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Short Communication

Cognitive Impairment Is a Common Comorbidity in Deceased COVID-19 Patients: A Hospital-Based Retrospective Cohort Study

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Abstract.
We analyzed the frequency of cognitive impairment (CI) in deceased COVID-19 patients at a tertiary hospital in Spain. Among the 477 adult cases who died after admission from March 1 to March 31, 2020, 281 had confirmed COVID-19. CI (21.1% dementia and 8.9% mild cognitive impairment) was a common comorbidity. Subjects with CI were older, tended to live in nursing homes, had shorter time from symptom onset to death, and were rarely admitted to the ICU, receiving palliative care more often. CI is a frequent comorbidity in deceased COVID-19 subjects and is associated with differences in care.

Keywords: Cognitive impairment, COVID-19, dementia, morbidity, mortality

INTRODUCTION

On January 7, 2020, Chinese investigators identified a novel coronavirus (SARS-CoV-2) as the cause of an outbreak of acute respiratory syndrome in Wuhan, China [1]. The situation then escalated

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rapidly, and an increasing number of cases were found in many countries. COVID-19 has had a substantial case fatality rate and a huge impact on society and healthcare. Previous reports have described some demographic groups as more vulnerable to death from COVID-19, such as being male, being of older age, or having comorbidities such as hypertension, diabetes, cardiovascular disease, or cancer [2]. Information on neurological comorbidities in COVID-19 has been scarce until now.

Recently, it has been noted that patients with dementia may have increased risk for COVID-19 because they have difficulty remembering safeguards, and many live in nursing homes where the disease can spread rapidly [3]. Nevertheless, the first clinical studies that analyzed comorbidities and death in COVID-19 did not investigate dementia or cognitive impairment (CI) [3–8]. In the present study, we analyze the frequency of CI and other neurological comorbidities in deceased patients with COVID-19 at our hospital. We also describe the differences in medical care received by patients with or without CI.

MATERIALS AND METHODS

In this retrospective study, we reviewed all patients older than 16 years who died after admission from March 1, 2020, to March 31, 2020, at our tertiary hospital in Madrid, Spain. Since 2011, the hospital has been using integrated electronic medical records that incorporate all medical encounters and diagnoses. All data from deceased patients were manually extracted from these records using a standardized data-collection form. Diagnoses of CI were made by neurologists, psychiatrists, geriatricians, internal medicine doctors, and general practitioners.

Patients were divided in three groups according to COVID-19 status, following the case definition of the European Centre for Diseases Prevention and control [9], as follows:

- Confirmed COVID-19 related death. These cases were confirmed through reverse transcription polymerase chain reaction (RT-PCR) assays performed on nasopharyngeal swabs.
- Probable COVID-19 related death. These cases had clinical, laboratory, and radiological features consistent with COVID-19, but the RT-PCR results were negative, or testing could not be performed.
- Death not related to COVID-19. These patients died from other causes.

The study was reviewed and approved by the hospital's ethics committee/institutional review board (EC/IRB).

Statistical analyses were undertaken using STATA software 14.0 (StataCorp, College Station, TX). Continuous variables were presented as medians and interquartile ranges (IQRs), and categorical variables were given as total numbers (n) and percentages (%). First, we compared two groups, those with confirmed COVID-19 and those with other causes of death. In our other analyses we used only confirmed COVID-19 cases, comparing those with and without CI. Categorical variables were compared using the χ^2 test. The means for the continuous variables were compared using independent group t tests. All tests were two-sided, and the significance level was set to $p < 0.05$.

RESULTS

There were 4,156 admissions during the study period, and 1,970 (47.4%) were COVID-19 cases. There were 477 deaths in total, of which 281 were from confirmed COVID-19 (58.9% of total deaths), 58 from probable COVID-19 (12.2%), and 138 from other causes (28.9%). The most common causes of death in the group of patients without evidence of COVID-19 were other infections ($n = 35$; 25.4%), malignant tumor progression ($n = 30$; 21.7%), respiratory failure ($n = 25$; 18.1%), and cardiovascular disease ($n = 18$; 13.0%).

The demographic characteristics and comorbidities of the three groups are shown in Table 1. Median age was higher in both COVID-19 groups than in the non-COVID-19 group, and the percentage of males was significantly higher in the confirmed COVID-19 group (62.3% versus 49.3%, $p < 0.01$). Comorbidities were common in the three groups. The proportion of subjects with CI was similar in each group at around 30%. There were not statistically significant differences for other neurological comorbidities.

In the confirmed COVID-19 group, CI was the fourth most frequent comorbidity, after hypertension (69.4%), diabetes (33.8%), and cardiovascular disease (33.5%). The analyses whose results are presented in Table 2 were conducted separately on those with and without CI. Subjects with CI were older, more of them lived in nursing homes, and they had chronic lung disease with less frequency. In this group, 21.1% had dementia (mild, 4.3%; moderate, 10.0%; and severe, 6.8%), and 8.9% had mild cogni-

Table 1
Clinical and demographic characteristics of deceased patients with COVID-19 or other causes

	Total subjects ($n=477$)	Probable COVID-19 ($n=58$)	Confirmed COVID-19 ($n=281$)	Other causes ($n=138$)	p
Age, y	80.5 (71.8, 87.0)	82.5 (67.9, 87,9)	81.4 (73.2, 86.9)	78.1 (65.0, 87.5)	0.0078
Sex, female	204 (42.8%)	28 (48.3%)	106 (37.7%)	70 (50.7%)	0.011
Smoking history	158 (33.1%)	17 (29.3%)	87 (31.0%)	54 (39.1%)	ns
Drinking history	42 (8.8%)	7 (12.1%)	22 (7.8%)	13 (9.4%)	ns
Medical comorbidities					
Hypertension	326 (68.3%)	43 (74.1%)	195 (69.4%)	88 (63.8%)	ns
Diabetes	156 (32.7%)	20 (34.5%)	95 (33.8%)	41 (29.7%)	ns
Cardiovascular disease	178 (37.3%)	26 (44.8%)	94 (33.5%)	58 (42.0%)	ns
Chronic lung disease	133 (27.9%)	16 (27.6%)	73 (26.0%)	44 (31.9%)	ns
Chronic kidney disease	100 (21.0%)	9 (15.5%)	62 (22.1%)	29 (21.0%)	ns
Chronic liver disease	29 (6.1%)	5 (8.6%)	14 (5.0%)	10 (7.3%)	ns
History of cancer	130 (27.3%)	9 (15.5%)	68 (24.2%)	53 (38.4%)	0.003
Cognitive impairment	139 (29.1%)	16 (27.6%)	84 (29.9%)	39 (28.3%)	ns
Mild cognitive impairment	38 (8.0%)	6 (10.3%)	25 (8.9%)	7 (5.1%)	0.013†
Mild dementia	23 (4.8%)	4 (6.9%)	12 (4.3%)	7 (5.1%)	–
Moderate dementia	35 (7.3%)	2 (3.5%)	28 (10.0%)	5 (3.6%)	–
Severe dementia	43 (9.0%)	4 (6.9%)	19 (6.8%)	20 (14.5%)	–
Other neurological comorbidities					
Previous stroke	62 (13.0%)	6 (10.3%)	33 (11.7%)	23 (16.7%)	ns
Parkinson's disease	10 (2.1%)	1 (1.7%)	6 (2.1%)	3 (2.2%)	ns
Amyotrophic lateral sclerosis	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	ns
Myasthenia gravis	2 (0.4%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	ns
Epilepsy	9 (1.9%)	0 (0.0%)	6 (2.1%)	3 (2.2%)	ns
Any comorbidity	446 (93.5%)	55 (94.8%)	262 (93.2%)	129 (93.5%)	ns
Number of comorbidities	3 (2, 4)	2 (2, 4)	3 (1, 4)	3 (2, 4)	ns

COVID-19, coronavirus disease 2019; n, number of deceased patients; ns, non-significant. Data are expressed as medians (Q1, Q3), or n (%). p values were calculated using the χ^2 test or t-test. *p values indicate statistical difference between confirmed COVID-19 and other causes of death. † χ^2 test comparing all cognitive impairment subcategories.

tive impairment. The most common diagnoses of CI in the confirmed COVID-19 group were Alzheimer's disease (9.3% of all patients) and mixed (7.2%) and vascular CI (4.8%). History of previous stroke or Parkinson's disease was more frequent in those with CI. Time from symptom onset to emergency department (ED) and from symptom onset to death was lower in subjects with CI, and fever upon arrival at the ED was less frequent (32.5% versus 52.2%, $p=0.004$). Encephalopathy was the most common neurological complication in both groups, and it was more common in patients with CI (32.1% versus 14.7%, $p<0.001$). Some aspects of medical care differed between the groups, as only one patient with CI was admitted to the ICU, and fewer patients with CI received non-invasive mechanical ventilation (7.1% versus 25.4%, $p<0.001$). Palliative care was provided more frequently in subjects with CI (79.2% versus 66.3%, $p=0.038$).

DISCUSSION

In March 2020, 339 people died of confirmed or suspected COVID-19 at our hospital, almost three times as many deaths as those from all other causes combined over the entire month. Severe COVID-19 affects older people with chronic diseases disproportionately. We found that CI is one of the most common comorbidities in confirmed COVID-19 subjects (30%). This is not surprising, because dementia is a prevalent and sometimes overlooked underlying cause of death [10], and respiratory infections are a leading immediate cause of death in this population [11]. Although the percentage of CI in deceased COVID-19 subjects is high, our results are not informative on the risk that CI has on mortality. However, recent reports have indicated that dementia could be a risk factor for mortality in COVID-19 [12–14]. Future research will undoubtedly clarify this issue and explore possible pathophysiological mechanisms for it [15]. For example, a recent report indicated that the APOE $\varepsilon4/\varepsilon4$ allele increases the risk for severe COVID-19 infection, independently of pre-existing dementia [16]. The higher proportion of encephalopathy in patients with CI also suggests that this group may be more vulnerable to neurological complications resulting from SARS-CoV2 infection.

Table 2
Demographic and clinical characteristics of confirmed COVID-19 deceased patients with and without cognitive impairment

	Total subjects ($n = 281$)	Cognitive impairment ($n = 84$)	No cognitive impairment ($n = 197$)	p
Age, y	81.4 (73.2, 86.9)	85.8 (79.1, 89.6)	79.0 (70.5, 85.3)	<0.0001
Sex, female	106 (37.7%)	35 (41.7%)	71 (36.0%)	ns
Accommodation type				<0.0001*
Community and family	136/196 (69.4%)	44/74 (59.5%)	92/122 (75.4%)	–
Live alone	28/196 (14.3%)	7/74 (9.5%)	21/122 (17.2%)	–
Residence and nursing home	32/196 (16.3%)	23/74 (31.1%)	9/122 (7.4%)	–
Smoking history	87 (31.0%)	20 (23.8%)	67 (34.0%)	ns
Drinking history	22 (7.8%)	7 (8.3%)	15 (7.6%)	ns
Medical comorbidities				
Hypertension	195 (69.4%)	60 (71.4%)	135 (68.5%)	ns
Diabetes	95 (33.8%)	33 (39.3%)	62 (31.5%)	ns
Cardiovascular disease	94 (33.5%)	28 (33.3%)	66 (33.5%)	ns
Chronic lung disease	73 (26.0%)	15 (17.9%)	58 (29.4%)	0.043
Chronic kidney disease	62 (22.1%)	17 (20.2%)	45 (22.8%)	ns
Chronic liver disease	14 (5.0%)	6 (7.1%)	8 (4.1%)	ns
History of cancer	68 (24.2%)	15 (17.9%)	53 (26.9%)	ns
Neurological comorbidities				
Previous stroke	33 (11.7%)	18 (21.4%)	15 (7.6%)	0.001
Parkinson's disease	6 (2.1%)	5 (6.0%)	1 (0.5%)	0.004
Epilepsy	6 (2.1%)	3 (3.6%)	3 (1.5%)	ns
Any comorbidity	254 (90.4%)	76 (90.5%)	178 (90.4%)	ns
Number of comorbidities	2 (1, 3)	2 (1, 3.5)	2 (1, 3)	ns
Time from illness onset to ED (d)	5 (3, 7)	4 (2, 7)	5 (3, 7)	0.0152
Time from illness onset to death	12 (8, 15)	11 (7, 14)	12 (8, 15.5)	0.0254
Time from ED admission to death	6 (3, 8)	6 (3, 8.5)	5 (4, 8)	ns
Clinical and laboratory values				
Respiratory rate (>24 bpm)	93/138 (67.4%)	27/37 (73.0%)	66/101 (65.4%)	ns
Oxygen saturation (<90%)	144/279 (51.6%)	37/84 (44.1%)	107/195 (54.9%)	ns
Fever (>37.5°C)	119/257 (46.3%)	25/77 (32.5%)	94/180 (52.2%)	0.004
CRP (>10 mg/dL)	184/273 (67.4)	50/81 (61.7%)	134/192 (70.0%)	ns
Lymphocyte ($<0.8 \times 10^9$/ L)	146/279 (52.3%)	41/83 (49.4%)	105/196 (53.6%)	ns
Neurological complications				
Stroke	2 (0.7%)	0 (0.0%)	2 (1.0%)	ns
Encephalopathy	56 (19.9%)	27 (32.1%)	29 (14.7%)	0.001
Seizures	3 (1.1%)	0 (0.0%)	3 (1.5%)	ns
ICU admission	27 (9.6%)	1 (1.2%)	26 (13.2%)	0.002
NIMV	56 (19.9%)	6 (7.1%)	50 (25.4%)	<0.0001
Palliative care	181/258 (70.2%)	61/77 (79.2%)	120/181 (66.3%)	0.038

n, number of deceased patients; ns, non-significant; ED, emergency department; d, days; bpm, breaths per minute; CRP, C-reactive protein; ICU, intensive care unit; NIMV, non-invasive mechanical ventilation. Data are expressed as medians (Q1, Q3), or n (%). p values were calculated by the χ^2 test or t-test. *χ^2 test comparing all subcategories.

As expected, somewhat different medical care was provided to COVID-19 patients with CI; they were rarely admitted to the ICU and were treated more frequently with palliative care to prioritize their comfort and symptom management. The low number of patients with mild cognitive impairment or mild dementia who were admitted to the ICU or treated with non-invasive mechanical ventilation may also reflect the fact that our healthcare system was overwhelmed during these weeks, which could have induced physicians to select younger patients with fewer comorbidities for ICU admission.

Our study has some limitations. First, due to its retrospective design, information on some variables may be incomplete. We reviewed all of the clinical notes in the electronic medical records, but some diagnoses of previous CI may not have been recorded in them. Second, only fatal cases of COVID-19 were included, so we could not determine whether CI was a risk factor for mortality in COVID-19. Third, the study is hospital-based, and many community-based cohort studies have shown that not all persons with dementia seek medical attention, especially those who are very old or have a lower socio-economic status [17]. More importantly, health authorities and research reports describe a high case fatality rate for COVID-19 in nursing homes [18], where many have died without hospital transfer. More than 20,000 people with

confirmed COVID-19 died in Spain, 7,132 of them in the Community of Madrid [19]. These numbers are distressing, but they probably only reflect part of the impact of COVID-19. The local health authorities have reported that from March 8 to April 17, 2020, 5,272 of the 44,132 nursing home residents in the Madrid region died with symptoms of COVID-19, but the disease could only be confirmed in 837 [20]. Considering that the estimated prevalence of dementia in nursing homes of Western European countries ranges from 50% to 75% [21], the number of deaths in people with dementia during the COVID-19 pandemic is likely high. The 30% of deceased COVID-19 patients with CI in our study could be an underestimate of the state of the community. More study of nursing home populations is needed, taking into account that dementia is usually under-reported in death certificates [22].

At least six clinical series have described clinical characteristics of fatal cases with confirmed COVID-19 in Asian populations [4–8, 23]. These studies have not included CI in the analysis of comorbidities in COVID-19. One report described the clinical characteristics of 54 deceased COVID-19 patients [23] and included as a comorbidity the category of neurologic disease, which grouped together dementia and stroke. The proportion of patients thus described was 18.5%, with a marked difference between those aged under 70 years (0%), and those over 70 years (29.4%). The results in the older group are comparable to our findings. A short report from Italy mentions a preliminary study in a subsample of 355 patients with COVID-19 who died and underwent chart review [24]. They were also old (mean age 79.5 years) and more frequently male, and 6.8% had dementia. This is a lower proportion than in our study (21.1%), but the brief clinical description does not allow more comparisons.

In summary, our study shows that CI is a common comorbidity in deceased COVID-19 patients, and it has been relatively overlooked until now. In fact, some guidelines do not include dementia as a vulnerable group for severe COVID-19. When new public health threats like COVID-19 emerge, society, governments, and research institutions should not forget existing medical priorities, like neurodegenerative diseases.

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