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

Sarah Damanti ,[1] Enrica Bozzolo,[1] Stefano Franchini,[2] Claudia Frangi,[3] Giuseppe Alvise Ramirez,[4] Carla Pedroso,[1] Giuseppe Di Lucca,[1] Raffaella Scotti,[1] Davide Valsecchi,[2] Marta Cilla,[1] Elena Cinel,[3] Chiara Santini,[3] Jacopo Castellani,[3] Emanuela Manzo ,[3] Stefania Vadruccio,[3] Marzia Spessot,[2] Giovanni Borghi,[4] Giacomo Monti,[1,4] Giovanni Landoni,[3,5] Patrizia Rovere-Querini,[3,4] Mona-Rita Yacoub,[4] Moreno Tresoldi[1]

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).

[1]Unit of General Medicine and Advanced Care, IRCCS San Raffaele Institute, Milan, Italy
[2]Emergency Department, IRCCS San Raffaele Scientific Institute, Milan, Italy
[3]Vita-Salute San Raffaele University, Milan, Italy
[4]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy
[5]Department of Anaesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

Correspondence to
Dr Sarah Damanti, San Raffaele Hospital, Milano, 542, Italy; damanti.sarah@hsr.it

M-RY and MT are joint senior authors.

Received 9 June 2021
Accepted 28 November 2022
Published Online First 15 December 2022

To cite: Damanti S, Bozzolo E, Franchini S, *et al*. *Emerg Med J* 2023;**40**:202–209.

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 (26%) vs 22 (3.1%), p<0.001). Age (OR 1.06, 95% CI 1.04 to 1.09, 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.[1] 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,[10] 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.[11] 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),[12] it goes under-recognised in approximately 75% of cases.[13] 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.

Table 1 Baseline characteristics of the studied population

	Total sample (N=826)	Delirium (N=123)	No delirium (N=703)	P value	Corrected P value*
Age, mean (SD)	63.7 (15.16)	76.9 (13.15)	61.3 (14.27)	<0.001	N.A.
Males, n (%)	544 (65.9%)	69 (56.1%)	475 (67.6%)	0.01	<0.001
Triage colour, n (%)†				<0.001	0.02
Green	409 (49.5%)	19 (15.4%)	390 (55.6%)		
Yellow	297 (36%)	56 (45.5%)	241 (34.3%)		
Red	119 (14.4%)	48 (39%)	71 (10.1%)		
Institutionalised, n (%)†	54 (6.5%)	32 (26%)	22 (3.1%)	<0.001	0.01
Stroke/TIA, n (%)‡	37 (4.5%)	24 (3.4%)	13 (10.6%)	<0.001	0.01
Parkinson, n (%)‡	9 (1.1%)	5 (4.1%)	4 (0.6%)	0.001	<0.001
Alzheimer's disease, n (%)‡	9 (1.1%)	6 (4.9%)	3 (0.4%)	<0.001	<0.001
Other dementias, n (%)§	54 (6.5%)	43 (35%)	11 (1.6%)	<0.001	<0.001
Epilepsy, n (%)¶	25 (3%)	12 (9.8%)	13 (1.9%)	<0.001	<0.001
Other neurological diseases, n (%)‡	62 (7.5%)	20 (16.3%)	42 (6%)	<0.001	<0.001
Depression, n (%)§	31 (3.8%)	12 (9.8%)	19 (2.7%)	<0.001	<0.001
Number of chronic drugs, median (IQR)¶	2 (IQR 0–5)	5 (IQR 3–8)	1 (IQR 0–4)	<0.001	0.025
Anticholinergic Burden score, median (IQR)**	0 (IQR 0–0)	1 (IQR 0–2)	0 (IQR 0–0)	<0.001	0.01
Psychoactive drugs, n (%)¶	78 (9.4%)	32 (26.2%)	46 (6.6%)	<0.001	<0.001
Sedative-hypnotics	50 (6.1%)	20 (16.4%)	30 (4.3%)	<0.001	<0.001
Antidepressants	60 (7.3%)	22 (18%)	38 (5.4%)	<0.001	<0.001
Antipsychotics	39 (4.7%)	24 (19.7%)	15 (2.1%)	<0.001	<0.001
Memantine	1 (0.1%)	1 (0.8%)	0 (0%)	0.02	0.01
Acetylcholinesterase inhibitors	5 (0.6%)	4 (3.3%)	1 (0.1%)	<0.001	<0.001
Dopaminergic drugs	12 (1.5%)	7 (5.7%)	5 (0.7%)	<0.001	<0.001

*Benjamini-Hochberg correction. Benjamini-Hochberg corrected p values were calculated by computing $p_{(k)}$=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 $p_{(k)}$=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.
‡Six missing.
§Five missing.
¶Eight missing.
**Fourteen missing.
n, number; TIA, transient ischaemic attack.

Table 2 Symptoms at ED presentation

	Delirium (N=123)	No delirium (N=703)	P value	Corrected P value*
Delirium symptoms in the ED, n (%)				
Alterations of consciousness	60 (48.8%)	0 (0%)	<0.001	<0.001
Disorientation	38 (31.4%)	0 (0%)	<0.001	<0.001
Inattention	8 (6.6%)	0 (0%)	<0.001	<0.001
Confusion	40 (33.1%)	0 (0%)	<0.001	<0.001
Lethargy	36 (29.5%)	0 (0%)	<0.001	<0.001
Agitation	51 (41.8%)	0 (0%)	<0.001	<0.001
Hallucinations	1 (0.8%)	0 (0%)	0.02	0.01
Aggressiveness	5 (4.1%)	0 (0%)	<0.001	<0.001
Disorganised thinking	3 (2.5%)	0 (0%)	<0.001	<0.001
Memory deficit	8 (6.6%)	0 (0%)	<0.001	<0.001
COVID-19 symptoms in the ED, n (%)				
Dysgeusia	10 (8.1%)	191 (27.4%)	<0.001	<0.001
Anosmia	12 (9.8%)	149 (21.3%)	0.003	<0.001
Fever	80 (65%)	612 (87.7%)	<0.001	<0.001
Cough	36 (29.3%)	415 (59.4%)	<0.001	<0.001
Rhinorrhea	7 (5.7%)	65 (9.3%)	0.19	0.07
Pharyngodynia	5 (4.1%)	81 (11.6%)	0.01	<0.001
Earache	3 (2.4%)	28 (4%)	0.4	0.14
Chest pain	8 (6.5%)	108 (15.5%)	0.01	<0.001
Myalgia	9 (7.3%)	154 (22%)	<0.001	<0.001
Arthralgia	9 (7.3%)	107 (15.3%)	0.02	0.01
Asthenia	22 (17.9%)	276 (39.5%)	<0.001	<0.001
Dyspnoea	75 (61%)	392 (56.1%)	0.31	0.11
Syncope	20 (16.3%)	34 (4.9%)	< 0.001	< 0.001
Headache	4 (3.3%)	111 (15.9%)	<0.001	<0.001
Confusion	40 (32.5%)	84 (12%)	<0.001	<0.001
Abdominal pain	8 (6.5%)	53 (7.6%)	0.67	0.21
Nausea/vomiting	10 (8.1%)	91 (13%)	0.13	0.05
Diarrhoea	11 (8.9%)	131 (18.8%)	0.008	<0.001
Conjunctivitis	7 (5.7%)	55 (7.9%)	0.4	0.14
Skin rash	2 (1.6%)	22 (3.1%)	0.35	0.13
Number of COVID-19 symptoms at ED admission, median (IQR)	2 (IQR 1.75–3)	3 (IQR 2–6)	<0.001	0.008
Duration of COVID-19 symptoms before ED admission (days), median (IQR)	4 (IQR 1–7)	7 (IQR 4–10)	<0.001	0.006

*Benjamini-Hochberg correction. Benjamini-Hochberg corrected p values were calculated by computing $p_{(k)}$=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 $p_{(k)}$=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.
n, number.

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

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, rhinorrhoea, 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, lethargy, agitation, hallucinations, aggressiveness, disorganised thinking, memory deficit), vital signs, laboratory values, PaO_2/FiO_2 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).[17] 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.[18] It was used in the US study conducted by Kennedy *et al* in COVID-19 ED patients.[15] 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 10] 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 neuropathies). 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, PaO_2/FiO_2 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.

Table 3 Signs at ED presentation

	Delirium (N=123)	No delirium (N=703)	P value	Corrected P value*
Systolic blood pressure at ED admission, median (IQR)	124.5 (IQR 100–140)	125 (IQR 115–140)	0.02	0.03
Diastolic blood pressure at ED admission, median (IQR)	70 (IQR 60–80)	75 (IQR 70–80)	<0.001	0.005
Heart rate at ED admission, median (IQR)	89 (IQR 80–102)	90 (IQR 80–100)	0.68	0.68
Respiratory rate at ED admission, median (IQR)	30 (IQR 24–35.7)	28 (20.5–34.7)	0.19	0.21
Leucocytes (^10 000/mmc) at ED admission, median (IQR)	9.1 (IQR 5.5–11.5)	6.5 (IQR 4.9–9.3)	<0.001	0.004
Haemoglobin (g/dL) at ED admission, median (IQR)	13.1 (IQR 11.4–14.5)	13.9 (IQR 12.4–14.9)	0.001	0.003
Platelets (^1000/mmc) at ED admission, median (IQR)	217 (IQR 161–317)	204 (IQR 158–270)	0.38	0.39
Urea (mg/dL) at ED admission, median (IQR)	57 (IQR 37–106)	33 (IQR 24–48)	<0.001	0.003
Creatinine (mg/dL) at ED admission, median (IQR)	1.2 (IQR 0.91–1.83)	0.96 (IQR 0.78–1.2)	<0.001	0.002
Na (mEq/L) at ED admission, median (IQR)	140 (IQR 135.5–143.6)	137.3 (IQR 134.5–139.5)	<0.001	0.002
K (mEq/L) at ED admission, median (IQR)	4.3 (IQR 3.9–4.7)	4.2 (IQR 3.9–4.5)	0.16	0.19
AST (U/L) at ED admission, median (IQR)	50 (IQR 28.2–96)	43 (IQR 29–61)	0.03	0.04
ALT(U/L) at ED admission, median (IQR)	28 (IQR 17.25–53)	35 (IQR 23–54)	0.03	0.04
LDH (U/L) at ED admission, median (IQR)	415 (IQR 282–580)	352 (IQR 262–449)	0.001	0.002
CRP (mg/L) at ED admission, median (IQR)	92.5 (IQR 47.9–153.5)	67 (IQR 26.2–122.9)	0.005	0.009
pH at ED admission, median (IQR)	7.46 (IQR 7.41–7.5)	7.47 (IQR 7.44–7.5)	0.03	0.05
PaO_2/FiO_2 at ED admission, median (IQR)	238 (IQR 151–300)	300 (IQR 242–342)	<0.001	0.002

*Benjamini-Hochberg correction. Benjamini-Hochberg corrected p values were calculated by computing $p_{(k)}$=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 $p_{(k)}$=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.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; LDH, lactate dehydrogenase; n, number.

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 χ^2 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.[20] 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).

Table 4 Predictors of delirium in the univariable regression analyses

Delirium				
	OR	95% CI	P value	Corrected*
Age	1.09	1.07 to 1.11	<0.001	0.002
Sex (male)	1.63	1.1 to 2.45	0.014	0.01
Triage colour				
Red	13.88	7.71 to 24.99	<0.001	0.03
Yellow	4.77	2.77 to 8.22	<0.001	0.01
Institutionalisation	10.85	6.04 to 19.49	<0.001	0.009
Stroke/TIA	3.33	1.65 to 6.74	0.001	0.001
Parkinson	7.38	1.95 to 27.89	0.003	0.003
Alzheimer's disease	11.93	2.94 to 48.37	0.001	0.001
Other dementias	33.76	16.74 to 68.1	< 0.001	0.007
Epilepsy	5.76	2.56 to 12.96	< 0.001	0.005
Other neurological diseases	3.05	1.72 to 5.40	<0.001	0.005
Depression	3.89	1.84 to 8.23	<0.001	0.004
Psychoactive drugs	5.07	3.07 to 8.38	<0.001	0.003
Sedative-hypnotics	4.39	2.4 to 8.01	<0.001	0.003
Antidepressants	3.84	2.18 to 6.77	<0.001	0.003
Antipsychotics	11.22	5.69 to 22.12	<0.001	0.002
Acetylcholinesterase inhibitors	23.76	2.63 to 214.45	0.005	0.006
Dopaminergic drugs	8.47	2.64 to 27.15	<0.001	0.002
Number of chronic drugs	1.23	1.17 to 1.30	<0.001	0.002
Anticholinergic Burden Score	1.9	1.60 to 2.26	<0.001	0.002
Number of COVID-19 symptoms at ED admission	0.84	0.78 to 0.91	<0.001	0.001
Duration of COVID-19 symptoms before ED admission	0.90	0.85 to 0.94	<0.001	0.002
PaO_2/FiO_2 at ED admission	0.99	0.993 to 0.997	<0.001	0.002
pH at ED admission	0.006	0 to 0.11	0.001	0.001
CRP at ED admission	1.001	0.99 to 1	0.295	0.29
LDH at ED admission	1.002	1.001 to 1.003	0.002	0.002
Leucocytes at ED admission	1.09	1.04 to 1.13	<0.001	0.001
Respiratory rate at ED admission	1.02	0.98 to 1.06	0.19	0.20

*Benjamini-Hochberg correction. Benjamini-Hochberg corrected p values were calculated by computing $p_{(k)}$=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 $p_{(k)}$=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.
CRP, C reactive protein; LDH, lactate dehydrogenase; TIA, transient ischaemic attack.

Table 5 Univariable regression analyses showing the association between delirium and clinical outcomes

Hospitalisation			
	OR	95% CI	P value
Delirium	1.37	0.74 to 2.54	0.31
ICU admission			
	OR	95% CI	P value
Delirium	0.61	0.31 to 1.21	0.16
Medical ward admission			
	OR	95% CI	P value
Delirium	1.15	0.47 to 2.77	0.76
Discharged at home after hospitalisation			
	OR	95% CI	P value
Delirium	0.2	0.13 to 0.30	<0.001
Transferred to another healthcare facility			
	OR	95% CI	P value
Delirium	0.15	0.02 to 1.12	0.06
Length of ED stay			
	B	95% CI	P value
Delirium	0.13	−0.1 to 0.36	0.26
Length of hospital stay			
	B	95% CI	P value
Delirium	2.18	−1.22 to 5.58	0.21

ICU, intensive care unit.

RESULTS

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 included in the study. Included and excluded patients did not differ for the main clinical characteristics (online supplemental table 1). The included sample (826 patients, 65.9% males) had a mean age of 63.7 years (SD 15.16) and was characterised by a low pharmacological burden (median number of chronic drugs 2, IQR 0–5). Moreover, half of the sample had a low severity triage colour (green in 49.5% of the patients). Among the included patients, 123 (14.9%, 95% CI 13% to 17%) had an acute alteration of consciousness and signs or symptoms of delirium during their ED stay and were therefore retrospectively classified as delirious according to the CHART-DEL instrument. When considering only older people (age ≥65 years), the prevalence of delirium rose to 26.8% (95% CI 23% to 32%). The random sample selected for assessing the inter-rater reliability 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 (76.9years 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.

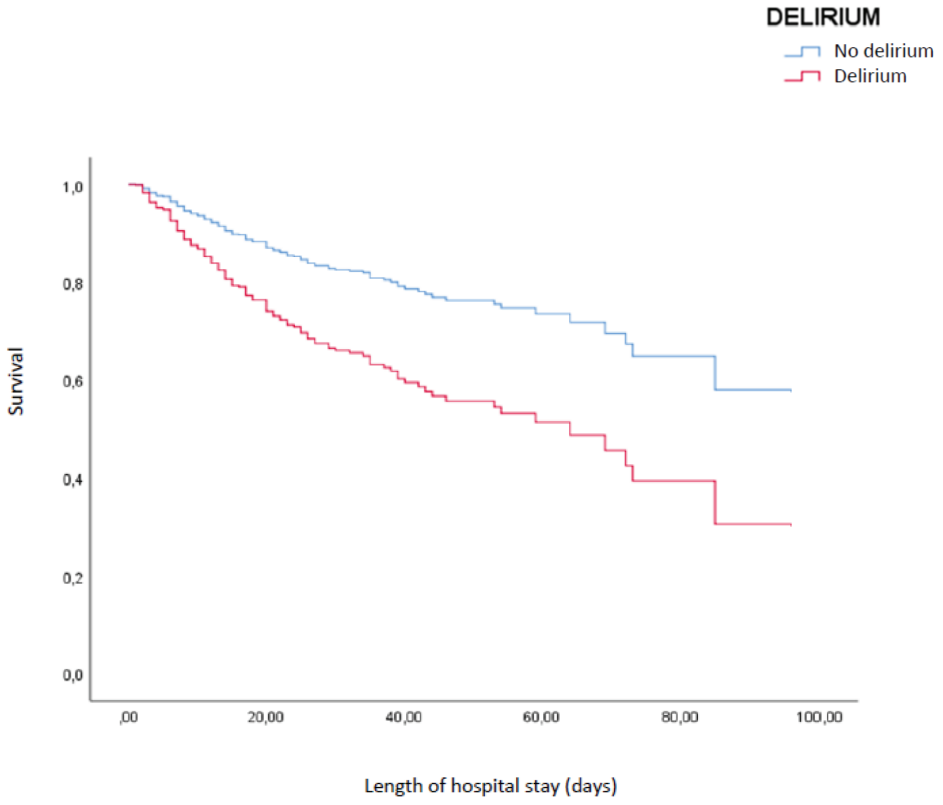
In spite of a smaller number of COVID-19 manifestations, patients with delirium received a more serious triage colour at ED admission (table 1) and had greater elevations in inflammatory

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



	Days	Patients entering the interval	Patients removed from the interval	Number at risk	Number of terminal events
No DELIRIUM	0	703	248	579	31
	10	424	181	333,5	36
	20	207	73	170,5	17
	30	117	39	97,5	6
	40	72	19	62,5	3
	50	50	21	39,5	3
	60	26	8	22	2
	70	16	9	11,5	2
	80	5	0	5	0
	90	5	3	3,5	0
	100	2	2	1	0
DELIRIUM	0	123	11	117,5	40
	10	72	13	65,5	9
	20	50	12	44	9
	30	29	9	24,5	4
	40	16	5	13,5	2
	50	9	4	7	0
	60	5	1	4,5	0
	70	4	1	3,5	0
	80	3	1	2,5	1
	90	1	0	1	1

Figure 1 Kaplan-Meir survival curves for patients with and without delirium (age-adjusted and sex-adjusted analysis).

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 ACB 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 literature[14] 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 dehydration[21] 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.[7]

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.[7]

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; Bailo Michele; Bellone Matteo; Boffini Nicola; Brioschi Elena; Calvisi Stefania Laura; Canetti Diana; Caretto Amelia; Castiglioni Barbara; Cerri Federica; Cicalese Maria Pia; Cilla Marta; D'Aliberti Teresa; Da Prat Valentina; Davalli Alberto; De Lorenzo Rebecca; Finazzi Renato; Frontino Giulio; Gagliardi Filippo; Guarneri Giovanni; Impellizzeri Matteo, Laurenzi Andrea; Lopez Ignazio Diego; Marinosci Alessandro; Martinenghi Sabina; Mastaglio Sara; Memoli Massimo; Miglio Martina; Molinari Chiara; Moroni Luca; Pajno Roberta; Panni Pietro; Pasetti Marcella; Piemontese Simona; Poloniato Antonella; Ripa Marco; Salmaggi Chiara; Sangalli Francesca; Scarpellini Paolo; Sgaramella Paola; Strada Silvia; Tassan Din Chiara; Tentori Stefano; Tiraboschi Mirta; Ventimiglia Eugenio; Vitali Giordano Pietro; Vitali Matteo; Elena Castelli, Mattia Di Meo, Gustavo Corti;

Agnese Gobbi; Clarissa Centurioni; Flavia Di Scala; Anna Morgillo; Colombo Sergio, Moizo Elena; Plumari Valentina Paola; Baiardo Redaelli Martina; Tambaro Elena; Carcò Francesco; Febres Daniela; Mennella Roberta; Silvani Paolo; Landoni Giovanni; Ortalda Alessandro; Lombardi Gaetano; Maimeri Nicolò; Miglio Martina. We also thank our head nurses: Maria Filomena Cardinali, Gledis Chaulan, Pina De Francesco, Chiara Gianesini; Caterina Macrì; Germana Mazzon, Ivana Piccinin, Silvia Radaelli, Simone Santomo, Katia Ruggieri.

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, or 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 NCT04318366). 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.

ORCID iDs
Sarah Damanti http://orcid.org/0000-0002-2399-3688
Emanuela Manzo http://orcid.org/0000-0002-7160-8633

REFERENCES

1 O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. *Age Ageing* 2020;49:497–8.
2 Zubair AS, McAlpine LS, Gardin T, *et al*. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol* 2020;77:1018.
3 Baig AM, Khaleeq A, Ali U, *et al*. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;11:995–8.
4 Maldonado JR. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry* 2018;33:1428–57.
5 Massé L, Antonacci M. Low cardiac output syndrome: identification and management. *Crit Care Nurs Clin North Am* 2005;17:375–83.
6 Morley JE, Vellas B. COVID-19 and older adult. *J Nutr Health Aging* 2020;24:364–5.
7 Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
8 Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. *Ann Neurol* 2020;88:1–11.
9 Ciceri F, Beretta L, Scandroglio AM. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *CC&R* 2020;22:95–7.
10 Kennedy M, Enander RA, Tadiri SP, *et al*. Delirium risk prediction, healthcare use and mortality of elderly adults in the emergency department. *J Am Geriatr Soc* 2014;62:462–9.
11 Limpawattana P, Phungoen P, Mitsungnern T, *et al*. Atypical presentations of older adults at the emergency department and associated factors. *Arch Gerontol Geriatr* 2016;62:97–102.
12 Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. *Emerg Med J* 2013;30:263–8.
13 Marcantonio ER. In the clinic. delirium. *Ann Intern Med* 2011;154:ITC6-1, ITC6-2, ITC6-3, ITC6-4, ITC6-5, ITC6-6, ITC6-7, ITC6-8, ITC6-9, ITC6-10, ITC6-11, ITC6-12, ITC6-13, ITC6-14, ITC6-15:quiz ITC6–16.
14 Sanders AB. Missed delirium in older emergency department patients: a quality-of-care problem. *Ann Emerg Med* 2002;39:338–41.
15 Kennedy M, Helfand BKI, Gou RY, *et al*. Delirium in older patients with COVID-19 presenting to the emergency department. *JAMA Network Open* 2020;3:e2029540.
16 Rovere-Querini P, Tresoldi C, Conte C, *et al*. Biobanking for COVID-19 research. *Panminerva Med* 2022;64:244–52.
17 Inouye SK, Leo-Summers L, Zhang Y, *et al*. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc* 2005;53:312–8.
18 Inouye SK, van Dyck CH, Alessi CA, *et al*. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–8.
19 Triage intraospedaliero nel sistema dell'emergenza-urgenza sanitaria.Gazzetta Ufficiale n. 285 del 7712/2001
20 Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B* 1995;57:289–300.
21 Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683.
22 Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med* 2017;377:1456–66.
23 Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry* 2004;12:7–21.
24 Marengoni A, Zucchelli A, Grande G, *et al*. The impact of delirium on outcomes for older adults hospitalised with COVID-19. *Age Ageing* 2020;49:923–6.
25 Wong CL, Holroyd-Leduc J, Simel DL, *et al*. Does this patient have delirium?: value of bedside instruments. *JAMA* 2010;304:779–86.

Table 1S: comparison of the main characteristics of the included and excluded patients

	Included patients (N = 826)	**Excluded patients (N=21)**	**p**	**Statistica test**
Age, mean (SD)	63.7 (SD 15.16)	70.9 (IQR 42.6 -81.1)	0.67	U Mann Whitney
Males, N (%)	544 (65.9%)	14 (66.7%)	0.94	Chi square test
Triage colour, N (%)			0.61	Chi square test
green	409 (49.5%)	10 (47.6%)		
yellow	297 (36%)	6 (28.6%)		
red	119 (14.4%)	4 (19%)		
Institutionalized, N (%)	54 (6.5%)	0 (0%)	0.63	Fisher exact test
Stroke/TIA, N (%)	37 (4.5)	0 (0%)	1	Fisher exact test
Parkinson, N (%)	9 (1.1%)	0 (0%)	1	Fisher exact test
Alzheimer disease, N (%)	9 (1.1%)	0 (0%)	1	Fisher exact test
Other dementias, N (%)	54 (6.5%)	0 (0%)	0.62	Fisher exact test
Epilepsy, N (%)	25 (3%)	0 (0%)	1	Fisher exact test
Other neurologic diseases, N (%)	62 (7.5%)	0 (0%)	0.63	Fisher exact test
Depression, N (%)	31 (3.8%)	2 (9.5%)	0.14	Fisher exact test
Number of chronic drugs, median (IQR)	2 (IQR 0 - 5)	2 (IQR 0 - 6)	0.79	U Mann Whitney
Anticholinergic burden score, median (IQR)	0 (IQR 0 - 0)	0 (IQR 0 - 0)	0.37	U Mann Whitney
Psychoactive drugs, N (%)	78 (9.4%)	1 (4.8%)	1	Fisher exact test
Sedative-hypnotics	50 (6.1%)	0 (0%)	1	Fisher exact test
Antidepressants	60 (7.3%)	1 (4.8%)	1	Fisher exact test
Antipsychotics	39 (4.7%)	0 (0%)	1	Fisher exact test
Memantine	1 (0.1%)	0 (0%)	1	Fisher exact test
Acetylcholinesterase inhibitors	5 (0.6%)	0 (0%)	1	Fisher exact test
Dopaminergic drugs	12 (1.5%)	0 (0%)	1	Fisher exact test

	Random sample (N = 66)	**Other patients (N=760)**
Age, mean (SD)	70.4 (IQR 55.56 - 79.25)	62.53 (IQR 52.73 - 75.36)
Males, N (%)	35 (53%)	509 (67%)
Triage colour, N (%)		
green	36 (54.5%)	373 (49.1%)
yellow	22 (33.3%)	275 (36.2%)
red	8 (12.1%)	111 (14.6%)
Institutionalized, N (%)	4 (6.1%)	50 (6.6%)
Stroke/TIA, N (%)	3 (4.5%)	34 (4.5%)
Parkinson, N (%)	0 (0%)	9 (1.2%)
Alzheimer disease, N (%)	0 (0%)	9 (1.2%)
Other dementias, N (%)	3 (4.5%)	51 (6.7%)
Epilepsy, N (%)	2 (3%)	23 (3%)
Other neurologic diseases, N (%)	3 (4.5%)	59 /7.8%)
Depression, N (%)	2 (3%)	29 (3.8%)
Number of chronic drugs, median (IQR)	2 (IQR 1 - 6.25)	2 (IQR 0 - 5)
Anticholinergic burden score, median (IQR)	0 (IQR 0 - 1)	0 (IQR 0 -0)
Psychoactive drugs, N (%)	8 (12.1%)	70 (9.2%)
Sedative-hypnotics	4 (6.1%)	46 (6.1%)
Antidepressants	4 (6.1%)	56 (7.4%)
Antipsychotics	2 (3%)	37 (4.9%)
Memantine	0 (0%)	1 (0.1%)
Acetylcholinesterase inhibitors	1 (1.5%)	4 (0.5%)
Dopaminergic drugs	0 (0%)	12 (1.6%)

p	Statistica test
0.10	U Mann Whitney
0.03	Chi square test
0.7	Chi square test
1	Fisher exact test
1	Fisher exact test
1	Fisher exact test
1	Fisher exact test
0.79	Fisher exact test
1	Fisher exact test
0.47	Fisher exact test
1	Fisher exact test
0.14	U Mann Whitney
0.20	U Mann Whitney
0.51	Chi square test
1	Fisher exact test
1	Fisher exact test
0.76	Fisher exact test
1	Fisher exact test
0.34	Fisher exact test
0.61	Fisher exact test