Socio-demographic and clinical factors

Socio-demographic characteristics (gender, age, place of residence) and information on coexisting conditions were obtained from the HDR, while details on drug consumption was retrieved from the PHARM Registry. All patients were characterized at the enrolment date with respect to age, and place of residence. A broad spectrum of diseases, identified through hospitalization episodes and medication use, were considered to measure the health status of the study population and improve the assessment of the level of frailty at the individual level [25]. We included in the analysis the following cardiovascular comorbidities during the two-year period before the enrolment date: disorders of lipid metabolism, hypertension, heart failure, ischemic heart disease (including previous cardiac revascularization), arrhythmia, atrial fibrillation, cerebrovascular diseases (including cerebrovascular revascularization), and peripheral vascular diseases. In the same time span, we retrieved information on hospital admission for the following diseases and conditions: diabetes, obesity, chronic obstructive pulmonary disease (COPD), asthma, pneumonia, neoplasms, electrolytes and base-acid balance disorders, chronic kidney diseases, gastric, duodenal, peptic, and gastrojejunal ulcer, Parkinson's disease, disease of the blood and blood-forming organs, chronic liver, pancreas and intestine diseases, fractur of neck femur, anxiety, alcohol use disorders, and depression (details on ICD-9-CM codes for cardiovascular comorbidities and other comorbidities are provided in Supplementary Table 1). Number of hospitalizations or visits to emergency departments within 6 months before the enrolment date were considered. The following categories of drugs were taken into account in a 1-year interval before the enrolment date: cardiac, antihypertensives, lipid modifying agents, statins, antiplatelet, proton pump inhibitors, insulin and analogues, blood glucose lowering drugs, antidepressants, antipsychotics, anxiolytics, antiepileptics, hypnotics and sedatives, antithrombotic agents, antibacterial therapies for systemic use, endocrine therapies, analgesic and immunostimulants drugs. In the same period, we investigated use of antidementia drugs, distinguishing use of memantine by acetylcholinesterase inhibitors (details on ATC codes are provided in the Supplementary Table 2). Moreover, in the same time span, we considered the number of neurologic and psychiatric outpatient visits, and those of other specialist clinics including general surgery, endocrinology, gastroenterology, physical medicine and rehabilitation, nephrology, orthopedics and traumatology, pulmonology, and urology. We also analyzed the risk of infection and 60-day death in the first (February-July 2020) and second pandemic phase (August-December 2020), defining a *phase* as a period characterized by a rising number of infections with a well-defined peak, and followed by a decrease.

Statistical analysis

Demographic and clinical characteristics were described separately for non-infected and infected subjects, and according to vital status. Chi-square test statistics were used to assess between-group differences ($p < 0.05$). Univariate and multivariate binomial regression models were performed to estimate, crude, and gender and age adjusted risk of SARS-CoV-2 infection and 60-day mortality, and their 95% CI. We estimated age-standardized incidence (SIRs) and mortality (SMRs) ratios, using age-specific infection and fatality rates of the whole population registered in the regional SARS-CoV-2 Surveillance System database. Multivariable logistic regression models, with a stepwise selection for the variables associated at univariate level with SARS-CoV-2 infection and death, were fitted to identify the potential determinants of infection status and 60-day mortality (p to enter = 0.11 and p to remove = 0.05). All analyses were performed using SAS Version 9.4.

Data availability

Anonymized data used for this study are available upon reasonable request.

Standard protocol approvals, registrations, and patient consents

Ethics committee or institutional review board approval and informed consent were not necessary. The Department of Epidemiology of the Lazio Regional Health Service is the regional referral center for epidemiological research, and it has full access to anonymized data from health information systems.

Approval from institutional or licensing committee was not necessary for this study.

The authors used data already collected at the beginning of the study and the data were analyzed anonymously according to the national privacy law (national legislative decree on privacy policy n. 196/30 June 2003). Individuals cannot be identified directly or through identifiers and results are shown in aggregate form.

RESULTS

Characteristics of the study population by infection status

Overall, 37,729 individuals with dementia were identified by the algorithm based on health administrative databases. Between January 1, 2020 and February 28, 2021, 2,548 (6.8%) patients were diagnosed with SARS-CoV-2 infection. Demographic and clinical characteristics of dementia patients according to infection status are shown in Table 1. Infected and non-infected subjects differed both in gender (females: 70% versus 65%) and age distribution (people aged ≥85 years: 43% versus 38%). Compared to uninfected patients, those with SARS-CoV-2 infection showed a higher prevalence of a number of cardiovascular comorbidities (in particular, hypertension and cerebrovascular diseases) and other comorbidities (including diabetes, COPD, pneumonia, and chronic renal diseases). Moreover, SARS-CoV-2 positive patients had more hospitalization episodes and emergency room visits compared with those not infected (≥2:5.6% versus 3.8% and 8.3% versus 6.5%, respectively). A greater consumption of several medications, such as antihypertensives, antiplatelet drugs, insulin, psychotropic drugs (including antipsychotics), and antithrombotic agents was observed among patients with SARS-CoV-2 infection. On the contrary, the proportion of infected patients who received memantine or acetylcholinesterase inhibitors and outpatient neurological visits was significantly lower than in SARS-CoV-2 negative cases (52.6% versus 60.0% and 24.6% versus 28.4%, respectively).

Risk of SARS-CoV-2 infection among dementia patients and main risk factors

The crude risk of infection was 6.7 per 100 population (95 CI% 6.5–70.0), and 5.9 per 100 (95 CI% 55.5–64.0) after adjusting for gender and age. SIR was 1.43 (95% CI 1.33–1.54) for males and 1.71 (95% CI 1.64–1.80) for females. The multivariable logistic regression model showed that previous hospitalization for cerebrovascular diseases (OR 1.14, 95% CI 1.02–1.29), pneumonia (OR 1.25, 95% CI 1.03–1.51), blood diseases (OR 1.20, 95% CI 1.01–1.42), femur fracture (OR 1.28, 95% CI 1.05–1.56), anxiety (OR 1.61, 95% CI 1.14–2.27), and antipsychotic (OR 1.66, 95% CI 1.53–1.80) and antithrombotic medications use (OR 1.12, 95% CI 1.02–1.23) had a statistically significant association with an increased risk of infection (Fig. 1). In this population of dementia patients, males were less likely to be infected by SARS-CoV-2 than females (OR 0.82, 95% CI 0.75–0.90). Furthermore, patients who had prescribed with acetylcholinesterase inhibitors (OR 0.90, 95% 0.82–0.99) or memantine (OR 0.91, 95% CI 0.83–1.00) showed a lower probability to be infected than those not taking any anti-dementia drug.

60-day mortality from infection onset and main risk factors

Among SARS-CoV-2 infected patients, 2013 were diagnosed up to December 31, 2020 and 31% ($n = 626$) of these died by the end of February 2021. The patient characteristics according to vital status are shown in Table 2. Deceased individuals were mainly over the age of 85 years and were living in the metropolitan area of Rome. Compared to 60-day survivors, patients who died showed a higher prevalence of cardiovascular comorbidities, chronic kidney diseases and diseases of the blood and blood-forming organs. Moreover, non-survivors had more hospitalizations (22.7% versus 17.7.%) and emergency room visits (21.8% versus 28.8%), a greater consumption of antipsychotics (51.4% versus 42.7%) and systemic antibacterial agents (67.3% versus 59.3%), and a

Table 1
Demographic and clinical characteristics of dementia patients by infection status

	Total		Non-infected		Infected		$p\ \chi^2$
	N	%	N	%	N	%	
Total	37,729		35,181	93.2	2,548	6.8	
Gender							<0.001
Male	13,004	34.5	12,237	34.8	764	30.1	
Female	24,725	65.5	22,944	65.2	1,784	69.9	
Age							*<0.001*
65–74	5,239	13.9	4,917	14.0	322	12.7	
75–84	17,987	47.7	16,852	47.9	1,135	44.7	
≥85	14,503	38.4	13,412	38.1	1,091	42.9	
Residence							*0.375*
City of Rome	19,919	52.8	18,552	52.7	1,367	53.8	
Province of Rome (excl. city of Rome)	8,014	21.2	7,466	21.2	548	21.6	
Other provinces of the Lazio region	9,796	26.0	9,163	26.0	633	24.9	
Cardiovascular comorbidities[a]							
Disorders of lipid metabolism	769	2.0	712	2.0	57	2.2	*0.448*
Hypertension	5,285	14.0	4,874	13.9	411	16.2	*0.002*
Heart failure	1,442	3.8	1,312	3.7	130	5.1	*0.005*
Ischemic heart disease	1,742	4.6	1,592	4.5	150	5.9	*0.002*
Arrhythmia	2,271	6.0	2,101	6.0	170	6.7	*0.151*
Atrial fibrillation	1,822	4.8	1,680	4.8	142	5.6	*0.070*
Cerebrovascular diseases	4,919	13.0	4,510	12.8	409	16.1	*<0.001*
Peripheral vascular diseases	489	1.3	449	1.3	40	1.6	*0.206*
Other comorbidities[a]							
Diabetes	2,196	5.8	2,008	5.7	188	7.4	*0.000*
Obesity	139	0.4	125	0.4	14	0.6	*0.118*
COPD	1,777	4.7	1,624	4.6	153	6.0	*0.001*
Asthma	29	0.1	25	0.1	4	0.2	*0.131*
Pneumonia	1,340	3.6	1,212	3.4	128	5.0	*<0.001*
Neoplasm	1,051	2.8	974	2.8	77	3.0	*0.452*
Electrolytes and base-acid balance disorders	1,237	3.3	1,146	3.3	91	3.6	*0.390*
Chronic kidney diseases	1,410	3.7	1,283	3.6	127	5.0	*0.000*
Gastric, duodenal, peptic, gastrojejunal ulcer	108	0.3	97	0.3	11	0.4	*0.152*
Parkinson's disease	764	2.0	714	2.0	50	2.0	*0.832*
Disease of the blood and blood-forming organs	1,916	5.1	1,731	4.9	185	7.3	*<0.001*
Chronic liver, pancreas, and intestine disease	210	0.6	196	0.6	14	0.6	*0.968*
Fracture of neck femur	1,251	3.3	1,123	3.2	128	5.0	*<0.001*
Anxiety	314	0.8	275	0.8	39	1.5	*<0.001*
Alcohol use disorders	10	0.0	9	0.0	1	0.0	*0.680*
Depression	115	0.3	104	0.3	11	0.4	*0.225*
Hospitalization episodes[b]							*<0.001*
None	31,534	83.6	29,467	83.7	2,067	81.3	
1	4,732	12.5	4,395	12.5	337	13.3	
2	1,084	2.9	979	2.8	105	4.1	
≥3	379	1.0	340	1.0	39	1.5	
Emergency room visit[b]							*0.001*
None	29,854	79.1	27,895	79.3	1,959	77.1	
1	5,392	14.3	5,014	14.2	378	14.9	
2	1,643	4.4	1,498	4.3	145	5.7	
≥3	840	2.2	774	2.2	66	2.6	
Outpatient visits, neurological branch[c]							*<0.001*
None	27,118	71.9	25,196	71.6	1,922	75.6	
1	4,160	11.0	3,888	11.0	272	10.7	
≥2	6,451	17.1	6,097	17.3	354	13.9	
Outpatient visits, psychiatric branch[c]							*0.253*
None	35,663	94.5	33,238	94.5	2,425	95.4	
1	618	1.6	585	1.7	33	1.3	
≥2	1,448	3.8	1,358	3.9	90	3.5	
Outpatient visits, other clinical specialties[c]							*0.022*
None	26,009	68.9	24,214	68.8	1,795	70.6	
1	4,978	13.2	4,629	13.2	349	13.7	
≥2	6,742	17.9	6,338	18.0	404	15.9	

(*Continued*)

Table 1
(*Continued*)

	Total		Non-infected		Infected		$p\ \chi^2$
	N	%	N	%	N	%	
Number of drugs[c]							*0.197*
None	1,681	4.5	1,586	4.5	95	3.7	
1–5	9,732	25.8	9,061	25.8	671	26.4	
6–10	12,411	32.9	11,592	32.9	819	32.2	
≥11	13,905	36.9	12,942	36.8	963	37.9	
Drugs prescription[c]							
Cardiac	5,441	14.4	5,064	14.4	377	14.8	*0.577*
Antihypertensive	29,168	77.3	27,139	77.1	2,029	79.9	*0.004*
Lipid modifying agents	15,002	39.8	14,060	40.0	942	37.1	*0.003*
Statins	13,135	34.8	12,288	34.9	847	33.3	*0.096*
Antiplatelet	23,226	61.6	21,604	61.4	1,622	63.8	*0.023*
Proton pump inhibitors	23,278	61.7	21,634	61.5	1,644	64.7	*0.003*
Insulin and analogues	2,506	6.6	2,306	6.6	200	7.9	*0.016*
Blood glucose lowering drugs	6,508	17.2	6,088	17.3	420	16.5	0.320
Antidepressants	15,976	42.3	14,892	42.3	1,084	42.7	*0.999*
Antipsychotics	11,923	31.6	10,806	30.7	1,117	44.0	*<0.001*
Anxiolytics	69	0.2	61	0.2	8	0.3	*0.107*
Antiepilectis	8,457	22.4	7,796	22.2	661	26.0	*<0.001*
Hypnotics and sedatives	71	0.2	66	0.2	5	0.2	*0.918*
Antithrombotic agents	27,014	71.6	25,120	71.4	1,894	74.5	*0.001*
Antibacterial for systemic use	22,109	58.6	205,58	58.4	1,551	61.0	0.014
Endocrine therapy	757	2.0	711	2.0	46	1.8	*0.465*
Analgesic drugs	3,879	10.3	3,620	10.3	259	10.2	*0.879*
Immunostimulants drugs	95	0.3	92	0.3	3	0.1	*0.164*
Memantine	9,534	25.3	8,961	25.5	573	22.6	*0.000*
Acetylcholinesterase inhibitors	12,926	34.3	12,163	34.6	763	30.0	*<0.001*

[a]Hospital admission in the 2-year period before the enrollment, [b]In the 6-month period before the enrollment; [c]In the 1-year period before the enrollment.

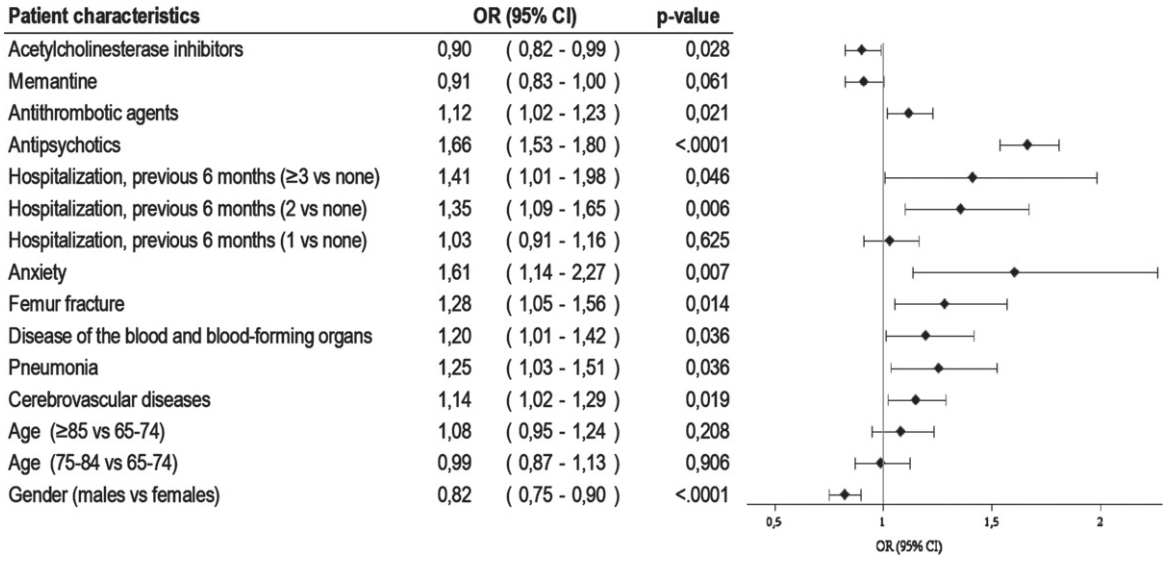

Fig. 1. Factors associated with SARS-CoV-2 infection among dementia patients.

lower use of any anti-dementia drug (2.1% versus 10.8%). There was a higher prevalence of symptomatic patients among those who died and a higher proportion of patients infected during the first pandemic phase. The crude 60-day risk of death was 31.0 per 100 (95 CI%: 28.8–33.6), growing up to 40.0 per 100 (95 CI%: 35.1–45.6) after adjusting for gender and age. Standardized mortality ratio (SMR) was 2.32

Table 2
Characteristics of dementia patients infected with SARS-CoV-2 by vital status within 60 days from the infection

	Total		Alive		Died		$p\ \chi 2$
	N	%	N	%	N	%	
Total	2,013		1,387	68.9	626	31.1	
Gender							*<0.001*
Male	597	30.3	366	26.4	231	37.8	
Female	1,416	71.9	1,021	73.6	395	64.6	
Age							*<0.001*
65–74	240	12.2	181	13.0	59	9.7	
75–84	874	44.4	633	45.6	241	39.4	
≥85	899	45.7	573	41.3	326	53.4	
Residence							*0.004*
City of Rome	1109	56.3	730	52.6	379	62.0	
Province of Rome (excl. city of Rome)	427	21.2	312	22.5	115	18.8	
Other provinces of the Lazio region	477	24.2	345	24.9	132	21.6	
Cardiovascular comorbidities[a]							
Disorders of lipid metabolism	44	2.2	33	2.4	11	1.8	*0.493*
Hypertension	319	16.2	212	15.3	107	17.5	*0.297*
Heart failure	103	5.2	66	4.8	37	6.1	*0.000*
Ischemic heart disease	112	5.7	66	4.8	46	7.5	*0.006*
Arrhythmia	135	6.9	85	6.1	50	8.2	*0.133*
Atrial fibrillation	113	5.7	66	4.8	47	7.7	*0.014*
Cerebrovascular diseases	329	16.7	220	15.9	109	17.8	*0.287*
Peripheral vascular diseases	32	1.6	18	1.3	14	2.3	*0.186*
Other comorbidities[a]							
Diabetes	150	7.6	96	6.9	54	8.8	*0.237*
Obesity	9	0.5	6	0.4	3	0.5	*0.691*
COPD	128	6.5	87	6.3	41	6.7	*0.917*
Asthma	3	0.2	2	0.1	1	0.2	*0.931*
Pneumonia	104	5.3	62	4.5	42	6.9	*0.057*
Neoplasm	56	2.8	32	2.3	24	3.9	*0.099*
Electrolytes and base-acid balance disorders	77	3.9	53	3.8	24	3.9	*0.689*
Chronic kidney diseases	103	5.2	57	4.1	46	7.5	*0.001*
Gastric, duodenal, peptic, gastrojejunal ulcer	8	0.4	4	0.3	4	0.7	*0.245*
Parkinson's disease	38	1.9	22	1.6	16	2.6	*0.105*
Disease of the blood and blood-forming organs	149	7.6	87	6.3	62	10.1	*0.005*
Chronic liver, pancreas and intestine disease	11	0.6	9	0.6	2	0.3	*0.356*
Fracture of neck femur	100	5.1	69	5.0	31	5.1	*0.962*
Anxiety	25	1.3	18	1.3	7	1.1	*0.741*
Alcohol use disorders	1	0.1	1	0.1	0	0.0	*0.502*
Depression	11	0.6	6	0.4	5	0.8	*0.300*
Hospitalization episodes[b]							*0.034*
None	1,628	82.7	1,141	82.3	487	79.7	
1	268	13.6	170	12.3	98	16.0	
2	83	4.2	52	3.7	31	5.1	
≥3	34	1.7	24	1.7	10	1.6	
Emergency room visit[b]							*0.007*
None	1,534	77.9	1,084	78.2	450	73.6	
1	299	15.2	187	13.5	112	18.3	
2	119	6.0	76	5.5	43	7.0	
≥3	61	3.1	40	2.9	21	3.4	
Outpatient visits, neurological branch[c]							*0.077*
None	1,535	78.0	1,038	74.8	497	81.3	
1	211	10.7	152	11.0	59	9.7	
≥2	267	13.6	197	14.2	70	11.5	
Outpatient visits, psychiatric branch[c]							*0.865*
None	1,922	97.6	1,322	95.3	600	98.2	
1	24	1.2	17	1.2	7	1.1	
≥2	67	3.4	45	3.2	22	3.6	
Outpatient visits, other clinical specialties[c]							*0.947*
None	1,435	72.9	990	71.4	445	72.8	
1	264	13.4	183	13.2	81	13.3	
≥2	314	15.9	214	15.4	100	16.4	

(*Continued*)

Table 2
(*Continued*)

	Total		Alive		Died		$p\ \chi 2$
	N	%	N	%	N	%	
Number of drugs[c]							*0.219*
None	82	4.2	62	4.5	20	3.3	
1–5	544	27.6	375	27.0	169	27.7	
6–10	647	32.9	457	32.9	190	31.1	
≥11	740	37.6	493	35.5	247	40.4	
Drugs prescription[c]							
Cardiac	293	14.9	193	13.9	100	16.4	*0.225*
Antihypertensive	1,609	81.7	1,094	78.9	515	84.3	*0.078*
Lipid modifying agents	733	37.2	516	37.2	217	35.5	*0.273*
Statins	660	33.5	462	33.3	198	32.4	*0.457*
Antiplatelet	1,284	65.2	883	63.7	401	65.6	*0.864*
Proton pump inhibitors	1,304	66.2	889	64.1	415	67.9	*0.339*
Insulin and analogues	160	8.1	109	7.9	51	8.3	*0.824*
Blood glucose lowering drugs	331	17.2	226	16.3	105	17.2	0.788
Antidepressants	829	42.1	575	41.5	254	41.6	*0.712*
Antipsychotics	906	46.0	592	42.7	314	51.4	*0.002*
Anxiolytics	6	0.3	4	0.3	2	0.3	*0.905*
Antiepilectis	522	26.5	354	25.5	168	27.5	*0.533*
Hypnotics and sedatives	4	0.2	2	0.1	2	0.3	*0.413*
Antithrombotic agents	1,494	75.9	1,020	73.5	474	77.6	*0.301*
Antibacterial for systemic use	1,234	62.7	823	59.3	411	67.3	*0.007*
Endocrine therapy	36	1.8	22	1.6	14	2.3	*0.308*
Analgesic drugs	200	10.2	147	10.6	53	8.7	*0.139*
Immunostimulants drugs	3	0.2	2	0.1	1	0.2	*0.933*
Memantine	422	1.1	293	0.8	129	5.1	*0.791*
Acetylcholinesterase inhibitors	580	1.5	435	1.2	145	5.7	*0.000*
Symptoms at diagnosis	1,192	60.5	921	66.4	271	44.4	*<0.001*
Infection period[d]							*<0.001*
First epidemic phase	257	13.1	146	10.5	111	18.2	
Second epidemic phase	1,754	89.1	1,240	89.4	514	84.1	

[a]Hospital admission in the 2-year period before the enrollment, [b]In the 6-month period before the enrollment; [c]In the 1-year period before the enrollment; [d]missing data for two individuals.

(95% CI 2.05–2.65) and 2.82 (95% CI 2.55–3.11) for males and females, respectively. Males (OR 1.69, 95% CI 1.35–2.11), the oldest old (OR 1.81, 95% CI 1.27–2.56), patients with symptoms at the diagnosis (OR 2.56, 95% CI 2.08–3.16), those with antipsychotic prescriptions (OR 1.26, 95% CI 1.03–1.55), and finally patients treated with systemic antibiotics (OR 1.24, 95% CI 1.01–1.53) were more likely to die within 60 days of the positive SARS-CoV-2 test (Fig. 2). Patients who developed the infection during the second pandemic phase (OR 0.67, 95% CI 0.49–0.90) and those residing outside the metropolitan area of Rome (OR 0.64, 95% CI 0.49–0.84) showed a reduced risk of death.

DISCUSSION

This large population-based cohort study evaluated the impact of SARS-CoV-2 infection among patients with dementia in a large Italian region, during the first year of the COVID-19 pandemic. Several studies reported that people with dementia are more likely to contract SARS-CoV-2 infection than people without and that dementia is in itself a risk factor for COVID-19-related mortality [8, 9, 26, 27]. However, very limited data comes from cohort studies of patients with dementia, analyzing what clinical and demographic characteristics affect the risk of SARS-CoV-2 infection and severity in this fragile population [28, 29].

We found both the risk of infection and mortality to be markedly higher in people with dementia as compared with general elderly population. A high burden of comorbidities and antipsychotic use were identified as risk factors for both infection and 60-day mortality, while severity of symptoms at diagnosis and male gender were specifically associated with an increased risk of COVID-19-related death.

Consistently with previous reports, individuals with dementia enrolled in our cohort were 60% more likely to get SARS-CoV-2 infection than people in

Patient characteristics	OR (95% CI)	p-value
Epidemic phase (second vs first)	0,67 (0,49 - 0,90)	0,009
Symptoms at the time of diagnosis	2,56 (2,08 - 3,16)	<0.001
Acetylcholinesterase inhibitors	0,75 (0,59 - 0,95)	0,018
Antibacterial for systemic use	1,24 (1,01 - 1,53)	0,043
Antipsychotics	1,26 (1,03 - 1,55)	0,025
Residence (other provinces of the Lazio region vs metropolitan area of Rome)	0,77 (0,60 - 1,00)	0,096
Residence (province of Rome vs metropolitan area of Rome)	0,64 (0,49 - 0,84)	0,003
Age (≥85 vs 65-74)	1,81 (1,27 - 2,56)	0,001
Age (75-84 vs 65-74)	1,17 (0,83 - 1,66)	0,369
Gender (males)	1,69 (1,35 - 2,11)	<0.001

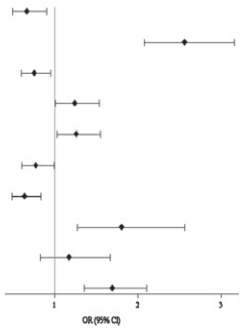

Fig. 2. Factors associated with 60-day mortality in dementia patients infected with SARS-CoV-2.

the general population. Indeed, a comparable likelihood of SARS-CoV-2 infection was estimated in a cohort of individuals with pre-existing dementia recruited in psychiatric inpatient settings [29]. Additionally, Wang and colleagues showed that people with dementia had a twofold increased risk of contracting COVID-19, with odds varying between 3.2 and 1.8 depending on type of dementia, an excess very close to that estimated in our study [30].

We observed that dementia patients with frequent hospitalization episodes, who have comorbidities such as blood, cerebrovascular and respiratory diseases, anxiety, those using antithrombotic agents and with a history of hip fracture presented a higher risk of infection. This greater susceptibility may reflect a more severe stage of dementia and, as a consequence, an increased frailty and higher level of care from caregivers that may convey the infection [31, 32]. In addition, more severe, non-self-sufficient individuals with dementia may be more likely to reside in long-term care facilities sharing confined and enclosed spaces with other people, enhancing the risk of exposure to COVID-19 and other infectious diseases. This finding highlights that special attention is needed toward these patients to prevent SARS-CoV-2 infection, considering these specific risk factors to guide healthcare workers, family members, and caregivers in implementing appropriate protection measures and monitoring.

After adjusting for age and comorbidities, women enrolled in our study looked less resistant to SARS-CoV-2 infection than men. Current evidence on sex and gender differences in the susceptibility to the infection is not conclusive, with studies reporting conflicting results both for the general population and people with cognitive impairment [9, 32–34]. Indeed, women have a greater resistance to viral infections compared with men, due to a stronger innate immunity, steroid hormones, and factors related to sex chromosomes [35]. Although some evidence is available of a greater resistance against SARS-CoV-2 in women [36], we cannot exclude that our result may be due to a higher prevalence of women residing in long-term care facilities, which are a risk contest for respiratory infections and that were particularly affected in the first pandemic phase [37].

Consistently with other reports, we found a COVID-19-associated crude case fatality rate of 31%, with a more than double risk of dying in dementia patients compared to the general population of the same age and gender [38, 39]. Our analysis revealed a strong association between presence of symptoms at diagnosis and short-term mortality. Recent research showed that in patients with Alzheimer's disease or other forms of dementia, more frequently had diabetes or cardiovascular disease and presented to the healthcare centers with more critical symptoms such as loss of consciousness, respiratory distress, and lower partial pressure of oxygen in arterial blood [40]. It has also been shown that the onset of COVID-19 disease in individuals with dementia often occurs with non-respiratory symptoms such as delirium or functional decline [41]. Anyway, our result highlights the need for increased attention to both specific and atypical clinical COVID-19 symptoms in this population of patients for early and rapid identification of the disease.

Of particular interest was the association between COVID-19 infection and 60-day mortality in dementia patients using antipsychotic (AP) medications. People with late-stage dementia and those residing in long-term care facilities represent the group most likely to receive a prescription for AP drugs [42]. The COVID-19 pandemic and infection control

measures have impacted greatly on routine activities and care of people with dementia, both living in an institutional setting and in the community, causing the onset/worsening of behavioral and psychological symptoms of dementia, with increased personal distress, and a higher risk of infection and mortality. Because of concerns about safety and limited efficacy, the use of APs has been declining in recent years [43], but some evidence is available that during the COVID-19 pandemic there was an increase in the proportion of dementia patients receiving these drugs [44]. A recent review found evidence of a strong association between antipsychotics intake and COVID-19-related death in patients with pre-existing mental disorders, including dementia [45]. The harmful effect of antipsychotics in patients with dementia may be enhanced by concomitant COVID-19, as seem to be confirmed by the excess mortality we observed in patients using AP compared with non-users, even taking into account a number of coexisting risk factors. The results of our study suggest limiting as much as possible AP prescription in persons with dementia, especially during the pandemic period. In contrast, the use of acetylcholinesterase inhibitors and memantine was slightly protective for infection and mortality. This result could be due to a lower severity of cognitive impairment e functional decline in patients treated with anti-dementia drugs and their well-documented protective effect against inflammatory processes [46].

Although men were less likely to get the infection, we observed that they faced higher risk of death compared to women, independent of age. Several COVID-19 studies have shown that men have a higher risk of developing a severe form of the disease compared with women and a higher death rate [47]. This finding is in line with the fact that, in general, respiratory infectious diseases are more severe among males and leads to higher mortality in males than in women [48]. Very interestingly, patients living outside the metropolitan area of Rome were less likely to die for COVID-related causes, while studies carried out in other countries have shown an opposite result, with rural/suburban areas associated with greater mortality burden than urban zones [49, 50]. There are several potential explanations for the observed urban/suburban mortality divide, including socioeconomic disparities in access and use of healthcare services, different availability and/or organization of community healthcare facilities and hospitals, and level of coordination and continuity of care across different care settings, the latter being critical elements of health care delivery for frail older adults. Moreover, the exposure to environmental risk factors (air pollution) may have exacerbated the COVID-19-related mortality risk in vulnerable groups living in the metropolitan area of Rome. Anyway, the observed heterogeneity in mortality deserves further and deeper investigation to target specific interventions for both healthcare organizations and population subgroups.

The current study has some limitations. Firstly, the lack of information on diverse potential determinants such as place of residence (long-term facilities or private homes), socio-economic position, and behavioral risk factors. Secondly, we cannot exclude that during the first phase, when public health emergency was severe and unexpected, the most severely infected patients were not even admitted to hospitals and died at home undiagnosed. Thirdly, to best identify patients' comorbidities and obtain a more exhaustive control of confounding, we used both hospital discharges and drug prescriptions. Drug prescription information are important complements to the hospital discharge data, as it is shown by the different proportion of patients identified from these two data sources. However, a certain amount of overlap between the two registries cannot be ruled out. Finally, administrative databases do not allow for a detailed description of patients' clinical characteristics. Consequently, we were unable to distinguish the different types of dementia and had to rely on hospital discharge information and drug prescription claims to define patients' comorbidities.

The main strengths of this study are the population-level approach and the large sample size. Moreover, to our knowledge, this is the first study analyzing the determinants of SARS CoV-2 infection and death from COVID-19 among dementia patients, using health administrative databases and a validated algorithm to identify the study population. Indeed, the study relies on good quality health administrative data, currently used not only for descriptive but also for analytical purposes. At last, it is noteworthy that the prompt availability of information coming from administrative databases allows to monitor health care delivery in the region, identify critical points in provision of and access to healthcare, in order to implement corrective measures. This aspect is particularly relevant in the current public health emergency due to COVID-19 pandemic.

In conclusion, given the magnitude of impact of COVID-19 pandemic on elderly patients, providing information on the actual rate of SARS-CoV-2

infection on people with dementia and specific determinants of worse outcomes, can support clinicians when considering prevention and treatment among individuals in this vulnerable group. Patients with dementia require close monitoring by both physicians and caregivers to minimize exposure to the virus, recognize timely signs/symptoms of COVID-19, and ensure proper disease management. The pandemic continues to influence our lives and threaten population health, in particular that of frail people. We have to keep in mind that although much has been learned about how to prevent infection and new drugs have been approved by international agencies or are currently under investigation, the most fragile subgroups of the population, such as the elderly with multimorbidity and dementia, need to be adequately monitored to reduce the deadly impact of COVID-19.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220369.

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