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Delirium in hospitalized patients with COVID-19 pneumonia: a prospective, cross-sectional, cohort study

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Abstract

Delirium is an acute confusional state characterized by altered level of consciousness and attention. Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), can manifest itself with this neuropsychiatric disorder. The endpoints of our study were: the frequency of delirium in subjects with COVID-19 pneumonia; the risk factors that predispose to this condition; and the impact of delirium on mortality. Subjects were consecutively enrolled in a Geriatric Unit from January 5th to March 5th, 2021. Inclusion criteria were: diagnosis of SARS-CoV-2 infection, a radiologically documented pneumonia, and the ability of providing informed consent. Exclusion criteria were: absence of radiological evidence of pneumonia, sepsis, and the need of intensive care unit treatment. All subjects were evaluated by means of Richmond Agitation Sedation Scale (RASS) and Confusion Assessment Method-Intensive Care Unit (CAM-ICU) at least twice per day. In the study cohort ($n=71$), twenty patients (28.2%) had delirium. Delirium was present on admission in 11.3%, and occurred during hospitalization in 19.0%. Compared to patients without delirium, patients who developed this neuropsychiatric disorder had a higher mortality rate (35% *vs* 5.9%) and an increased average hospital length of stay (21 days *vs* 17 days). In the multivariate analysis delirium was associated with frailty (OR = 2.81; CI = 1.4–5.8) and helmet ventilation (OR = 141.05; CI = 4.3–4663.9). Delirium was an independent predictor of mortality. Nearly a third of subjects (28.2%) had delirium during hospitalization for COVID-19. This finding supports the notion that delirium is a common complication of SARS-CoV2 infection. Since delirium is associated with longer hospital stay, and it is an independent marker of increased mortality, clinicians should assess and prevent it.

Keywords COVID-19 · Delirium · Helmet-CPAP · Frailty · Comfortable care

Introduction

Delirium is an acute confusional state characterized by altered level of consciousness and attention that develops over a short time and fluctuates in severity [1]. Based on motor behavior, delirium can be subdivided into 'hypoactive', 'hyperactive' and 'mixed' subtypes; the worst prognosis is associated with the hypoactive form which is also the most frequent [2]. Neuroinflammation, imbalance in neurotransmitters, and hypoxia are among the main pathophysiological mechanisms involved in the pathogenesis of delirium [3–5].

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a pandemic on March 11, 2020, by the World Health Organization [6]. The most common clinical presentation of COVID-19 is a respiratory and/or gastrointestinal

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syndrome [7]. Atypical presentations have been described as well, including neuropsychiatric symptoms, such as headache, and disturbances of consciousness [8]. Delirium is a common initial manifestation of COVID-19, often without other typical symptoms or signs, as shown by a recent multicenter cohort study conducted in the setting of COVID-19 Emergency Departments [9]. Moreover, delirium is a frequent complication of COVID-19 hospitalization and is associated with a worse prognosis, in terms of severity and mortality, as reported by recent studies [10–12]. At the beginning of the pandemic, delirium in COVID-19 has been mainly studied in intensive care units (ICU) where its prevalence has been estimated to be around 55%; successively, an increasing number of studies assessed COVID-19-related delirium in non-ICU hospitalized patients, reporting a prevalence of 32.4% [13].

The primary objective of this study was to measure the frequency of delirium in older subjects hospitalized for COVID-19 related pneumonia. As a secondary aim, we investigated the clinical, therapeutic and laboratory variables associated with this neuropsychiatric disorder. Finally, we analyzed the impact of delirium on mortality.

Materials and methods

Patients

The study was performed according to a cross-sectional design. Subjects were consecutively enrolled among patients admitted to the Geriatric Unit of the Edoardo Bassini Hospital, Milan, Italy. The enrollment period went from January 5th to March 5th, 2021. Inclusion criteria were: diagnosis of SARS-CoV-2 infection, a radiologically documented pneumonia, and the ability of providing informed consent. Diagnosis of SARS-CoV-2 infection was confirmed after viral detection by reverse transcriptase polymerase chain reaction on nasal or throat swabs [14]. Pneumonia was suspected due to the presence of respiratory symptoms or fever and confirmed by chest CT imaging showing alveolar-interstitial damage with the typical peripheral ground-glass opacities [15] or by chest X-ray showing a multifocal and peripheral pattern, associated with interstitial and alveolar opacities [16]. Exclusion criteria were: absence of CT or X-ray typical lesions suggestive for pneumonia, extreme severity of clinical conditions requiring intubation and intensive care unit treatment, and presence of serum procalcitonin values higher than 10 ng/ml, which were considered highly indicative of septic state. All subjects or caregivers gave written informed consent before enrollment. The study was performed in agreement with the Helsinki declaration, and was approved by the local Ethical Committee Milan Area 3.

Clinical information collected

For each subject, the following clinical data were recorded: sex, age, history of hypertension (systolic blood pressure ≥ 135 mmHg and/or diastolic ≥ 85 mmHg), diabetes (fasting serum glucose > 127 mg/dl), Chronic Obstructive Pulmonary Disease (COPD), cancer, myocardial infarction, chronic kidney disease, dementia, presence of atrial fibrillation (documented by Electrocardiogram, ECG), use of psychoactive drugs prior to hospitalization, use of antiviral therapy, use of dexamethasone, and type of ventilatory support used (non-helmet or helmet ventilation). Patients were assessed for frailty using the clinical frailty scale score (CFS), a validated tool which consists of clinical descriptors and nine pictographs [17]. In our analysis the variable "frailty" was dichotomized, according to a cut-off value of CFS > 5 (CFS ≤ 5 indicates mild frailty, CFS > 5 indicates moderate to severe frailty).

On admission, also laboratory variables were assessed in order to establish their potential role as predictors of delirium. These variables included: P_{aO2}, P_{a02}/F_{iO2} ratio, P_{aCO2}, and venous blood routine exams (hemoglobin, red blood cell count, lymphocyte count, platelet count, D-dimer, C-reactive Protein (CRP), procalcitonin (PCT), creatinine, alanine aminotransferase (ALT) and creatine-phosphokinase (CPK)).

Algorithm used to treat hypoxia and COVID-19

Hypoxia treatment was initially based on the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P_{aO2}/F_{iO2}) on room air, and respiratory rate using a practical algorithm [18]. Patients with oxygen saturation measured by pulse oximetry $< 95\%$ or $P_{a02}/F_{iO2} > 200$ received oxygen through oxygen mask with or without reservoir. Continuous Positive Airway Pressure (CPAP) criteria were $P_{aO2}/F_{iO2} < 200$, $P_{aO2} < 60$ mmHg, and respiratory rate > 30/minute. CPAP, when indicated, was delivered through high-flow generator using a helmet (H-CPAP) as interface with a PEEP valve (StarMed, Italy). CPAP was started at 10 cmH_2O in all patients, and F_{iO2} was set to 40–60% to achieve $P_{aO2} \geq 60$ mmHg. To reduce the noise inside the helmet, generated by the gas flow, a Heat and Moisture Exchanger (HME) filter on the helmet gas inspiratory limb was employed. The counterweights system was used to anchor the helmet during H-CPAP to reduce patient discomfort; patients were put in a semi-supine or sitting position. Patients on H-CPAP who did not show signs of respiratory distress and maintained a $SpO_2 > 94\%$ with a $F_{iO2} < 50\%$ and a PEEP ≤ 5 cmH_2O underwent a weaning trial. Weaning was started when no

desaturation or tachypnea appeared during H-CPAP interruptions for eating, with $P_{a02}/F_{iO2} > 250$. The interruptions were then progressively lengthened and patients maintaining a $P_{a02}/F_{iO2} > 250$ on oxygen mask without reservoir for at least 24 h were considered successfully weaned from H-CPAP. High flow oxygen was not used as a treatment in our protocol.

Patients were eligible for remdesivir if oxygen saturation was 94% or less, while they were breathing ambient air or were receiving supplemental oxygen. Exclusion criteria for antiviral therapy included mechanical ventilation, interval from symptom onset > 9 days, transaminases levels greater than 5 times the upper limit of the normal range, and estimated creatinine clearance < 50 ml/min [19]. Dexamethasone 6 mg once daily IV for up to 10 days was prescribed to those who were receiving either H-CPAP or oxygen alone [20].

Delirium assessment

Delirium was assessed by two physicians of the hospital ward (AC, LC), who visited the subjects at least twice per day, using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU). CAM-ICU is an adaptation of the Confusion Assessment Method (CAM) score for use in ICU [21]. If the CAM-ICU was positive, subjects were further evaluated by a neurologist (AC) using the DSM-V criteria to confirm the diagnosis of delirium [1].The Richmond Agitation Sedation Scale (RASS) was used to classify delirium into hyperactive, hypoactive and mixed subtypes [22].

Regardless of the two daily assessments, subjects were screened at any time in case of development of fluctuation in mental status, altered consciousness, fluctuating attention, or disorganized thinking.

Statistical analysis

In text and tables, numerical variables are presented as median followed by interquartile range (IQR), categorical variables as number (n) followed by percentage (%). The distribution of all the study variables was tested for normality with the Shapiro–Wilk test.

The study population was divided into two subgroups: patients with delirium (DLR +) and patients without delirium (DLR–). In the univariate analysis, all variables were compared between the subgroups DLR + vs DLR–. Due to non-normal distribution, non-parametric tests were adopted: the Mann–Whitney *U*-test was used to compare numerical variables, and the Pearson's chi-square (χ^2) for the categorical variables. The level of significance was set at $p < 0.05$.

Successively, to adjust the effect size for potential confounders, a multivariate analysis was performed, with delirium (condition DLR +) as the dependent variable. Variables used in the univariate analysis were entered into a multivariate logistic regression analysis to determine adjusted odds ratios. The multivariate model was built choosing variables for the significance in the univariate comparison and for clinical relevance [23]. The goodness of fit for the logistic regression model was evaluated with the Hosmer–Lemeshow test and the Nagelkerke R_2.

As further analysis, we evaluated the impact of delirium on mortality, using a logistic regression analysis in which death was the dependent variable, and age, and frailty were assessed as possible confounders.

All statistics were performed by means of the Statistical Package for Social Science (SPSS®) software version 22 (SPSS, Inc., Chicago, IL, USA).

Results

During the study period, 111 subjects were admitted to Geriatric Unit and screened for enrollment (Fig. 1). Forty subjects were excluded because they did not fulfill the inclusion and exclusion criteria; finally, 71 subjects were enrolled, 41 men (57.7%) and 30 women (42.3%); median age was 77 (IQR: 68–82). The main demographic and clinical features of the study population are summarized in Table 1.

Delirium was diagnosed in 20 subjects (28.2%); among these, the 'hypoactive' type was observed in 10 cases (50%), the 'hyperactive' in 4 cases (20%), 6 subjects had 'mixed-type' delirium (30%). Symptoms of delirium were present at hospital admission in 8/71 patients (11.3%); of the remaining 63 patients, 12 developed delirium during hospitalization (19.0%). In patients who developed delirium during hospitalization, delirium occurred after a mean of 3.5 days after hospital admission.

All the numerical variables showed a non-normal distribution, thus univariate comparisons were made with non-parametrical tests. Subjects with delirium were older (DLR +: 81 vs DLR–: 74 years; *U*-test = 723.0, $p = < 0.001$) and showed higher frailty index (DLR +: 6 vs DLR–: 3; *U*-test = 833.0, $p < 0.001$). Significant differences between the two groups were observed in high grade of frailty, defined as CFS > 5, (DLR +: 15/20 vs DLR-: 5/51; $\chi^2 = 30.527$, $p < 0.01$), helmet ventilation (DLR +: 9/20 vs DLR–: 9/51; $\chi^2 = 6.999$, $p = 0.03$), dementia (DLR +: 9/20 vs DLR–: 4/51; $\chi^2 = 12.933$, $p < 0.001$), use of psychoactive drugs (DLR +: 10/20 vs DLR–: 6/51; $\chi^2 = 11.699$, $p = 0.001$), previous stroke (DLR +: 7/20 vs DLR–: 6/51; $\chi^2 = 4.997$, $p = 0.025$), and neoplastic diseases (DLR +: 6/20 vs DLR–: 5/51; $\chi^2 = 4.314$, $p = 0.04$). As concerns the impact of delirium on outcome measures, patients with delirium had longer hospitalization, though not significantly (DLR +: 21 days vs DLR–: 17 days), and showed higher mortality rate (DLR +: 7/20 vs DLR–: 3/51; $\chi^2 = 10.066$,

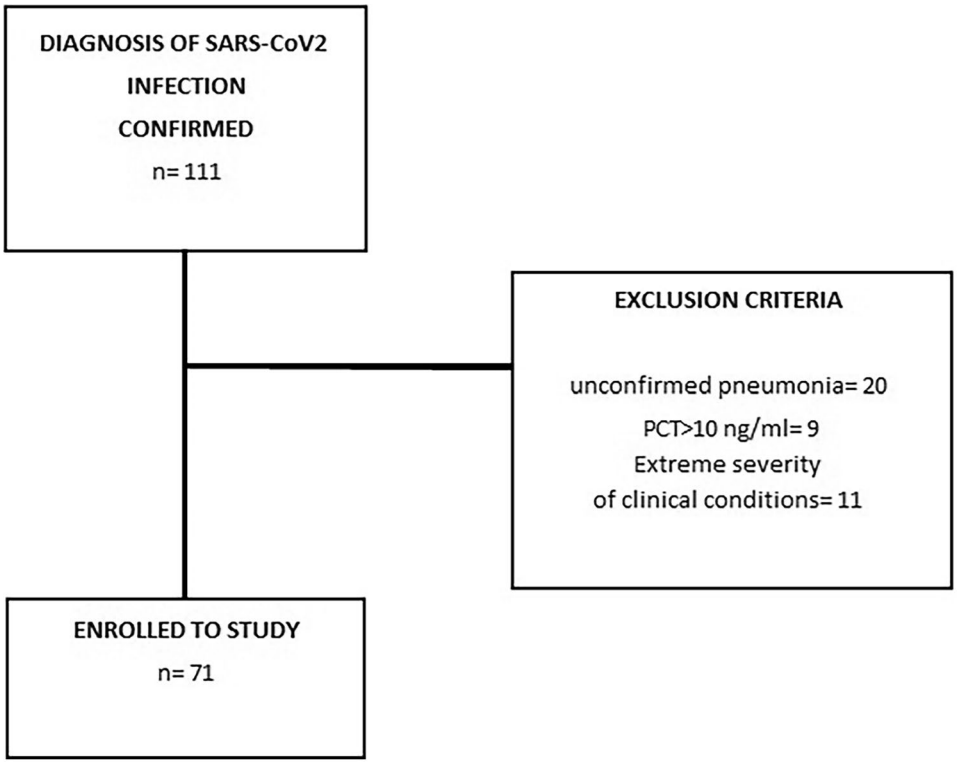

Fig. 1 Flow chart of the study. *PCT* procalcitonin

$p < 0.01$). No significant difference was observed in the other clinical parameters considered. Results of the univariate comparison are shown in Table 1.

In the multivariate analysis, delirium (condition DLR +) was significantly associated with frailty (OR = 2.81; CI = 1.4–5.7), and with helmet ventilation (OR = 141.05; CI = 4.3–4663.9). No variable was significantly associated with the DLR– condition. The Hosmer–Lemeshow test was not significant ($p = 0.939$); Nagelkerke R_2 was 0.782. Detailed results of the multivariate analysis are displayed in Table 2, forest plot is in Fig. 2.

Among the factors associated with outcome in our population, mortality, after correction for frailty and age, was significantly associated with delirium (OR 7.094, CI 1.020–49.384). Results of this multivariate analysis of mortality are shown in Table 3.

Discussion

The primary endpoint of our study was the incidence of delirium in subjects with COVID-19-related pneumonia admitted to a noncritical care unit.

Overall, 20/71 patients (28.2%) had delirium; of these, eight (11.3%) showed delirium upon admission and 12 (19.0%) developed delirium during hospitalization. This finding supports the evidence that delirium is a common complication of SARS-CoV-2 infection. The frequencies of delirium, in our cohort, are slightly lower than those reported in a recent systematic review assessing delirium in COVID-19 patients aged over 65 years (28.2% upon admission and 25.2% during hospitalization) [13]. This discrepancy could be explained by the fact that the majority of our patients were screened for delirium after an average time of 7 days from the COVID-19 symptoms onset. In our cohort, hypoactive delirium was the predominant motor subtype (50%), followed by mixed delirium (30%) and hyperactive delirium (20%). Our findings are in line with previous reports concerning the prevalence of the different motor subtypes of delirium [2].

The secondary endpoint of our study was the identification of factors associated with delirium onset. Delirium is rarely caused by a single factor; rather, it represents a multifactorial syndrome caused by a complex interrelationship between predisposing factors ("baseline admission patient vulnerability") and precipitating factors ("insults") occurring during hospitalization [24]. In our study, predisposing factors associated with delirium occurrence were older age, dementia, use of psychoactive drugs prior to hospital admission, previous stroke, and history of cancer. Delirium was independently associated with frailty. Frailty is a geriatric condition characterized by increased vulnerability for adverse events. Many studies have demonstrated that frailty increases the risk of delirium underscoring the need for early screening of frailty in hospitalized patients [25–27]. The reason for this increased susceptibility is likely related to

Table 1 Demographic, laboratory, and clinical characteristics of the study cohort, and univariate comparison between the DLR + vs DLR– groups

	STUDY COHORT ($n=71$)		DLR + ($n=20$)		DLR- ($n=51$)		p
	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	
Demographics							
Sex		41 (57.7)		11 (55)		30 (58.8)	0.77
Age	77 (68–82)		81 (75–86)		74 (64–82)		**< 0.01**
Frailty	3 (2–5)		6 (5–7)		3 (1–3)		**< 0.01**
Death		10 (14.1)		7 (35)		3 (5.9)	**< 0.01**
Laboratory variables **(n.r)**							
PaO2 (mmHg)	62 (53–73)		61 (53–68)		64 (55–74)		0.44
PaO2/FiO2	281 (196–343)		267 (219–299)		286 (154–343)		0.63
PaCO2 (mmHg)	31 (29–35)		31 (29–36)		32 (29–35)		0.90
D-dimer (µg/l)	765 (517–1437)		1079 (565–1800)		753 (517–1382)		0.47
Hb (g/dl)	14.15 (12.9–15.2)		13.55 (12.4–15.3)		14.25 (13.0–15.0)		0.64
Red cells ($n \times 10^{12}$/l)	4.66 (4.25–5.07)		4.67 (4.31–5.05)		4.66 (4.22–5.00)		0.90
Platelets ($n \times 10^{9}$/l)	221 (152–273)		216.5 (150.3–263.3)		221 (156–292)		0.58
Lymphocytes ($n \times 10^{9}$/l)	0.91 (0.67–1.20)		0.875 (0.60–1.10)		0.92 (0.71–1.00)		0.25
Creatinine (mg/dl)	0.92 (0.80–1.25)		1,04 (0.78–1.35)		0.92 (0.81–1)		0.63
ALT (UI/l)	29 (18–39)		29 (18–42)		28 (19–39)		0.68
CK (UI/l)	105 (63–201)		107 (69–228)		100 (61–198)		0.53
CRP (mg/dl)	6.6 (2.5–13.8)		7.15 (3.1–13.8)		6.46 (2.3–12.0)		0.71
PCT (ng/ml)	0.7 (0.4–1.1)		0.9 (0.7–1.6)		0.6 (0.4–1.0)		0.06
Comorbidities							
Dementia		13 (18.3)		9 (45)		4 (7.8)	**< 0.01**
Previous Stroke		13 (18.3)		7 (35)		6 (11.8)	0.03
COPD		12 (16.9)		3 (15)		9 (17.6)	0.76
CKD		8 (11.3)		4 (20)		4 (7.8)	0.16
Diabetes		21 (29.6)		7 (35)		14 (27.5)	0.60
Myocardial infarction		15 (21.1)		5 (25)		10 (19.6)	0.65
Atrial Fibrillation		14 (19.7)		5 (25)		9 (17.6)	0.51
Hypertension		37 (52.1)		12 (60)		25 (49.0)	0.50
Cancer		11 (15.5)		6 (30)		5 (9.8)	**0.04**
Treatments							
H-CPAP		18 (25.4)		9 (45)		9 (17.6)	**0.03**
Dexamethasone		69 (97.2)		20 (100)		49 (96.1)	0.37
Remdesivir		18 (25.4)		6 (30)		12 (23.5)	0.50
Enoxaparin		59 (83.1)		18 (90)		41 (80.4)	0.19
Psychoactive drugs		16 (22.5)		10 (50)		6 (11.8)	**< 0.01**

ALT aspartate alanine transaminase, *CPK* creatine-kinase, *CRP* C-reactive protein, *PCT* procalcitonin, *AF* atrial fibrillation, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *H-CPAP* helmet-continuous positive airway pressure

the pathophysiological link between frailty and delirium. In 2017 Maldonado introduced the concept of "systems integration failure hypothesis" underlining that inflammation, oxidative stress, neuroendocrine dysregulation and circadian dysregulation were all delirium substrates [28]. All of the cited substrates are also implicated in the pathophysiology of Frailty Syndrome. Our study showed that moderate or severe frailty characterizes the subgroup of patients with higher risk of delirium. Considering that subjects with CFS > 5 are often affected by moderate/severe grade of disability, our study indirectly suggests that also disability may be a predisposing factor for delirium development [29].

Regarding precipitating factors, we found that helmet ventilation was associated with delirium occurrence. The role of helmet ventilation for delirium development was confirmed also after adjustment for potentially confounding factors (Fig. 2; Table 2). Eighteen out of 71 patients required H-CPAP during hospitalization, and nine of them

Table 2 Multivariate logistic regression analysis with delirium as dependent variable

	Dependent variable: Delirium			
	p	OR	CI (lower)	CI (upper)
Age	0.315	1.087	0.923	1.280
Frailty	< 0.01	2.812	1.374	5.755
Dementia	0.847	1.307	0.087	19.679
Psychoactive drugs	0.052	19.538	0.976	391.017
Previous stroke	0.443	2.521	0.238	26.737
Neoplastic diseases	0.708	0.565	0.028	11.286
H-CPAP	0.021	141.056	4.266	4663.959

OR odds ratio, *H-CPAP* helmet-CPAP

Table 3 Multivariate (logistic regression) analysis; dependent variable: Death

	Dependent variable: Death			
		OR	CI (lower)	CI (upper)
Age	0.401	1.030	0.951	1.133
Frailty	0.905	0.973	0.619	1.529
Delirium	0.048	7.094	1.020	49.384

OR odds ratio

(50%) developed delirium. Only in one case, delirium development was prior to helmet application, while in the remaining cases delirium occurred after an average of 1.3 days from H-CPAP application. As mentioned in the methods, H-CPAP was applied in the case of worsening of respiratory exchanges documented by P_{a02}/F_{iO2} and P_{a02} values. It is worth to underline that patients who received H-CPAP suffered from severe hypoxemia [5, 30]. H-CPAP, an alternative way to deliver continuous positive airway pressure without aerosolization in the environment, is an effective treatment of COVID-19 respiratory failure [31]. Compared to facial mask CPAP, the use of a helmet has the advantage of reducing aerosolization and exposure to SARS-CoV-2 [32], occurrence of skin lesions [33] and gastric distension [34]. However, use of the helmet is not free from disadvantages, including noise, armpits pain, and possible claustrophobia. The helmet use is associated with significantly greater noise than nasal or facial masks and long-term exposure to loud noise may increase the subject's discomfort [35]. In addition to these sources of discomfort, it is reasonable to underline that subjects with H-CPAP have extreme limitations of movements and therefore resistance may be encountered when the subject is asked to switch to prone position. Movement limitation is a known precipitating factor for delirium development as shown by recent works addressing that physical restraint and prohibited self-transfer may favor

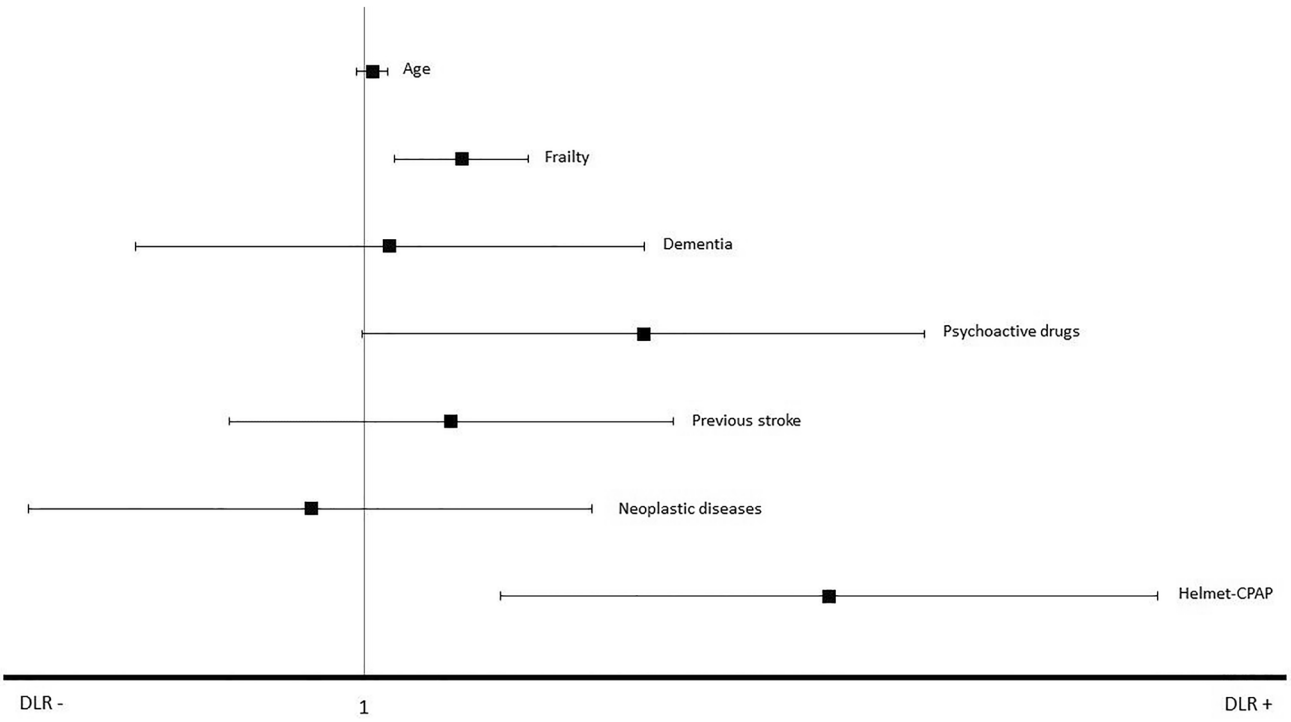

Fig. 2 Results of multivariate logistic regression analysis. Confidence intervals are represented in logarithmic scale. *DLR+* patients with delirium, *DLR–* patients without delirium

delirium occurrence [36–39]. Overall, our study suggests that the patient's discomfort may play a role in favoring the onset of delirium.

Finally, our study confirms the notion that delirium is associated with a worse prognosis also in patients with COVID-19 pneumonia, as demonstrated by increased mortality in the subgroup of patients with delirium.

The current study presents some limitations. The most relevant limits are represented by the relatively low number of cases, and the impossibility of a blinded assessment of delirium. On the other hand, the main strength is the adoption of a prospective enrollment. Indeed, the majority of published studies chose a retrospective design, probably due to the difficulties in collecting data from COVID-19-hospitalized patients, such as protective equipment limitations to effective doctor-patient communication [40], or high level of working stress [41].

To conclude, our study confirms that delirium is a common issue in older and frail patients hospitalized for COVID-19 pneumonia, that it can be triggered by uncomfortable care, and that it is associated with a worse outcome.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval Ethical approval for this study was obtained from the local Ethical Committee Milan Area 3.

Informed consent All participants gave written informed consent before enrollment.

Disclosures All authors report no disclosure.

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