Predictors and outcomes of delirium in the emergency department during the first wave of the COVID-19 pandemic in Milan

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Handling editor Mary Dawood

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/emermed-2021-211749).

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Received 9 June 2021
Accepted 28 November 2022

ABSTRACT

Background Respiratory infections can be complicated by acute brain failure. We assessed delirium prevalence, predictors and outcomes in COVID-19 ED patients.

Methods This was a retrospective observational study conducted at the San Raffaele ED (Italy). Patients age >18 years attending the ED between 26 February 2020 and 30 May 2020 and who had a positive molecular nasopharyngeal swab for SARS-CoV-2 were included. The Chart-Based Delirium Identification Instrument (CHART-DEL) was used to retrospectively assess delirium. Univariable and multivariable logistic regression analyses were used to evaluate delirium predictors. Univariable binary logistic regression analyses, linear regression analyses and Cox regression analyses were used to assess the association between delirium and clinical outcomes. Age-adjusted and sex-adjusted models were then run for the significant predictors of the univariable models.

Results Among the 826 included patients, 123 cases (14.9%) of delirium were retrospectively detected through the CHART-DEL method. Patients with delirium were older (76.9±13.15 vs 61.3±14.27 years, p<0.001) and more frequently living in a long-term health facility (32% vs 22%, p<0.001). Age (OR 1.06, 95% CI 1.01 to 1.17, p<0.001), dementia (OR 17.5, 95% CI 7.27 to 42.16, p<0.001), epilepsy (OR 6.96, 95% CI 2.48 to 19.51, p<0.001) and the number of chronic medications (OR 1.09, 95% CI 1.01 to 1.17, p=0.03) were significant predictors of delirium in multivariable analyses. Delirium was associated with increased in-hospital mortality (adjusted HR 2.16, 95% CI 1.55 to 3.03, p<0.001) and with a reduced probability of being discharged home compared with being institutionalised (adjusted OR 0.39, 95% CI 0.25 to 0.61, p<0.001).

Conclusions Chart review frequently identified ED delirium in patients with COVID-19. Age, dementia, epilepsy and polypharmacy were significant predictors of ED delirium. Delirium was associated with an increased in-hospital mortality and with a reduced probability of being discharged home after hospitalisation. The findings of this single-centre retrospective study require validation in future studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Delirium can be an atypical presentation of respiratory infections, including COVID-19.
⇒ In older American patients with COVID-19, delirium was reported in 28% of people at the ED presentation.
⇒ Age older than 75 years, institutionalisation and assisted living, chronic psychoactive medications, stroke, Parkinson’s disease, vision and hearing impairments were reported as risk factors for ED delirium in older patients with COVID-19.

WHAT THIS STUDY ADDS

⇒ In this retrospective chart review from a single centre in Italy, the prevalence of delirium was 14.9% in the global sample and rose to 26.8%, when considering only older people.
⇒ Age, dementia, epilepsy and the number of chronic drugs were the risk factors for delirium.
⇒ In spite of being associated with a more subtle COVID-19 presentation, COVID-19 patients with delirium had a greater in-hospital mortality and a reduced probability of being discharged home compared with being institutionalised after hospitalisation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the findings of this retrospective study will be confirmed, prospective screening may be useful to identify patients with delirium risk factors so that appropriate treatment is given to avoid the negative consequences of this geriatric syndrome.

INTRODUCTION

Respiratory infections can be complicated by acute brain failure, especially in older adults; this association has been confirmed in cases of SARS-CoV-2 infection. Data from the first wave of the COVID-19 pandemic indicated an alteration in mental status in about 20%–30% of
hospitalised patients with rates up to 60%–70% in severely ill cases. 2

The mechanisms that underlie this association are multiple. SARS-CoV-2 can directly cause neuronal damage 3 after reaching the central nervous system (CNS) via olfactory nerves or via haematogenous spread. 4 Moreover, the intense inflammatory response to the virus can result in a cytokine storm in the CNS which impairs brain function. Hypoxia, which is more pronounced in severely ill patients, is also deleterious for neurons. Other proposed mechanisms may involve a hypercoagulable status, resulting in ischaemic damage to the brain, low cardiac output syndrome and metabolic alterations. 5–9

The development of delirium depends on both the presence of precipitating factors and the subject’s baseline vulnerability. 7 If more predisposing factors are present, fewer or lower intensity precipitants can be sufficient to cause delirium. 7 Accordingly, frail adults are more susceptible to delirium, 8 especially when exposed to such a potent precipitating factor as SARS-CoV-2.

In older people, delirium can be the only presenting sign of an infection or disease. 10 Delirium can be considered a marker of the underlying disease severity and has been considered as a sort of geriatric ‘vital sign’. 1

Previous data revealed that while delirium is present in 7%–20% of patients in the ED (and in about 10% of older people), 11 it goes under-recognised in approximately 75% of cases. 12 When delirium is the only or earliest manifestation, an underlying illness may go underdiagnosed. Furthermore, the perpetuation of the delirious state may lead to adverse short-term and long-term outcomes, 14 which also implies increasing health-related costs. 9

A retrospective American study of people over 65 with test + or radiologically likely COVID-19 found delirium was an ED presenting symptom in 28% of cases and confirmed the association of known predisposing factors (age, institutionalisation, psychoactive medications, cerebrovascular diseases, Parkinson’s disease, hearing and visual impairments) for delirium. 15 Delirium was associated with negative clinical outcomes including hospitalisation, intensive care unit stay (ICU) and in-hospital mortality. 15

However, most other studies looking at the prevalence of delirium in COVID-19 include only hospitalised patients, suggesting the need for additional studies on the prevalence, risk factors and outcome of patients presenting with COVID-19 and delirium to EDs. The primary objective of this study was to determine the prevalence of delirium associated with confirmed SARS-CoV-2 infection among all patients presenting to the ED of a tertiary care hospital of Milan during the first wave of the COVID-19 pandemic and to identify factors associated with the presence of delirium during the SARS-CoV-2 infection. We also analysed the association of delirium with clinical outcomes.

**METHODS**

This retrospective study was part of the COVID-19 institutional clinical-biological cohort assessing patients with COVID-19 (Covid-BioB, ClinicalTrials.gov NCT04318366). 16 The study was approved by the local ethics committee.

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### Table 1  Baseline characteristics of the studied population

<table>
<thead>
<tr>
<th></th>
<th>Total sample (N=826)</th>
<th>Delirium (N=123)</th>
<th>No delirium (N=703)</th>
<th>P value</th>
<th>Corrected P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>63.7 (15.16)</td>
<td>76.9 (13.15)</td>
<td>61.3 (14.27)</td>
<td>&lt;0.001</td>
<td>N.A.</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>544 (65.9%)</td>
<td>69 (56.1%)</td>
<td>475 (67.6%)</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triage colour, n (%)†</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Green</td>
<td>409 (49.5%)</td>
<td>19 (15.4%)</td>
<td>390 (55.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td>297 (36%)</td>
<td>56 (45.5%)</td>
<td>241 (34.3%)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Red</td>
<td>119 (14.4%)</td>
<td>48 (39%)</td>
<td>71 (10.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institutionalised, n (%)†</td>
<td>54 (6.5%)</td>
<td>32 (26%)</td>
<td>22 (3.1%)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)†</td>
<td>37 (4.5%)</td>
<td>24 (19.4%)</td>
<td>13 (10.6%)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Parkinson, n (%)†</td>
<td>9 (1.1%)</td>
<td>5 (4.1%)</td>
<td>4 (0.6%)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alzheimer’s disease, n (%)‡</td>
<td>9 (1.1%)</td>
<td>6 (4.9%)</td>
<td>3 (0.4%)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Other dementias, n (%)§</td>
<td>54 (6.5%)</td>
<td>43 (35%)</td>
<td>11 (1.6%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epilepsy, n (%)§</td>
<td>25 (3%)</td>
<td>12 (9.8%)</td>
<td>13 (1.9%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other neurological diseases, n (%)†</td>
<td>62 (7.5%)</td>
<td>20 (16.3%)</td>
<td>42 (6%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression, n (%)§</td>
<td>31 (3.8%)</td>
<td>12 (9.8%)</td>
<td>19 (2.7%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of chronic drugs, median (IQR¶)</td>
<td>2 (IQR 0–5)</td>
<td>5 (IQR 3–8)</td>
<td>1 (IQR 0–4)</td>
<td>&lt;0.001</td>
<td>0.025</td>
</tr>
<tr>
<td>Anticholinergic Burden score, median (IQR)**</td>
<td>0 (IQR 0–0)</td>
<td>1 (IQR 0–2)</td>
<td>0 (IQR 0–0)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Psychoactive drugs, n (%)¶</td>
<td>78 (9.4%)</td>
<td>32 (26.2%)</td>
<td>46 (6.6%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedative-hypnotics</td>
<td>50 (6.1%)</td>
<td>20 (16.4%)</td>
<td>30 (4.3%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>60 (7.3%)</td>
<td>22 (18%)</td>
<td>38 (5.4%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>39 (4.7%)</td>
<td>24 (19.7%)</td>
<td>15 (2.1%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memantine</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>5 (0.6%)</td>
<td>4 (3.3%)</td>
<td>1 (0.1%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dopaminergic drugs</td>
<td>12 (1.5%)</td>
<td>7 (5.7%)</td>
<td>5 (0.7%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Benjamini-Hochberg correction. Benjamini-Hochberg corrected p values were calculated by computing pcorr = m/k for all sorted p values (p=sorted p values; m=total number of sorted p values; k=corresponding rank). Then p values were adjusted from the bigger to the smallest. If the value pcorr = m/k was bigger than the previous adjusted p value, the corresponding corrected p value was equal to the previous one since numbers should not increase.

†Four missing.

‡Five missing.

§Six missing.

¶Eight missing.

**Fourteen missing.

n, number; TIA, transient ischaemic attack.
Eight supervised internal and emergency medicine residents performed a medical chart audit of all adult patients presenting to the ED of the San Raffaele Hospital, Milan, Italy, during the first wave of the COVID-19 pandemic (between 26 February 2020 and 30 May 2020). The residents who abstracted the data had no conflict of interest, were blinded to the study objectives and were very familiar with the computer system from which data were extracted.

Inclusion and exclusion criteria, the definition of the variables to be collected and their coding rules were documented in a coding guide for the abstractors before data collection (available on request). The standard case record form was pilot tested on a set of medical records not included in the study. During data abstraction, residents were periodically monitored by senior physicians.

Demographic data, comorbidities (including an anamnesis of dementia), medications, typical COVID-19 manifestations (dysgeusia, anosmia, fever, cough, rhinorrhea, pharyngodynia, earache, chest pain, myalgia, arthralgia, asthenia, dyspnoea, syncope, headache, confusion, abdominal pain, nausea/vomiting, diarrhoea, conjunctivitis, skin rash) and delirium symptoms (alterations of consciousness, disorientation, inattention, confusion, delirium, agitation, hallucinations, aggressiveness, disorganised thinking, memory deficit), vital signs, laboratory values, PaO2/FiO2 values and SARS-CoV-2 real-time PCR nasopharyngeal swab test results were extracted from the electronic patient data management system.

Since no delirium screening tool is routinely used in the ED of our hospital, the diagnosis of delirium was retrospectively performed through the Chart-Based Delirium Identification Instrument (CHART-DEL).15 According to the CHART-DEL method, the diagnosis of delirium can be formulated if an acute change in mental status and a key sign or symptom of delirium is found in the medical records by chart abstraction. This tool has previously been demonstrated to be a reliable method of identifying delirium from medical records, with a sensitivity of 74% and a specificity of 83% when validated against the confusion assessment method.15 It was used in the US study conducted by Kennedy et al in COVID-19 ED patients.5 To estimate the inter-rater reliability between the abstractors, we calculated Cohen’s Kappa coefficient on a random sample of 66 charts. In uncertain cases, medical records were reviewed by two senior clinicians (SD and MI).

Risk factors for delirium
Based on prior literature,7,16 we investigated the following factors as potentially associated with delirium: age, gender, triage colour code, living in a long-term healthcare facility before hospital admission, number of chronic medications, use of psychoactive drugs, Anticholinergic Burden (ACB) scale score, history of cognitive impairment, depression, epilepsy, cerebrovascular and other neurological diseases (such as multiple sclerosis and neuropsychopathies). In Italy, the patients are triaged into three colour codes: (1) red: needing immediate medical attention; (2) yellow: needing urgent medical attention; (3) green: needing delayed medical attention.19 Depression was used as a separate risk factor since this illness has been specifically associated with delirium.7 We considered the number of chronic medications as a proxy of patients’ complexity. We included the ACB score as drugs with anticholinergic effects have negative effects on attention, sleep and memory, and acetylcholine deficit has been regarded as a possible aetiology of delirium. We also collected signs and symptoms suggestive of COVID-19 severity as delirium predictors: number and duration of COVID-19 symptoms at ED admission, PaO2/FiO2 at ED admission, pH at ED admission, C reactive protein (CRP) at ED admission, lactate dehydrogenase (LDH) at ED admission, leucocytes at ED admission and respiratory rate at ED admission.

Population
All patients 18 years old or older who accessed the ED of the San Raffaele Hospital between 26 February 2020 and 30 May 2020 and who had a positive molecular nasopharyngeal swab for SARS-CoV-2 were included in the study. We excluded individuals who lacked a description of their cognitive status in the medical records.

Data collection and measurements

Table 2 Symptoms at ED presentation

<table>
<thead>
<tr>
<th>Delirium (N=123)</th>
<th>No delirium (N=703)</th>
<th>P value</th>
<th>Corrected P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium symptoms in the ED, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alterations of consciousness</td>
<td>60 (48.8%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disorientation</td>
<td>38 (31.4%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inattention</td>
<td>8 (6.6%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Confusion</td>
<td>40 (33.1%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lethargy</td>
<td>36 (29.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agitation</td>
<td>51 (41.8%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1 (0.8%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>5 (4.1%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disorganised thinking</td>
<td>3 (2.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory deficit</td>
<td>8 (6.6%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COVID-19 symptoms in the ED, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10 (8.1%)</td>
<td>191 (27.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anosmia</td>
<td>12 (9.8%)</td>
<td>149 (21.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fever</td>
<td>80 (65%)</td>
<td>612 (87.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>36 (29.3%)</td>
<td>415 (59.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pharyngodynia</td>
<td>7 (5.7%)</td>
<td>65 (9.3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>5 (4.1%)</td>
<td>81 (11.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Earache</td>
<td>3 (2.4%)</td>
<td>28 (4%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (7.3%)</td>
<td>154 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (7.3%)</td>
<td>107 (15.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 (17.9%)</td>
<td>154 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (4.1%)</td>
<td>276 (39.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>7 (5.7%)</td>
<td>65 (9.3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Lethargy</td>
<td>36 (29.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Benjamini-Hochberg correction. Benjamin-Hochberg corrected p values were calculated by computing p_{corr}=m/k for all sorted p values (p=sorted p values; m=total number of sorted p values; k=corresponding rank). Then p values were adjusted from the biggest to the smallest. If the value p_{corr}=m/k was bigger than the previous adjusted p value, the corresponding corrected p value was equal to the previous one since numbers should not increase.

Note: For the table, we have included only symptoms that were significantly different between the delirium and non-delirium groups. The full list of symptoms can be found in the original article.
Outcomes
Our primary outcomes were the prevalence of delirium in patients with COVID-19 and the factors associated with delirium in these patients. Secondary outcomes were the association of delirium with length of ED stay, hospitalisation and length of hospitalisation, ICU admission, being discharged home after hospitalisation, being transferred to another healthcare facility after hospitalisation and in-hospital mortality.

Statistical analyses
Our sample size was based on the number of patients seen during the period. Demographic data were analysed using descriptive statistics. The percentage of patients with COVID-19 presenting with delirium was calculated. The clinical characteristics and outcomes of people with COVID-19 presenting with or without delirium were compared with Student’s t-test for continuous variables or the χ² test for dichotomous variables. In case of non-normal distribution of continuous variables, the Mann-Whitney test was used.

Binary logistic regression models were used to assess which variables were associated with delirium in the ED. Delirium was the dependent variable; the independent variables were age, gender, triage colour code, living in a long-term healthcare facility before hospital admission, number of chronic drugs, use of psychoactive drugs, ACB scale score, history of cognitive impairment, depression, epilepsy, cerebrovascular and other neurological diseases (including neurological diseases such as multiple sclerosis and neuropathies). A multivariable model with a backward selection of the variables showing significant associations with delirium at univariable analyses was also run.

To evaluate the association between delirium (independent variable) and its outcomes (dependent variables), univariate logistic regression analyses were run for each of the following outcomes: hospitalisation, ICU admission, medical ward admission, being discharged to home after hospitalisation, being transferred to another healthcare facility. For the outcomes length of ED stay and length of hospitalisation, we performed univariable linear regression analyses. Unadjusted Cox regression analyses were performed to test whether delirium was associated with in-hospital mortality. Age-adjusted and sex-adjusted analyses were also performed for the significant predictors and outcomes of delirium. Analyses were adjusted for age and sex because these two variables were demonstrated to be associated with COVID-19 predictors and outcomes. We did not adjust analyses for body mass index (BMI) because unfortunately we did not have BMI data for all the hospitalised patients. We did not correct the analyses for ethnicity because ethnicity was almost homogeneous in our study, with the majority of patients being Caucasian. Moreover, the correction for ethnicity would have been subjected to confounding socioeconomic variables and would have been difficult to correlate with genetic factors.

The Hosmer and Lemeshow test was used to evaluate the goodness of fit of the regression models. Since the number of missing data for some variables included was extremely small, no imputation was performed and missing values were omitted from the analysis.

The Benjamini-Hochberg procedure was applied to decrease the false discovery rate (FDR), which is the expected proportion of ‘discoveries’ (rejected null hypotheses) that may be associated with multiple testing. The FDR is a method of conceptualising the rate of type I errors in null hypothesis testing when conducting multiple comparisons. FDR-controlling procedures are designed to control the FDR, which is the expected proportion of ‘discoveries’ (rejected null hypotheses) that are false (incorrect rejections of the null). Equivalently, the FDR is the expected ratio of the number of false positive classifications (false discoveries) to the total number of positive classifications (rejections of the null). The total number of rejections of the null includes both the number of false positives (FP) and true positives (TP). This method applies sequential modified Bonferroni corrections for multiple hypothesis testing and controls the number of small p values due to chance.

All statistical analyses were performed with SPSS V.25.0 (SPSS).
Among the 847 patients who accessed the San Raffaele Hospital ED during the study period and had a positive nasal swab for SARS-CoV-2, 826 individuals (97.52% of all records) had a description of their cognitive status in medical records and were therefore retrospectively classified as delirious according to the CHART-DELI instrument. Cohen’s Kappa coefficient for inter-rater reliability for the diagnosis of delirium was 0.66 (95% CI 0.43 to 0.89; p<0.001).

The prevalence of all forms of dementia, neurological disease and depression was higher among the group who manifested delirium in the ED compared with patients who did not. Similarly, the pharmacologic (median number of chronic medications: 5 vs 1) and anticholinergic burden (median anticholinergic burden score 1 vs 0) and the use of psychoactive drugs (26.2% vs 6.6%) were higher in patients who experienced delirium.

The main manifestations of patients with delirium in the ED were alteration of consciousness (48.8%), agitation (41.8%), confusion (33.1%), disorientation (31.4%) and lethargy (29.5%) (table 2). Patients with delirium presented with fewer typical COVID-19 manifestations (median 2 vs 3) compared with the ones without delirium but had more confusion and syncope. The duration of COVID-19 manifestations before ED admission was shorter in patients with delirium compared with patients without delirium: median 4 days vs 7 days.

In spite of a smaller number of COVID-19 manifestations, patients with delirium received a more serious triage colour at ED admission (table 1) and had greater elevations in inflammatory
did not differ from the total sample of the patients included in the study except for the percentage of male patients (online supplemental table 2). Cohen’s Kappa coefficient for inter-rater reliability for the diagnosis of delirium was 0.66 (95% CI 0.43 to 0.89; p<0.001).

Table 1 illustrates the baseline features of the study population. Patients with delirium were older (76.9 years vs 61.3 years) and lived more frequently in a long-term healthcare facility (26% vs 3.1%).

The prevalence of all forms of dementia, neurological disease and depression was higher among the group who manifested delirium in the ED compared with patients who did not. Similarly, the pharmacologic (median number of chronic medications: 5 vs 1) and anticholinergic burden (median anticholinergic burden score 1 vs 0) and the use of psychoactive drugs (26.2% vs 6.6%) were higher in patients who experienced delirium.

The main manifestations of patients with delirium in the ED were alteration of consciousness (48.8%), agitation (41.8%), confusion (33.1%), disorientation (31.4%) and lethargy (29.5%) (table 2). Patients with delirium presented with fewer typical COVID-19 manifestations (median 2 vs 3) compared with the ones without delirium but had more confusion and syncope. The duration of COVID-19 manifestations before ED admission was shorter in patients with delirium compared with patients without delirium: median 4 days vs 7 days.

In spite of a smaller number of COVID-19 manifestations, patients with delirium received a more serious triage colour at ED admission (table 1) and had greater elevations in inflammatory
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indices and greater alterations of hepatic, renal and respiratory functions (table 3).

In univariable regression analyses, all previously known risk factors were predictors of delirium in patients with COVID-19: age, male sex, institutionalisation, neurological or psychiatric comorbidities, polypharmacy, anticholinergic burden, use of psychoactive drugs. Among the blood tests LDH, leucocytes, pH and PaO$_2$/FiO$_2$ predicted delirium. On the other hand, number and duration of COVID-19 symptoms were inversely associated with delirium (table 4).

In the multivariable model age (adjusted OR 1.06, 95% CI 1.04 to 1.09, p<0.001), dementia (adjusted OR 17.5, 95% CI 7.27 to 42.16, p<0.001), epilepsy (adjusted OR 6.96, 95% CI 2.48 to 19.51, p<0.001) and the number of chronic drugs (adjusted OR 1.09, 95% CI 1.01 to 1.17, p=0.03) were significantly associated with delirium.

The majority of patients were hospitalised (86.4%). In univariate analyses, frequency of hospitalisation was similar for patients with and without delirium (110 (89.4%) vs 604 (86.0%) patients, p=0.12) (table 5). Length of ED (2, IQR 1–2 in both
groups) and hospital stays were similar in patients with delirium versus patients without delirium (13 days, IQR 5–28 vs 12 days, IQR 6–22) and there were no differences in the frequency of ICU admission (6 (4.9%) in patients with delirium vs 38 (5.4%) patients without delirium, p=0.19). Delirium was a significant predictor of a reduced probability of being discharged home both in unadjusted (table 5) and at the age-adjusted and sex-adjusted regression analyses (adjusted OR 0.39, 95% CI 0.25 to 0.61, p<0.001).

Delirium was associated with a higher in-hospital mortality both at the unadjusted (HR 3.37, 95% CI 2.47 to 4.61, p<0.001) and at the age-adjusted and sex-adjusted (HR 2.16, 95% CI 1.55 to 3.03, p<0.001) Cox analyses (figure 1).

DISCUSSION

In this retrospective study, we found that among patients with SARS-CoV-2 infection presenting to the ED of a large tertiary hospital, an alteration of consciousness consistent with the diagnosis of delirium was present in 14.5% of the sample. Patients with delirium were older, more comorbid, lived more frequently in a long-term healthcare facility, received a greater number of chronic and psychoactive drugs and had a higher AGB score. COVID-19 manifested with less typical symptoms in patients with delirium, in spite of the severity of the SARS-CoV-2 disease as evidenced by the triage level assigned and inflammatory markers.

Our findings on overall delirium prevalence of 14.5% are in line with prior non-COVID-19 literature14 that describes the occurrence of delirium among 7% and 20% of patients at ED admission. However, we found a higher prevalence of delirium in older patients with COVID-19 (26.8%) than previously reported in older people not suffering from COVID-19 (about 12%).

Many factors could have contributed to the higher prevalence of delirium in older people infected by SARS-CoV-2: the direct neurotropism of SARS-CoV-2 virus, cerebral hypoxic damage, the intense inflammatory response, the presence of fever and dehydration21 that synergically act as delirium stimuli. In our sample, patients with delirium presented higher inflammatory indices and had a greater alteration of renal function (a possible consequence of fever and dehydration).

Our study findings in older people are similar to those by Kennedy et al in the USA, who studied delirium in older patients with COVID-19.15 The prevalence of delirium was similar (26.8% vs 28% in the sample by Kennedy et al) in spite that Kennedy et al assessed delirium with a mixed method both prospectively (through a specific delirium assessment tool) and retrospectively (through the medical chart abstraction). We detected a lower percentage of alteration of consciousness (48.8% vs 54%), disorientation (31.4% vs 43%) and hypoactive symptoms (4.4% vs 20%) compared with Kennedy et al,15 while agitation was more frequent in our study (41.8% vs 16%).

As previously reported in both COVID-19 and non-COVID-19, age was a risk factor for developing delirium. Older people have many delirium predisposing factors and thus less intense stimuli are necessary to trigger delirium. The number of chronic medications, but not psychoactive drugs, predicted delirium in the multivariable model in our study. The number of chronic medications can be considered as a proxy of patients’ complexity. Indeed, the comorbidity burden has been associated with an increased risk of developing delirium.

In our sample, dementia and epilepsy significantly predicted delirium, whereas Kennedy et al identified Parkinson’s disease as a risk factor. However, Kennedy et al excluded both dementia and mental health conditions from the multivariable model due to multicollinearity. Dementia is the major risk factor for delirium and previous studies reported that two-thirds of the cases of delirium are found in individuals suffering from dementia.22 23 People suffering from dementia are highly vulnerable and can develop delirium with only minor insults.

Our study confirmed the possible subtle presentation of COVID-19 in a consistent number of patients (123 people) who manifested less typical COVID-19 symptoms, although they actually had more severe disease as indicated by other clinical and laboratory markers. COVID-19 patients with delirium may have under-reported the number of the typical COVID-19 manifestations because of their altered sensorium or may have really manifested fewer COVID-19 symptoms. Indeed, delirium can be the only manifestation of both infective and non-infective diseases in older people.

Delirium is both a warning sign and a prognostic marker. Lack of recognition of delirium in the context of COVID-19 may result in an underestimation of the severity of the infection. Moreover, untreated delirium can predispose patients to short-term and long-term adverse outcomes (eg, in-hospital mortality,24 cognitive and functional decline).25 In our sample, mortality in patients with delirium was higher compared with the study of Kennedy et al (53.7% vs 37%) despite the younger age of our sample (63.7 years vs 77.7 years). Also, when considering only older patients (≥65 years), mortality remained higher in our study (57.7% vs 37%).

Some limitations of our study have to be mentioned. Findings from single-centre studies may not be generalisable. The use of the CHART-DEL instrument to retrospectively diagnose delirium may have led to an underestimation of its prevalence due to under-reporting of typical signs and symptoms in ED electronic health records. The clinical documentation was not originally recorded for this research purpose and the description of the cognitive status of the patients during the ED visits could have been scant due to the emergency setting of the first wave of the COVID-19 pandemic. Moreover, the agreement between chart reviewers was only moderate according to Cohen’s Kappa coefficient.

In conclusion, our chart review study identified that delirium was frequent in patients with COVID-19 in the ED and that patients with delirium demonstrated fewer other signs of COVID-19. Age, dementia, epilepsy and polypharmacy were significant predictors of ED delirium. Moreover, delirium was associated with increased in-hospital mortality and with a reduced probability of being discharged home after hospitalisation. Future prospective studies could evaluate whether the use of delirium screening tools in the ED can correctly identify delirium in patients with COVID-19 and whether screening for delirium can improve outcomes.

Acknowledgements We thank our collaborators: Abutalebi Jubin; Acerno Stefania; Angelillo Piera; Assanelli Andrea; Ballo Michele; Bellone Matteo; Boffini Nicola; Brenchi Elena; Calvisi Stefania Laura; Canetti Diana; Canetti Amelia; Castiglioni Barbara; Cerri Federica; Cicalese Maria Pia; Cilia Marta; D’Alberiti Teresa; Da Prat Albeteo; Davalli Albertro; De Lorenzo Rebecca; Finazzi Renato; Frontino Giulio; Gagliardi Filippo; Guarneri Giovanni; Impellizzeri Matteo; Laurenzi Andrea; Lopez Ignazio Diego; Marongiu Alessandro; Martinenghi Sabina; Mastaglio Sara; Memoli Massimo; Miglio Martina; Molinari Chiara; Moroni Luca; Pajno Roberta; Pannari Pietro; Pasetti Marcella; Piemontese Simona; Poloniato Antonella; Ripa Marco; Salmaggi Chiara; Sangalli Francesca; Scarpellini Paolo; Sparramela Paola; Strada Silvia; Tassan Din Ciara; Tentori Stefano; Traboschi Mira; Ventimiglia Eugenio; Vitali Giordano Pietro; Vitali Matteo; Elena Castelli; Mattia Di Meo, Gustavo Corti;
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Agnese Gobbi; Clarissa Centurioni; Flavia Di Scala; Anna Morgillo; Colombo Sergio, Moizzo Elena; Plumari Valentina Paola; Baiardo Redaelli Martina; Tambaro Elena; Carcò Francesco; Fedres Daniela; Mennella Roberto; Silvani Paolo; Landoni Giovanni; Ortalda Alessandro; Lombardi Gaetano; Maimeri Nicolò; Miglia Martina. We also thank our head nurses: Maria Filomena Cardinale, Gledis Chaulan, Pina De Francesco, Chiara Gianesini, Caterina Macrì; Germana Mazzon, Ivana Piccinin, Silvia Radaelli, Simone Santomo, Katia Ruggeri.

Contributors All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted. SD is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This was an observational study part of the COVID-19 institutional (San Raffaele Hospital) clinical-biological cohort assessing patients with COVID-19 (Covid-BioB, ClinicalTrials.gov NCT04318386). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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