Early Onset Delirium During Hospitalization Increases In-Hospital and Postdischarge Mortality in COVID-19 Patients:

A Multicenter Prospective Study

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Abstract

Objective: Delirium is a common feature in COVID-19 patients. Although its association with in-hospital mortality has previously been reported, data concerning postdischarge mortality and delirium subtypes are scarce. We evaluated the association between delirium and its subtypes and both in-hospital and postdischarge mortality.

Methods: This multicenter longitudinal clinical-based study was conducted in Monza and Brescia, Italy. The study population included 1,324 patients (median age: 68 years) with COVID-19 admitted to 4 acute clinical wards in northern Italy during the first pandemic waves (February 2020 to January 2021). Delirium within 48 hours of hospital admission was assessed through validated scores and/or clinically according to *DSM-5* criteria. The association of delirium—and its subtypes—with in-hospital and postdischarge mortality (over a median observation period of 257 [interquartile range: 189–410] days) was evaluated through Cox proportional hazards models.

Results: The 223 patients (16.8%) presenting delirium had around 2-fold increased in-hospital (hazard ratio [HR] = 1.94; 95% CI, 1.38–2.73) and postdischarge (HR = 2.01; 95% CI, 1.48–2.73) mortality than those without delirium. All delirium subtypes were associated with greater risk of death compared to the absence of delirium, but hypoactive delirium revealed the strongest associations with both in-hospital (HR = 2.03; 95% CI, 1.32–3.13) and postdischarge (HR = 2.22; 95% CI, 1.52–3.26) mortality.

Conclusions: In patients with COVID-19, early onset delirium is associated not only with in-hospital mortality but also with shorter postdischarge survival. This suggests that delirium detection and management are crucial to improving the prognosis of COVID-19 patients.

Trial Registration: ClinicalTrials.gov identifier: NCT04412265.

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Delirium is a neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition that develop over a short period and fluctuate during the day.[1] It usually presents with 3 psychomotor subtypes, namely hyperactive, hypoactive, and mixed,[2] and is more likely to present within the first days of hospitalization.[3–5] Delirium is associated with negative health-related outcomes, including high morbidity, disability, and mortality.[6] As delirium is usually the clinical manifestation of an underlying clinical condition in an individual with predisposing factors (eg, frailty or cognitive impairment), it is not surprising that it is a common clinical feature in individuals with COVID-19 disease, especially the oldest and frailest patients.[7,8]

According to a recent systematic review and meta-analysis[9] including 48 observational studies, almost 1 out of 4 patients with COVID-19 had delirium. This figure peaks at up to 65% when patients in intensive care units are considered.[10] The high occurrence of delirium in older patients with COVID-19 can be explained by a direct invasion of the central nervous system (CNS) by the virus, as well as by specific disease-related factors (eg, fever, hypoxia, inflammation), treatments (eg,

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Clinical Points

- Early onset delirium during hospitalization in COVID-19 patients is frequent across all forms: hyperactive, hypoactive, and mixed.
- Delirium is strongly associated with both in-hospital and postdischarge mortality.
- Hypoactive delirium seems to have the strongest impact on survival, but further studies are needed to confirm this finding.

steroids, noninvasive ventilation), and social factors (eg, isolation).[11,12] Delirium has been associated with a 3 times higher in-hospital mortality rate compared to no delirium.[9,13] Further, delirium has been described as a presenting symptom of this acute disease that is potentially underrecognized, with resulting delayed treatment.[14]

Despite increasing attention from researchers and clinicians to delirium during the COVID-19 pandemic, several questions remain unanswered: Is delirium at hospital admission a risk factor for COVID-19 mortality? Does the association between delirium and mortality change during the hospital stay and postdischarge? Is there a delirium subtype (hypoactive, hyperactive, or mixed) that is associated with shorter survival?

Understanding the clinical characteristics and prognosis of delirium in COVID-19 is currently a clinical and research priority, considering that both COVID-19 and delirium are particularly common in older adults and guidelines are lacking.[15,16]

In this multicenter, longitudinal study, we aimed to investigate the association between early onset delirium and its subtypes at hospital admission and both in-hospital and postdischarge mortality in COVID-19 patients. To reach this aim, we considered data collected in the FRACOVID study, a multicenter prospective study that took place in Lombardy, Italy, the region most burdened by the pandemic,[17] accounting for around 400,000 cases and more than 25,000 deaths for SARS-CoV-2 infection during only the year 2020.[18]

METHODS

Study Design and Population

Data for this study come from the FRACOVID Project, an observational multicenter study, the primary aim of which was to evaluate the impact of frailty on adverse health-related outcomes in middle-aged and older individuals hospitalized for SARS-CoV-2 infection.[19] The study protocol is registered with ClinicalTrials.gov (identifier: NCT04412265). The project involved 2 hospitals in northern Italy, including the acute Geriatric and Infectious Disease wards of the San Gerardo Hospital (Monza, Italy) and the acute Geriatric and Infectious Disease wards of the Spedali Civili (Brescia, Italy).

The study population was composed of consecutive COVID-19 patients hospitalized from February 23, 2020, to January 3, 2021, who met the following inclusion criteria: individuals older than 18 years, with a diagnosis of COVID-19 from a positive SARS-CoV-2 nasopharyngeal swab polymerase chain reaction test, who underwent clinical and instrumental examinations. For this study, from the 1,375 patients initially enrolled in the project, we excluded 51 individuals with no information on delirium at ward admission, obtaining a final analytic sample of 1,324 patients.

The study protocol obtained ethical approval from the Brianza Institutional Review Board (approval code 3356–07/08/2020). All patients, or their proxies (for those unable to give their consent), gave oral consent for participation in the study at ward admission. In the site of Spedali Civili in Montichiari Hospital where patients were admitted during the first wave, data were collected retrospectively. The results of this study are reported following the STROBE Recommendations.

Data Collection

Data collection was performed by trained fellows and researchers using a structured case report form (CRF) and the online Research Electronic Data Capture (REDCap) platform. For each participant, the following information was collected from personal interviews (or phone interviews with patient's proxies) and medical records: sociodemographic characteristics, smoking habits, the onset date of COVID-19 signs/symptoms, functional status, chronic diseases, use of drugs, frailty, and the health status of the patient at ward admission (including vital signs, need for oxygen therapy, and results from biochemical analyses and radiologic examination) and during hospitalization (prescribed therapy, need for transfer to a higher intensity care unit).

For this study, the following chronic conditions were considered: hypertension, heart disease, atrial fibrillation, peripheral vascular disease, heart failure, stroke, diabetes mellitus, depression, osteoarthritis, osteoporosis, chronic obstructive pulmonary disease, chronic kidney failure, liver diseases, thyroid disorders, hearing deficits, vision deficits, Parkinson's disease, peptic ulcer, rheumatologic diseases, anemia, cancer, and dementia. From the sum of the above conditions, we derived the total number of chronic diseases as a measure of multimorbidity. The presence of a diagnosis of dementia was considered a separate covariate due to its high impact on the possible onset of delirium.

Frailty was assessed based on the Frailty Index (FI), considering the ratio between the number of deficits each patient presented and the total number of deficits considered (details can be found in a previous publication[19]). The obtained FI ranges from 0 to 1, with higher values corresponding to increasing frailty.[20] Among the biochemical analyses, we considered serum levels of leukocytes, hemoglobin, platelets, C-reactive

protein (CRP), and creatinine. Concerning the radiologic examinations (chest X-ray or CT scan), we recorded the presence of unilateral or bilateral pneumonia.

Exposure Assessment

For this study, in light of the higher incidence of delirium in the first 2 days of hospitalization,[3–5] we considered early onset delirium, ie, delirium within 24–48 hours after hospital admission. Delirium was assessed through the following methods:

1. Modified Richmond Agitation-Sedation Scale (mRASS), a validated measure of the level of consciousness,[21,22] which has been shown to capture delirium also in patients with cognitive impairment.[23] The scale rating ranges from −5 to +4, with 0 indicating alert and calm conditions, negative scores indicating states of decreasing consciousness, and positive scores indicating states of increasing agitation.
2. 4 A's Test (4AT), a screening tool for delirium that has been validated in older inpatients[24] and has demonstrated high sensitivity and specificity to detect delirium at a cutoff of ≥ 4.[25] The 4AT, however, has also been tested in younger populations of patients who have undergone surgery and proved to be a reliable tool for identifying delirium.[26] The 4AT includes the evaluation of patients' alertness, attention, spatial-temporal orientation, and possible acute change or fluctuating course in alertness, cognition, or other mental functions.
3. Clinical evaluation, using the criteria proposed in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) for the delirium diagnosis.[27]

Delirium diagnosis in this study was defined as at least 1 among the following: mRASS < 0 or > 0, 4AT ≥ 4, or a clinical diagnosis of delirium.

In patients who had available information on the subtype of delirium (n = 1,281) from either the clinical evaluation or the mRASS score, we further classified delirium as hyperactive, hypoactive, or mixed.

Study Outcomes

For this study, we considered as outcome all-cause in-hospital mortality derived from medical records. Moreover, participants' vital status was derived from regional registers until June 2021, reaching a median observation time after the discharge of 257 (interquartile range, 189–410) days.

Statistical Analyses

The characteristics of the total sample and by delirium subtype are reported as mean and standard deviation (SD) or as number and percentage (%) for quantitative and qualitative variables, respectively. Comparisons between patients who developed delirium vs those who did not and between different delirium subtypes were performed using the Student *t* test, analysis of variance, or the χ^2 or Fisher tests, as appropriate.

Survival was estimated and illustrated by the Kaplan-Meier method and compared between individuals who presented with delirium and those who did not using the log-rank test.

The association of delirium with in-hospital and postdischarge mortality was assessed using multivariable Cox regression models, after verifying the proportional hazards assumption. In the first step, we considered delirium (yes vs no) as the main exposure; in the second step, we considered as exposure the different delirium subtypes (hyperactive, hypoactive, mixed or unspecified vs no delirium). Models were adjusted for factors that, according to a scientific and biological rationale, could play a confounding role in the tested association. Covariates included age (both linear and quadratic terms), sex, COVID-19 wave, oxygen requirements and CRP levels at ward admission, number of chronic diseases, and dementia.

For the analysis of in-hospital mortality, the observation time was computed as the time between ward admission and discharge, transfer to another ward/hospital, or death, whichever occurred first. For the analysis of postdischarge mortality, we computed the time from ward admission to death or the follow-up evaluation (June 2021), whichever occurred first. Patients who were not found in the mortality registers (n = 17, 1.3%; of these, 5 had delirium) were censored at hospital discharge.

Since 5 patients had more than 1 ward admission, we considered both hospitalizations for the evaluation of in-hospital mortality. Conversely, for these patients, only the last hospitalization was taken into account for the assessment of postdischarge mortality in order to avoid the overlap in the observation periods after the 2 hospitalizations.

Sensitivity analyses were performed, first, considering delirium detected only using the mRASS and 4AT scales, and, second, adjusting the models for frailty. All analyses were performed using R software (version 3.5.2).[28]

RESULTS

Of the 1,324 study participants, 223 (16.8%) presented delirium at hospital admission. Among them, 67 (30%) had hyperactive, 95 (42.6%) had hypoactive, and 61 (27.4%) had mixed (n = 18) or unspecified delirium subtype (n = 43). The characteristics of the total sample according to the presence or absence of delirium and by subtype are reported in Table 1.

As shown, the mean age of the sample was 66.7 years (SD = 14.6), and 63.6% were men. More than 67% of patients were aged over 60 years, and only 4.1% were younger than 40. Around 10% of the participants had

Table 1.

Characteristics of the Total Sample and by Delirium Type[a]

	Overall	Delirium			Delirium type			
		No	Yes	*P* value[b]	Hyperactive	Hypoactive	Mixed or unspecified	*P* value[c]
n	1,324	1,101	223		67	95	61	
Age, mean (SD), y	66.72 (14.62)	64.63 (14.40)	77.04 (10.89)	<.001	70.96 (13.73)	78.74 (8.88)	81.07 (6.77)	<.001
Age > 60 y	889 (67.1)	685 (62.2)	204 (91.5)	<.001	50 (74.6)	93 (97.9)	61 (100.0)	<.001
Sex, male	842 (63.6)	705 (64.0)	137 (61.4)	.51	43 (64.2)	55 (57.9)	39 (63.9)	.645
Marital status[d]				<.001				.239
Living maritally	768 (74.3)	674 (77.4)	94 (58.0)		27 (62.8)	35 (49.3)	32 (66.7)	
Widowed	155 (15.0)	99 (11.4)	56 (34.6)		13 (30.2)	28 (39.4)	15 (31.2)	
Separated/divorced	21 (2.0)	19 (2.2)	2 (1.2)		0 (0.0)	1 (1.4)	1 (2.1)	
Never married	89 (8.6)	79 (9.1)	10 (6.2)		3 (7.0)	7 (9.9)	0 (0.0)	
Mobility[d]				<.001				.042
Not walking	123 (10.7)	66 (6.9)	57 (30.0)		12 (20.3)	30 (37.5)	15 (29.4)	
Use of walking aids	94 (8.2)	56 (5.8)	38 (20.0)		8 (13.6)	17 (21.2)	13 (25.5)	
Autonomous	935 (81.2)	840 (87.3)	95 (50.0)		39 (66.1)	33 (41.2)	23 (45.1)	
Dementia[d]	129 (9.8)	50 (4.5)	79 (35.4)	<.001	15 (22.4)	39 (41.1)	25 (41.0)	.028
No. of chronic diseases, mean (SD)[e]	2.15 (2.13)	1.89 (1.97)	3.41 (2.46)	<.001	2.42 (1.90)	3.84 (2.80)	3.84 (2.15)	<.001

[a]Values expressed as n (%) unless otherwise noted.
[b]*P* values for the comparison between patients with vs without delirium.
[c]*P* values for the comparison between patients with different delirium subtypes.
[d]Number of participants with missing data: marital status (n = 291), mobility (n = 172), dementia (n = 1).
[e]The count of chronic diseases does not include dementia.

Table 2.

Hospitalization-Related Characteristics of the 1,324 COVID-19 Patients Included in the Study[a]

	Overall	Delirium			Delirium type			
		No	Yes	*P* value[b]	Hyperactive	Hypoactive	Mixed or unspecified	*P* value[c]
n	1,324	1,101	223		67	95	61	
COVID-19 wave				<.001				.007
1	694 (52.4)	607 (55.1)	87 (39.0)		18 (26.9)	36 (37.9)	33 (54.1)	
2	630 (47.6)	494 (44.9)	136 (61.0)		49 (73.1)	59 (62.1)	28 (45.9)	
Oxygen therapy at ward admission				.001				.19
None	349 (26.4)	304 (27.6)	45 (20.2)		16 (23.9)	19 (20.0)	10 (16.4)	
Nasal cannula	342 (25.8)	297 (27.0)	45 (20.2)		17 (25.4)	18 (18.9)	10 (16.4)	
Venturi mask	269 (20.3)	220 (20.0)	49 (22.0)		13 (19.4)	18 (18.9)	18 (29.5)	
Reservoir mask	229 (17.3)	174 (15.8)	55 (24.7)		10 (14.9)	31 (32.6)	14 (23.0)	
CPAP	135 (10.2)	106 (9.6)	29 (13.0)		11 (16.4)	9 (9.5)	9 (14.8)	
Biochemical parameters[d]								
Hemoglobin, g/dL, mean (SD)	12.99 (1.87)	13.06 (1.85)	12.68 (1.94)	.006	12.66 (1.91)	12.64 (1.89)	12.76 (2.08)	.929
WBC, $\times 10^3/\mu L$, mean (SD)	7.34 (7.45)	7.24 (7.96)	7.86 (4.04)	.261	7.08 (3.52)	8.44 (4.68)	7.81 (3.31)	.111
Platelets, $\times 10^3/\mu L$, mean (SD)	223.51 (100.27)	227.29 (101.62)	204.80 (91.21)	.002	209.93 (104.14)	210.70 (93.10)	190.15 (70.88)	.338
CRP, mg/L, mean (SD)	7.66 (7.91)	7.39 (7.99)	9.01 (7.33)	.007	8.22 (6.26)	8.82 (7.73)	10.20 (7.74)	.320
Serum creatinine, mg/dL, mean (SD)	1.13 (0.82)	1.07 (0.77)	1.40 (0.97)	<.001	1.29 (0.88)	1.52 (1.12)	1.35 (0.81)	.311
Radiologic results[d]				.197				.768
No pneumonia	145 (11.1)	123 (11.3)	22 (10.0)		5 (7.5)	12 (12.8)	5 (8.6)	
Unilateral pneumonia	285 (21.8)	246 (22.7)	39 (17.8)		11 (16.4)	18 (19.1)	10 (17.2)	
Bilateral pneumonia	875 (67.0)	717 (66.0)	158 (72.1)		51 (76.1)	64 (68.1)	43 (74.1)	

[a]Values expressed as n (%) unless otherwise noted.
[b]*P* values for the comparison between patients with vs without delirium.
[c]*P* values for the comparison between patients with different delirium types.
[d]Number of participants with missing data: CRP (n = 71), hemoglobin (n = 7), platelets (n = 9), serum creatinine (n = 13), radiologic results (n = 19), WBC (n = 21).
Abbreviations: CPAP = continuous positive airway pressure, CRP = C-reactive protein, WBC = white blood cells.

Figure 1.

Kaplan-Meier Survival Curves for Participants Who Presented and Did Not Present Delirium During the First 48 Hours of Hospitalization

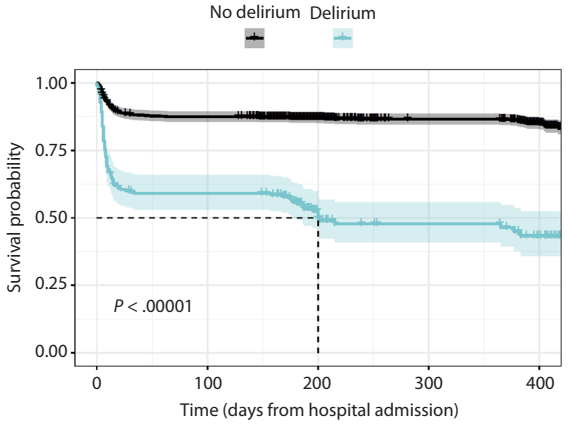

Table 3.

Association Between Delirium and Delirium Type and In-Hospital and Postdischarge Mortality, Hazard Ratio (95% CI)[a]

	In-hospital mortality		Postdischarge mortality	
	Unadjusted model (n = 1,324, events = 228)	Adjusted model[b] (n = 1,094, events = 177)	Unadjusted model (n = 1,319, events = 271)	Adjusted model[b] (n = 1,089, events = 215)
Delirium (yes vs no)	3.61 (2.77–4.72) *P* < .001	1.94 (1.38–2.73) *P* < .001	4.63 (3.63–5.91) *P* < .001	2.01 (1.48–2.73) *P* < .001
Delirium type				
No	ref	ref	ref	ref
Hyperactive	2.53 (1.57–4.10) *P* < .001	1.91 (1.05–3.46) *P* = .03	3.13 (2.05–4.78) *P* < .001	1.98 (1.18–3.32) *P* = .01
Hypoactive	3.44 (2.40–4.94) *P* < .001	2.03 (1.32–3.13) *P* = .001	4.82 (3.48–6.67) *P* < .001	2.22 (1.52–3.26) *P* < .001
Mixed or unspecified	5.10 (3.50–7.44) *P* < .001	1.84 (1.14–2.98) *P* = .01	6.31 (4.42–9.00) *P* < .001	1.78 (1.15–2.75) *P* = .01

[a]Estimates are derived from Cox proportional hazards models. In the adjusted models, 230 observations were excluded from the total sample due to missing data. In the unadjusted model for postdischarge mortality, we considered only the last hospitalization for the 5 participants who had more than 1 ward admission over the observation period.

[b]Model adjusted for age (linear and quadratic terms), sex, dementia, number of chronic diseases, prehospitalization mobility level, COVID-19 wave, and need of oxygen therapy and C-reactive protein at ward admission.

Abbreviation: ref = reference.

a low mobility level and suffered from dementia, and the mean number of chronic diseases was 2.15 (SD = 2.13). Patients who presented delirium were more likely to be older, to be widowed, to have worse mobility and cognitive functions, and to have a higher number of chronic diseases than those without delirium. The most prevalent chronic conditions in our sample, especially in patients who developed delirium, were cardiovascular diseases and diabetes mellitus (Supplementary Table 1). Comparing individuals by delirium subtype, we found that those with hyperactive delirium were more frequently younger and healthier (in terms of mobility, dementia prevalence, and number of chronic diseases) than patients with hypoactive or mixed/unspecified delirium.

Concerning the COVID-19 related characteristics at ward admission (Table 2), patients who developed delirium were more likely to need low- or high-flow oxygen therapy and to present with lower hemoglobin and platelet values and higher CRP and creatinine levels. No substantial differences were found when comparing patients by delirium subtype.

In the study sample, 228 patients (17.2%) died during hospitalization (12.4% of those without delirium and 40.8% of those with delirium). Considering mortality both in-hospital and during the postdischarge period, we observed that out of the 1,319 individuals (after the exclusion of 5 patients who had 2 hospitalizations for COVID-19 during the observation period), 271 (20.6%) died over a median follow-up of 261 days (first–third quartile: 189–410). Of these events, 160 (14.6%) occurred in patients who did not present delirium, and 111 (49.8%) occurred in the delirium group. The estimated 1-year survival for individuals who did not have delirium was 86.4% (95% CI, 84.3%–88.5%), and it was 46.4% (95% CI, 39.3%–54.8%) in those with delirium. As illustrated in the Kaplan-Meier curve for both groups (Figure 1), patients with delirium maintained a lower survival probability than those free from delirium over the entire observation period.

By Cox multivariable regression analysis (Table 3), after adjusting for potential confounders, the occurrence of delirium during the first 48 hours of hospitalization was associated with an approximately 2-fold increase in the risk of in-hospital (HR = 1.94; 95% CI, 1.38–2.73) and postdischarge (HR = 2.01; 95% CI, 1.48–2.73) mortality.

All delirium subtypes appeared to be associated with higher in-hospital and postdischarge mortality, compared with patients who did not present delirium (Supplementary Figure 1). The hypoactive subtype presented the highest hazard for in-hospital (HR = 2.03; 95% CI, 1.32–3.13) and postdischarge (HR = 2.22; 95% CI, 1.52–3.26) mortality. Results were confirmed also after considering delirium detected only by validated scales (Supplementary Table 2) and when adjusting for frailty (Supplementary Table 3).

DISCUSSION

In this longitudinal multicenter study including more than 1,000 patients with COVID-19, we found that individuals who experienced delirium within 48 hours of ward admission had shorter in-hospital and postdischarge survival than those without delirium. All delirium subtypes (ie, hyperactive, hypoactive, and mixed) were associated with mortality, especially the hypoactive form.

While the association between delirium and mortality in COVID-19 patients has previously been acknowledged,[29] no studies have addressed in-hospital and postdischarge mortality with respect to delirium subtypes in COVID-19. Delirium is a common clinical presentation of COVID-19: recent studies have reported that up to 10%–30% of COVID-19 patients presented with or developed delirium during their hospitalization.[8,9,30] Our results are in line with these figures, since we observed that 17% of individuals with COVID-19 suffered from delirium at ward admission. Delirium is a sign of disease severity and/or greater underlying frailty, and it has thus been associated with longer hospitalization, lower functional status, poorer cognitive performance and a higher risk of nursing home admission.[9,31–33] Concerning mortality, despite some contrasting results,[34] most of the available findings point toward an association, and a recent meta-analysis including patients with COVID-19 reported that delirium was associated with a 3-fold increase in mortality.[9]

Notably, previous studies mainly focused on short-term and/or in-hospital mortality, while evidence concerning delirium and postdischarge mortality is extremely scarce.[34,35] One recent study has shown a 4-fold increase (OR = 4.54; 95% CI, 3.25–6.38) in the risk of death at 30 days after discharge in patients who had delirium during COVID-19, compared with those without delirium.[34] According to our findings, delirium seemed to be an independent risk factor for mortality not only during the hospitalization but also over the 6 to 7 months after discharge. The association between delirium and postdischarge mortality is of paramount importance since it poses some interesting clinical hypotheses. First, delirium itself may have negative consequences, even when both delirium and COVID-19 have been successfully treated, as has been shown in previous non-COVID samples.[33] Second, early delirium during COVID-19 may be a marker of disease severity. It has been suggested that delirium may be due to the direct invasion of the CNS by SARS-CoV-2, hypercoagulability, and the cytokine storm, all features related to disease severity and associated with long-term adverse outcomes.[11,12,36,37] Of note, slightly higher inflammation and oxygen requirements were observed in our patients who presented delirium compared with their delirium-free counterparts. Third, the observed excess mortality in patients with delirium may reflect a subgroup of frail patients; frailty has been independently associated with increased mortality in both COVID-19[19,38–40] and non–COVID-19 patients, and it is a well-known risk factor for delirium.[41,42] Further, frailty is an independent risk factor for medium-term mortality especially in older persons.[42] In our sample, patients with delirium were more likely to present with multimorbidity, suggesting that they may be characterized by a certain vulnerability with respect to the consequences of COVID-19 in the longer term. The observation that hypoactive delirium was the subtype most strongly associated with mortality indirectly supports this hypothesis, given that hypoactive and mixed delirium seem to be more common in sick and frail patients.[43,44] This suggests that when evaluating adverse outcomes in COVID-19, it may be less relevant to untangle the effect of delirium/frailty/multimorbidity, whereas it could be very important to assess all these conditions. Despite these considerations, the fact that the association between delirium and mortality was still significant after adjusting for parameters such as CRP, oxygen requirements, the number of chronic diseases and frailty suggests the involvement of other aspects in explaining the relationship. For instance, the occurrence of delirium at hospital admission may influence the choice of treatments, especially those that require a certain degree of cooperation from the patient. These additional factors may also have long-term consequences.

A great novelty of this study is the focus on delirium subtypes, whose frequency was in line with previous findings.[29,45] Interestingly, we observed that all delirium subtypes were associated with increased mortality, with the hypoactive form carrying the highest hazard for both in-hospital and postdischarge mortality. This is congruent with previous literature that identified the hypoactive subtype of delirium as the form most frequently associated with negative health-related outcomes, including institutionalization, physical and cognitive decline, and in-hospital and postdischarge mortality.[32,46,47] Notably, hypoactive delirium is often underdetected leading to delays in hospitalization and treatment of underlying conditions.[48] This observation once again underscores the need to increase awareness among clinicians and health care providers regarding delirium, especially the hypoactive and mixed subtypes, with a view to prompting early identification and management.

Besides the neurotropism of the virus, several external factors can be responsible for the impact of COVID-19 on neurologic health and cognitive deterioration. Among others, the presence of fever, frequently accompanied by hypoxia especially in older patients with multiple chronic diseases (eg, obesity, chronic pulmonary disease), is related to the onset of delirium. In addition, some treatments like steroids, prolonged mechanical ventilation, and deep sedation may impact cognitive function and increase the probability of suffering from delirium in predisposed individuals.[49,50] Finally, social isolation may also play a major role, and in vulnerable groups, such as older people, can be a crucial trigger of

acute clinical deterioration and delirium occurrence. Overall, whether COVID-19 could determine long-term cognitive and neuropsychiatric sequelae is still a matter of investigation. However, some recent studies suggest that COVID-19 may have some direct and indirect effects on cognitive performance in the long run, especially on attention, memory, and executive function domains.[51]

To the best of our knowledge, this is the first prospective study assessing in-hospital and postdischarge mortality in COVID-19 patients presenting with delirium and investigating the role of different delirium subtypes in this association. These findings are derived from a large, multicenter, well-characterized clinical cohort. Of note, delirium was comprehensively defined using 2 scales and clinical assessment.

Some limitations must be mentioned. First of all, some data have been collected retrospectively, thus limiting the quality of the data themselves or making it more likely that some clinically relevant data (eg, the educational level of the study participants) are incomplete. However, it should be mentioned that this study refers to the most burdensome periods of the COVID-19 pandemic, when health care providers experienced an exceptional overload of patients and scarcity of medical resources. Secondly, despite the detailed assessment of delirium (through either a clinical evaluation or validated scales), some cases may have been missed, especially the hypoactive subtypes, which were more difficult to detect, especially in critical patients under ventilatory support. However, this might have led to an underestimation of the results concerning the hypoactive and mixed delirium subtypes. Moreover, we considered delirium only within the first 48 hours of hospitalization. Therefore, further investigations should evaluate the impact of delirium arising later during the hospital stay on health-related outcomes. An additional limitation is that the FRACOVID project considered only the hospital setting, so we expect that the prevalence of delirium and its association with mortality could be more marked in other contexts, eg, nursing homes, where there is a higher proportion of frail individuals.[45,52,53] Finally, our data were collected during the first pandemic waves, when the severity of COVID-19 was greater than that caused by the latest variants. Therefore, our results may not be generalizable to all SARS-CoV-2 variants. However, we believe that COVID-19 may represent a prototype of severe infectious disease, and our findings suggest that early onset delirium may be a prognostic factor of this kind of condition.

In conclusion, COVID-19 patients with delirium within the first 48 hours from ward admission experience shorter in-hospital and postdischarge survival, and this association was observed for all delirium subtypes, especially the hypoactive form.

These findings suggest that delirium is an important prognostic factor in COVID-19, either because it represents a marker of disease severity or because of underlying frailty of patients, or both. All clinical professionals caring for patients with COVID-19 should screen their patients for delirium with a view to prompt detection, monitoring, and management of this severe condition, with the final aim of improving the clinical prognosis of COVID-19 patients.

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Supplementary Material

Article Title: Early Onset Delirium During Hospitalization Increases In-Hospital and Postdischarge Mortality in COVID-19 Patients: A Multicenter Prospective Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

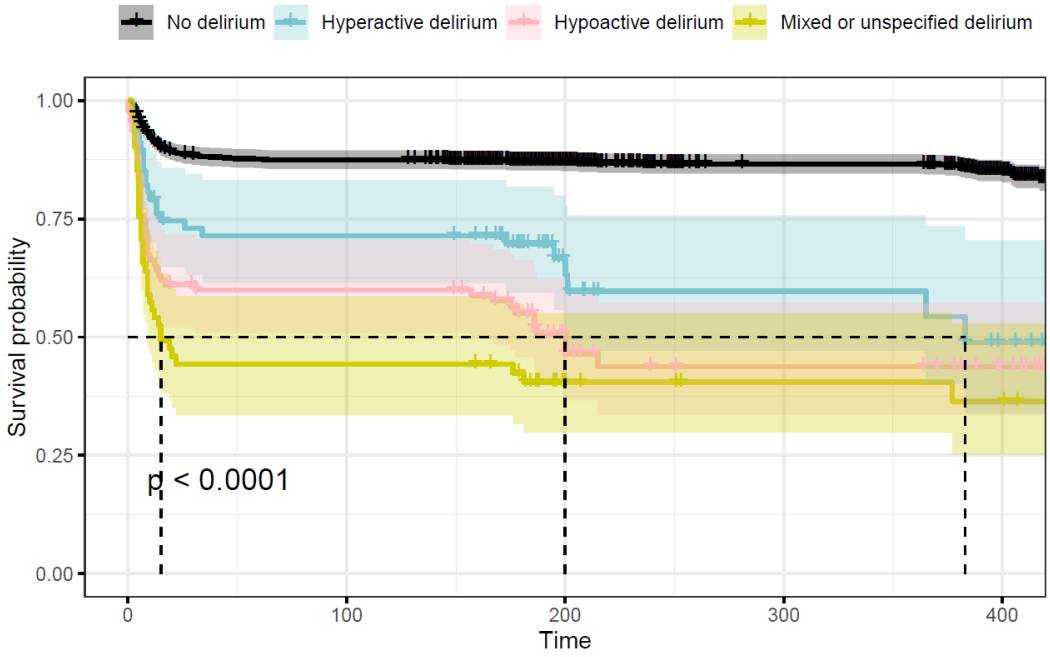
SUPPLEMENTARY MATERIAL

Supplementary Table 1. Prevalence of chronic diseases in the total sample and by delirium

		Delirium			Delirium type			
	Overall	**No**	**Yes**	**p-value[a]**	**Hyperactive**	**Hypoactive**	**Mixed or unspecified**	**p-value[b]**
n	1324	1101	223		67	95	61	
Hypertension	696 (52.6)	542 (49.3)	154 (69.1)	<0.001	32 (47.8)	74 (77.9)	48 (78.7)	<0.001
Heart disease	318 (24.1)	229 (20.8)	89 (40.1)	<0.001	17 (25.8)	42 (44.2)	30 (49.2)	0.015
Atrial fibrillation	119 (9.0)	80 (7.3)	39 (17.6)	<0.001	7 (10.6)	19 (20.0)	13 (21.3)	0.203
Peripheral vasculopathy	127 (9.6)	77 (7.0)	50 (22.6)	<0.001	6 (9.1)	28 (29.8)	16 (26.2)	0.006
Heart failure	53 (4.0)	30 (2.7)	23 (10.4)	<0.001	3 (4.5)	12 (12.6)	8 (13.1)	0.18
Stroke	68 (5.1)	43 (3.9)	25 (11.3)	<0.001	3 (4.5)	12 (12.6)	10 (16.4)	0.092
Diabetes mellitus	281 (21.2)	216 (19.6)	65 (29.3)	0.002	17 (25.8)	26 (27.4)	22 (36.1)	0.383
Depression	68 (5.2)	45 (4.1)	23 (10.6)	<0.001	2 (3.3)	14 (14.7)	7 (11.7)	0.074
Osteoarthritis	109 (8.3)	79 (7.2)	30 (13.8)	0.002	6 (9.5)	13 (14.0)	11 (18.0)	0.389
Osteoporosis	65 (5.0)	45 (4.1)	20 (9.2)	0.003	4 (6.3)	12 (12.9)	4 (6.6)	0.266
COPD	142 (10.7)	111 (10.1)	31 (14.0)	0.113	11 (16.7)	13 (13.7)	7 (11.5)	0.697
Chronic kidney failure	112 (8.5)	70 (6.4)	42 (19.0)	<0.001	8 (12.1)	21 (22.3)	13 (21.3)	0.232
Liver diseases	71 (5.4)	61 (5.5)	10 (4.5)	0.644	3 (4.5)	5 (5.3)	2 (3.3)	0.843
Thyroid disorders	111 (8.4)	91 (8.3)	20 (9.0)	0.817	6 (9.1)	9 (9.5)	5 (8.2)	0.963
Hearing deficits	82 (6.2)	52 (4.7)	30 (13.6)	<0.001	6 (9.2)	19 (20.2)	5 (8.2)	0.048
Vision deficits	68 (5.2)	48 (4.4)	20 (9.3)	0.006	4 (6.2)	11 (11.7)	5 (8.8)	0.489
Parkinson disease	26 (2.0)	14 (1.3)	12 (5.4)	<0.001	3 (4.5)	5 (5.3)	4 (6.6)	0.879
Peptic ulcer	25 (1.9)	16 (1.5)	9 (4.1)	0.02	5 (7.7)	2 (2.1)	2 (3.3)	0.2
Rheumatologic disease	54 (4.1)	48 (4.4)	6 (2.7)	0.34	5 (7.6)	1 (1.1)	0 (0.0)	0.013
Anemia	70 (5.3)	44 (4.0)	26 (11.7)	<0.001	4 (6.1)	13 (13.7)	9 (14.8)	0.23
Cancer	172 (13.0)	137 (12.4)	35 (15.8)	0.217	9 (13.6)	13 (13.7)	13 (21.3)	0.378

[a]p-values for the comparison between patients with vs. without delirium; [b]p-values for the comparison between patients with different delirium type. *Abbreviations*: COPD, chronic obstructive pulmonary disease.

Supplementary Figure 1. Kaplan-Meier survival curves for participants by type of delirium



Notes. Time is expressed in days from hospital admission.

Supplementary Table 2. Considering delirium assessed only through the mRASS or 4AT scales

	Hazard Ratios (95% Confidence Interval) [a] **p-values**	
	In-hospital mortality (n=922, events=136)	**Post-discharge mortality (n=917, events=169)**
Delirium (yes vs no)	1.86 (1.25-2.76) p=0.002	1.88 (1.33-2.65) p<0.001

[a]Model is adjusted for: age (linear and quadratic terms), sex, dementia, number of chronic diseases, pre-hospitalization mobility level, Covid-19 wave, and need for oxygen therapy and C-Reactive Protein at ward admission.

Supplementary Table 3. Association between delirium and mortality after adjusting for frailty

	Hazard Ratios (95% Confidence Interval)[a] p-values	
	In-hospital mortality (n=1324, events=228)	**Post-discharge mortality (n=1319, events=271)**
Delirium (yes vs no)	1.90 (1.42-2.54) p<0.001	2.02 (1.55-2.65) p<0.001
Delirium type		
No	[ref]	[ref]
Hyperactive	1.87 (1.14-3.06) p=0.01	2.09 (1.35-3.23) p<0.001
Hypoactive	1.79 (1.22-2.63) p=0.003	1.92 (1.36-2.72) p<0.001
Mixed or unspecified	2.04 (1.38-3.02) p<0.001	2.12 (1.46-3.07) p<0.001

[a]Model adjusted for: age (both linear and quadratic terms), sex, COVID-19 wave, and frailty index.