Delirium in Patients with SARS-CoV-2 Infection: A Multicenter Study

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OBJECTIVES: The aims of this study are to report the prevalence of delirium on admission to the unit in patients hospitalized with SARS-CoV-2 infection, to identify the factors associated with delirium, and to evaluate the association between delirium and in-hospital mortality.

DESIGN: Multicenter observational cohort study.

SETTINGS: Acute medical units in four Italian hospitals.

PARTICIPANTS: A total of 516 patients (median age 78 years) admitted to the participating centers with SARS-CoV-2 infection from February 22 to May 17, 2020.

MEASUREMENTS: Comprehensive medical assessment with detailed history, physical examinations, functional status, laboratory and imaging procedures. On admission, delirium was determined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria, 4AT, m-Richmond Agitation Sedation Scale, or clinical impression depending on the site. The primary outcomes were delirium rates and in-hospital mortality.

RESULTS: Overall, 73 (14.1%, 95% confidence interval (CI) = 11.0–17.3%) patients presented delirium on admission. Factors significantly associated with delirium were dementia (odds ratio, OR = 4.66, 95% CI = 2.03–10.69), the number of chronic diseases (OR = 1.20, 95% CI = 1.03; 1.40), and chest X-ray or CT opacity (OR = 3.29, 95% CI = 1.12–9.64 and 3.35, 95% CI = 1.07–10.47, for multiple or bilateral opacities and single opacity vs no opacity, respectively). There were 148 (33.4%) in-hospital deaths in the no-delirium group and 43 (58.9%) in the delirium group (P-value assessed using the Gray test <.001). As assessed by a multivariable Cox model, patients with delirium on admission showed an almost twofold increased hazard ratio for in-hospital mortality with respect to patients without delirium (hazard ratio = 1.88, 95% CI = 1.25–2.83).

CONCLUSION: Delirium is prevalent and associated with in-hospital mortality among older patients hospitalized with SARS-CoV-2 infection. **J Am Geriatr Soc 00:1-7, 2020.**

Keywords: COVID-19; older adults; hospital; mortality; delirium

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INTRODUCTION

Soon after the start of the severe acute respiratory syndrome 2 (SARS-CoV-2) novel coronavirus (COVID-19) pandemic, it became clear that older adults are among those most at risk of health-related negative outcomes. Rates of

morbidity and mortality associated with COVID-19 have been found to be much higher in older adults than in all other age groups.[1,2] It has also been recognized that atypical presentations of COVID-19 are more frequent in these segments of the population.[3,4]

Delirium is an atypical presenting symptom of many acute diseases and a very common condition among older hospital inpatients.[5,6] The fact that delirium has negative prognostic implications for older people[6,7] suggests that accurate data on its estimated prevalence and outcomes in patients with SARS-CoV-2 infection are urgently needed to allow planning of appropriate interventions for people who will be hospitalized with COVID-19 in the coming months.

To date, delirium prevalence in COVID-19 varies greatly between studies, with some, published in the early months of the pandemic, reporting high or very high rates,[3,8-11] and other more recent ones finding lower prevalence.[12-14] Furthermore, there are only a few studies that have investigated the risk factors of delirium in patients with COVID-19[15,16] and there are contrasting findings regarding the potential association of delirium with mortality in this context.[3,8,9,13-15] There is therefore a need for further exploration of these issues.

The aims of this study, conducted in a large population of patients admitted to acute medical and rehabilitation wards with SARS-CoV-2 infection, are to report the prevalence of delirium on admission to the units, identify the factors associated with delirium occurrence, and evaluate the association between delirium and in-hospital mortality.

METHODS

Study Population

This observational study was conducted at four different hospitals in northern Italy: one large, urban, tertiary hospital ("San Gerardo," 650 beds) in Monza, two urban, private hospitals ("Poliambulanza," 600 beds, and "Sant'Anna," 300 beds) in Brescia, and one small, private, rehabilitation hospital (Fondazione Teresa Camplani, 120 beds) in Cremona.

Data collection complied fully with European law on personal data protection. Oral informed consent for participation in this study was obtained from patients or proxy respondents on admission, and the study protocol was approved by the Brianza Institutional Review Board.

The study population comprised consecutive patients admitted, between February 22, 2020 and May 17, 2020, to two acute geriatric units (at the San Gerardo and Poliambulanza hospitals, respectively), one acute medical unit (Sant'Anna hospital), and one rehabilitation unit (Fondazione Teresa Camplani hospital) with a positive polymerase chain reaction nasopharyngeal swab test for SARS-CoV-2. The patients admitted to the three acute units came from the emergency department, while those admitted to the rehabilitation unit were transferred from the acute wards of the hospital (Cremona). There was no preliminary selection of patients by physicians at the participating centers. Exclusion criteria were aged less than 65 years and/or initial admission to an intensive care unit (ICU). Patients were followed until death, discharge or transfer from the above-mentioned units. Follow-up was updated on June 16, 2020 (date inclusive).

Comprehensive Medical Assessment

All patients underwent by the attending physician a comprehensive medical assessment on unit's admission, which included detailed history and physical examination. Data on all clinical characteristics, including patient demographics (age, sex), smoking habits, functional status, cognitive status, clinical and pharmacological history, chest X-ray or CT, use of continuous positive airway pressure (CPAP), and laboratory results were collected in a structured data form. However, the tools used for these assessments differed between the centers. In centers 1 (San Gerardo hospital) and 2 (Sant'Anna hospital), functional status was assessed using some items of Katz's Activities of Daily Living (ADL) scale[17] and the Instrumental ADL,[18] while the Barthel Index[19] was used in Centers 3 (Poliambulanza Hospital) and 4 (Fondazione Teresa Camplani Hospital). To combine these different functional status measures, we built an indicator of functional disability. Accordingly, functional disability corresponded to: dependence in bathing or dressing (for Centers 1 and 2) or a Barthel Index score[19] 90 or more/100 one month before hospitalization (for Centers 3 and 4). In all four centers, dementia was diagnosed in the presence of a documented history. Comorbidity was measured using the Cumulative Illness Rating Scale (CIRS)[20] in Centers 3 and 4, and using a checklist of chronic diseases in Centers 1 and 2. Diagnosis of nutritional disorders (including both malnutrition and obesity) was based on the attending physicians' clinical judgment.

We also recorded the presence and degree of chest X-ray or CT infiltrates or opacities and the use of use of continuous positive airway pressure (CPAP) for respiratory support. Furthermore, in all centers, serum levels of albumin (except Center 4), leukocytes and C-reactive protein (CRP) were recorded.

Delirium Assessment

Under normal circumstances, patients at centers are routinely assessed for delirium as follows: at Centers 1 and 4, the patients are usually screened by geriatricians with the 4-AT tool[21] and the diagnosis of delirium is confirmed according to the DSM-5 criteria.[22] The modified Richmond Agitation-Sedation Scale (m-RASS)[23] is used to evaluate the patient's arousal and support the diagnosis of delirium. At Centers 2 and 3, the physicians on site do not routinely employ screening tools for delirium and the diagnosis of the condition is based on their clinical impression. During the COVID-19 emergency, however, the medical staff has changed in all centers but Center 4, including various specialists which were not trained in delirium evaluation (i.e., thoracic surgeons, dermatologists and gastroenterologists). Consequently, the methods to diagnose delirium have varied from usual practice, depending on the center and the expertise of physicians: at Center 1, when the attending physician was a geriatrician, delirium diagnoses were made using the same procedures as in non-emergency situations. However, when a geriatrician was not on duty, these diagnoses were based

on the physician's clinical impressions. At the other centers, delirium diagnosis was made employing the same procedures as in normal circumstances (i.e., based on the physician's clinical impression at Centers 2 and 3, while based on 4AT screening and DSM-5 confirmation at Center 4).

Because an altered arousal is highly specific for delirium[24] and the m-RASS score (i.e., a measure of arousal) was obtained on patient's admission in three centers, we decided to retrospectively re-classify as delirium all the cases in Center 1 in which the diagnosis was not obtained by a geriatrician and the m-RASS score was different than 0. At Center 2, the cases of delirium were reclassified using the same latter approach (i.e., a m-RASS score different than 0). At Center 3, the m-RASS score was disregarded to reclassify the delirium episodes.

The Supplementary Table S1 summarizes the methods to assess delirium at each center during COVID-19 emergency.

Primary and Secondary Outcomes

The primary outcome was the rate of delirium among all patients with SARS-Cov-2 infection on admission to the participating centers. The secondary outcome was all-cause in-hospital mortality.

Data Collection

Clinical, demographic, and laboratory data were prospectively collected in an electronic database. At the end of the study period these data and all clinical and nursing notes were reviewed.

Dates of in-hospital deaths were also recorded.

Statistical Analyses

Continuous variables were described with median and interquartile range (IQR), and categorical data were expressed as frequency and percentage values. The clinical features of the patients with and without delirium on admission were compared by Mann-Whitney test and Fisher test for continuous and categorical data, respectively.

A generalized linear mixed model with logit link was applied to evaluate factors associated with delirium on admission, including variables selected a priori (sex, age, functional disability, dementia, number of chronic diseases, use of CPAP, nutritional status, chest X-ray or CT findings, and serum CRP). Center was included as random effect.

The crude cumulative incidence of in-hospital mortality was estimated by Aalen-Johansen, accounting for the competing event discharge; in-hospital mortality was then compared between patients with and those without delirium using the Gray test. To evaluate the association between delirium on admission and in-hospital mortality we applied a multivariable Cox regression model stratified for center and including potential confounders selected a priori (sex, age, functional disability, dementia, number of chronic diseases, use of CPAP, nutritional status, chest X-ray or CT findings and serum CRP). The proportional hazard assumption was fulfilled and no interaction between delirium and other factors was found.

A sensitivity analysis was conducted excluding the center without m-RASS evaluation and the largest sample size (i.e., Center 3) to test the robustness of the results against possible misclassification of delirium in this center.

Due to missing values in predictors (functional disability 3.3%, use of CPAP 1.6%, nutritional status 26%, serum CRP 0.2%), we performed multiple imputation using the chained equations (MICE) method, assuming data were missing at random. Ten imputed datasets were created using all the variables in Table 1, as well as outcomes and other partially available information (i.e., other hematological variables, maximum ventilator support during hospital stay, nursing home resident/need for caregiver, respiratory frequency on admission).

The results were obtained using SAS (version 9.4) and R (version 3.5.2) software.

RESULTS

In total, 553 patients were initially identified, 143 from Center 1, 108 from Center 2, 264 from Center 3, and 38 from Center 4. However, 37 patients were excluded as they had first been admitted to an ICU. The final study sample thus numbered 516 patients. The median age was 78 years (range 65–99), and 318 (62%) were men. Table 1 reports the clinical features of the patients according to the presence/absence of delirium.

Overall, 73 (14.1%, 95% confidence interval (CI) = 11.0–17.3%) patients had delirium on admission: 29 patients (21%) at center 1, 22 (21%) at Center 2, 11 (5%) at Center 3, and 11 (29%) at Center 4. Patients with delirium were on average 7 years older than those without, had an increased number of pre-existing diseases and were using more prescription drugs on admission. In addition, they had higher prevalence rates of dementia and malnutrition and were more frequently dependent in ADL before hospitalization. However, some between-center differences were found in the patients' clinical features (Supplementary Table S2).

Table 2 shows the multivariable regression model for the detection of delirium on admission. Dementia (odds ratio (OR) = 4.66, 95% CI = 2.03–10.69), the number of chronic diseases (OR = 1.20, 95% CI = 1.03; 1.40) and chest X-ray or CT opacities (OR = 3.29, 95% CI = 1.12–9.64 and OR = 3.35, 95%CI = 1.07–10.47, for multiple or bilateral opacities and single opacity vs no opacity, respectively) were significantly associated with delirium. These results were consistent in the sensitivity analysis, i.e., after excluding Center 3 (Supplementary Table S3).

Overall, follow-up lasted a median of 19 days; 191 (37%) patients died during hospitalization, while 278 were discharged and 47 were transferred to other hospitals or lower intensity wards.

The crude cumulative incidence of in-hospital death is shown in Figure 1. At 30 days from admission, there were 145 deaths (mortality 33.8%, 95% CI = 29.3–38.3%) in the no-delirium group and 38 (53.2%, 95% CI = 41.6–64.8) in the delirium group (Gray test P-value <.001). At the same time point (30 days), 50.1% (95% CI = 45.3–54.9%) of the patients with no delirium and 24.2% (95%CI = 14.2–34.3) of the patients with delirium had been discharged from hospital.

Table 1. Patients' Characteristics on Admission by Delirium Presence

Characteristics on Admission	Total (n = 516)	No Delirium (n = 443)	Delirium (n = 73)	P-value
Age (median (IQR))	78 (73, 84)	77 (72, 83)	84 (79, 88)	<.001
Male gender, n (%)	318 (62)	284 (64)	34 (47)	.006
Smoke (current or previous), n (%)	95 (31)	84 (31)	11 (28)	.853
Past or current medical history				
Hypertension, n (%)	343 (66)	293 (66)	50 (68)	.789
Cardiac diseases, n (%)[a]	212 (41)	176 (40)	36 (49)	.126
Diabetes mellitus, n (%)	138 (27)	118 (27)	20 (27)	.887
Respiratory diseases, n (%)[b]	63 (12)	53 (12)	10 (14)	.699
N of chronic diseases (excluding dementia), (median (IQR))	2 (1, 4)	2 (1, 3)	3 (2, 5)	<.001
Dementia, n (%)	85 (16)	50 (11)	35 (48)	<.001
Malnutrition No, n (%)	281 (74)	252 (77)	30 (54)	<.001
Undernutrition, n (%)	42 (11)	23 (7)	19 (34)	
Obesity, n (%)	58 (15)	51 (16)	7 (12)	
Drugs (median (IQR))	5 (2, 8)	4 (2, 8)	6 (4, 8)	.007
Dependence in self-bathing, n (%)	84 (35)	50 (26)	34 (72)	<.001
Dependence in self-dressing, n (%)	77 (32)	44 (23)	33 (72)	<.001
Barthel Index (pre-admission), (median (IQR))	100 (79, 100)	100 (80, 100)	90 (50, 100)	.019
Functional disability, n (%)[c]	171 (34)	126 (29)	45 (66)	<.001
Chest X-ray or CT results, n (%)				.026
No opacity	46 (9)	39 (9)	7 (10)	
Single opacity	74 (14)	56 (13)	18 (25)	
Multiple or bilateral opacities	396 (77)	348 (79)	48 (66)	
Use of continuous positive airway pressure, n (%)	53 (10)	43 (10)	10 (14)	.299
Lab serum levels (median ((IQR))				
White blood cell count (×10^9/L)	7.0 (5.0, 9.7)	7.0 (5.0, 9.5)	6.9 (4.9, 10.2)	.88
C-reactive protein (mg/dl)	8.7 (4.0, 15.3)	8.9 (4.3, 15.4)	7.5 (3.0, 14.5)	.282
Albumin (g/dl)	3.1 (2.8, 3.3)	3.1 (2.8, 3.3)	3.2 (2.8, 3.3)	.975

Abbreviations: CT, computed tomography; IQR, interquartile range.
[a]Cardiac diseases included congestive heart failure, coronary heart diseases and atrial fibrillation.
[b]Chronic respiratory diseases include chronic obstructive pulmonary disease and asthma.
[c]Functional disability was defined as the presence of a dependence in bathing or dressing (for Centers 1 and 2) or a Barthel Index ≤90 (Centers 3 and 4).

In a multivariable Cox regression analysis (Table 3) adjusting for possible confounders, patients with delirium on admission showed an almost two-fold chance of in-hospital mortality compared with the ones without (hazard ratio (HR) = 1.88, 95% CI = 1.25–2.83). These results were consistent even after excluding center 3 (HR = 2.00, 95% CI = 1.23–3.25).

DISCUSSION

Our study indicates that delirium occurs commonly in hospitalized older adults with COVID-19 and carries important prognostic significance. Dementia, pre-existing comorbidity and pulmonary opacity were significantly associated with the presence of delirium on admission and delirium was significantly associated with increased in-hospital mortality.

Delirium should be therefore routinely screened for in older adults with COVID-19 and interventions to improve outcomes should be implemented.

Previous studies evaluating delirium in COVID-19 patients generally found it to show a high prevalence, ranging from 29%[3] to 42%.[8,9] In the only study that focused on patients with pre-existing dementia, it was 67%.[11] Our results, showing a lower prevalence, partially disagree with the findings of these studies. This difference may be related to the characteristics of the patient samples, to our exclusion of patients initially admitted to the ICU, and to the methods used to assess delirium. Notably, the majority of the above-mentioned studies did not specify the criteria used to diagnose delirium,[3,8,9] and two studies failed to state whether delirium was assessed only on admission or throughout the hospital stay.[9,11] Our results are, instead, in keeping with those of Mao et al,[25] who found a 14.8% prevalence of impaired consciousness, and Garcez et al,[14] who reported a 12% prevalence of delirium on hospital admission. However, when our analyses excluded the data from Center 3, which diagnosed delirium exclusively on the basis of physician clinical impression, our results concur with those of three recent studies that found delirium prevalence rates of around 25%.[10,12,13]

The observed variability in delirium prevalence between the units participating in our study may be partially explained by differences in physician expertise and methods in delirium detection.

The finding that dementia, pre-existing comorbidity and pulmonary opacity were significantly associated with delirium on admission was somewhat expected according to previous literature.[5,26,27] However, a recent study found that age, history of epilepsy, antipsychotic drugs, vasodilators, urea and lactate dehydrogenase, but not dementia and

Table 2. Multivariable Logistic Model on Delirium on Admission After Multiple Imputation (516 Patients 73 with Delirium on Admission). Center Included as Random Effect

	OR (95% CI)	*P*-value
Sex (male vs female)	0.79 (0.43; 1.47)	.462
Age (for each year)	1.01 (0.96; 1.06)	.691
Functional disability (yes vs no)	1.74 (0.75; 4.03)	.193
Dementia (present vs absent)	4.66 (2.03; 10.69)	<.001
N. of chronic diseases (excluding dementia)	1.20 (1.03; 1.40)	.018
Use of continuous positive airway pressure (yes vs no)	1.44 (0.6; 3.48)	.414
Nutritional status (malnourished vs no)	1.95 (0.82; 4.64)	.129
Nutritional status (obese vs no)	1.66 (0.62; 4.42)	.306
Chest X-ray or CT (multiple or bilateral opacities vs no opacity)	3.29 (1.12; 9.64)	.030
Chest X-ray or CT (single opacity vs no opacity)	3.35 (1.07; 10.47)	.038
C-reactive protein (for each mg/dl)	1.02 (0.99; 1.06)	.231

Abbreviations: 95% CI, 95% confidence interval; CT, computed tomography; OR, odds ratio.

Table 3. Multivariable Cox Model on In-Hospital Mortality (Stratified for Center) After Multiple Imputation (516 Patients, 191 Deaths)

	Hazard Ratio (95%CI)	*P*-value
Delirium (yes vs no)	1.88 (1.25; 2.83)	.003
Sex (male vs female)	1.39 (1.00; 1.94)	.052
Age (for each year)	1.05 (1.02; 1.07)	<.001
Functional disability (yes vs no)	1.32 (0.89; 1.96)	.167
Dementia (present vs absent)	1.13 (0.71; 1.82)	.602
No. of chronic diseases (excluding dementia)	1.16 (1.07; 1.26)	.001
Use of continuous positive airway pressure (Yes vs No)	2.77 (1.83; 4.19)	<.001
Nutritional status (malnourished vs no)	0.67 (0.39; 1.14)	.139
Nutritional status (obese vs no)	1.17 (0.76; 1.81)	.481
Chest X-ray or CT (multiple or bilateral opacities vs no opacity)	1.85 (0.96; 3.55)	.065
Chest X-ray or CT (single opacity vs no opacity)	1.54 (0.75; 3.15)	.237
C-reactive protein (for each mg/dl)	1.02 (1.01; 1.04)	.008

Abbreviations: 95% CI, 95% confidence interval; CT, computed tomography.

comorbidity were associated with delirium.[15] The present study, thus, adds knowledge in this field.

The prevalence of delirium psychomotor subtypes in our study is also noteworthy. We found that the m-RASS, where used, gave scores of −1 and below in a sizeable proportion of patients, suggesting hypoactive delirium. This conflicts with what emerged in the only other study that evaluated psychomotor subtypes of COVID-19-related delirium, with hyperactive presentations as predominant.[28] Our findings are important in view of the prognostic implications of hypoactive delirium highlighted in non-COVID-19 case cohorts.[29,30]
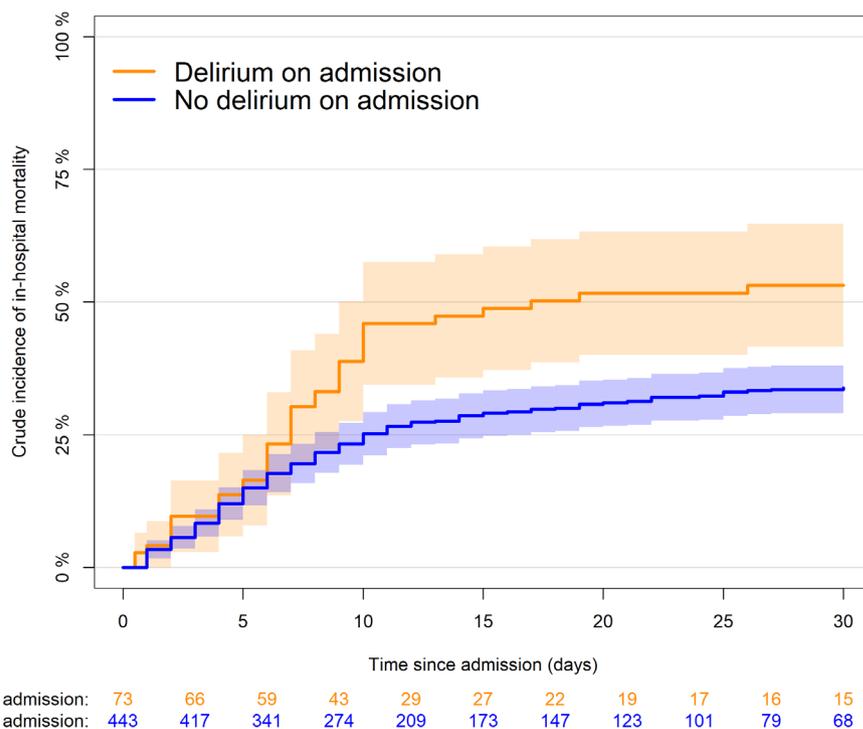

Figure 1. Crude cumulative incidence of in-hospital mortality by delirium on admission (Gray test *P* < .0001). Shaded area represents confidence intervals.

A further important finding of our study is that delirium was significantly associated with increased in-hospital mortality. The relationship between delirium and mortality in COVID-19 has been assessed in very few studies, with inconclusive results. There was no evidence of excess mortality in the study by De Smet et al,[9] while Knopp et al[3] found the opposite. The present study supports the notion that delirium is a marker of clinical severity in older patients with COVID-19. Our evidence that male gender, pre-existing comorbidity, use of CPAP, pulmonary opacity and high serum CRP levels were associated with increased mortality is in line with previous studies.[2,23-25]

Our findings have several clinical implications. First, the finding that delirium prevalence was markedly higher in the centers where delirium diagnoses were based on m-RASS or DSM-5 criteria indirectly suggests that all COVID-19 patients should be screened for this condition using a standardized approach. A second implication concerns the risk factors of delirium. In fact, in light of the results of our study, clinicians should become more suspicious of delirium when patients with COVID 19 are admitted to a hospital unit with either dementia or comorbidity. A third implication regards the prognosis associated with delirium. In fact, the detection of delirium in COVID-19 patients should prompt the medical team to immediately initiate, whenever possible, treatment of delirium-precipitating factors and/or to start discussing end-of-life decisions with family members. Furthermore, we recommend that specific training in delirium be given to all physicians who may be involved in the care of these patients should the pandemic worsen.

Overall, our findings add to the growing body of literature on delirium in COVID-19. First of all, it is one of the few multicenter studies[11,25] thus far conducted on delirium in these patients. Previous reports concern studies conducted in a single centers[3,8-10,13,14] and/or in smaller samples.[8,9,13] Moreover, this study also clarifies the factors associated with delirium, which may be helpful for rapid identification of at-risk subjects. Finally, it strongly supports the role of delirium as an independent predictor of mortality in COVID-19, an aspect not clearly brought out by previous studies.[3] Another strength of the study is the large sample size and the multicenter design. To our knowledge, it is the largest multicenter study assessing the prevalence of delirium in older COVID-19 hospital inpatients.

However, the study presents several limitations. First, although delirium was largely diagnosed thanks to the routine use of delirium screening in most of the participating centers, we acknowledge that, given the exceptionality of the period, some cases of delirium may have been missed. However, at the height of a pandemic, it is unreasonable to assume that medical staff will have the time and the state of mind necessary to perform a thorough assessment followed by a non-pharmacological intervention for delirium management. Second, since the data were collected retrospectively from electronic health records, some missing items (e.g., malnutrition/obesity) may have introduced biases; however, we accounted for this by multiple imputations. Third, the cohorts of patients included in the study were not well balanced between the centers. This, too, may have introduced biases, given that the average delirium prevalence of our population may have been driven mainly by the center with the largest case load. Nevertheless, we performed a sensitivity analysis excluding the center with the largest cohort and also the lowest rate of delirium (Center 3), and the results remained consistent.

In conclusion, delirium was found to be present in about one in seven patients aged 65 years or over, hospitalized with COVID-19. Dementia, pre-existing comorbidity and chest X-ray or CT opacities were significantly associated with the presence of delirium on admission. Furthermore, delirium, along with male gender, age, pre-existing comorbidity, the use of CPAP as respiratory support and serum CRP on admission were significantly associated with increased in-hospital mortality.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Methods to Assess Delirium at Each Study Center During COVID-19 Emergency.

Supplementary Table S2: Patients' Characteristics on Admission in the Study Centers.

Supplementary Table S3: Sensitivity Analysis on the Multivariable Logistic Model on Delirium on Admission Excluding Center 3.