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Research Article

Delirium in Older Patients With COVID-19: Prevalence, Risk Factors, and Clinical Relevance

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Abstract

Background: Delirium prevalence increases with age and is associated with poor outcomes. We aimed to investigate the prevalence and risk factors for delirium in older patients hospitalized with COVID-19, as well as its association with length of stay and mortality.
Method: This was a retrospective study of patients aged 65 years and older hospitalized with COVID-19. Data were collected from computerized medical records and all patients had delirium assessment at admission. Risk factors for delirium as well as the outcomes mentioned above were studied by 2-group comparison, logistic regression, and Cox proportional hazard models.
Results: Of a total of 235 Caucasian patients, 48 (20.4%) presented with delirium, which was hypoactive in 41.6% of cases, and hyperactive and mixed in 35.4% and 23.0%, respectively. Patients with cognitive impairment had a nearly 4 times higher risk of developing delirium compared to patients who were cognitively normal before SARS-CoV-2 infection (odds ratio 3.7; 95% CI: 1.7–7.9, $p = .001$). The presence of delirium did not modify the time from symptoms' onset to hospitalization or the length of stay in acute care, but it was associated with an increased risk of dying (hazard ratio 2.1; 95% CI: 1.2–3.7, $p = .0113$).
Conclusion: Delirium was a prevalent condition in older people admitted with COVID-19 and preexisting cognitive impairment was its main risk factor. Delirium was associated with higher in-hospital mortality. These results highlight the importance of early recognition of delirium especially when premorbid cognitive comorbidities are present.

Keywords: COVID-19, Delirium, Dementia, Mild cognitive impairment, Mortality

Since the influenza pandemic in 1918, the world did not experience another scenario of similar magnitude as during the current COVID-19 pandemic. However, the increased life expectancy and longevity observed in the last century changed the scope of at-risk populations, adding the importance of studies regarding old people (1,2). At present, they have been considered as a vulnerable group with an increased risk of SARS-CoV-2 infection (3) and worse outcomes (4–6). Moreover, male sex and functional status were identified as significant indicators of worse prognosis by many recent studies in older populations (7).

Delirium occurrence increases with aging, affecting at least 20% of older patients hospitalized in acute care (8). It results from the interaction between predisposing factors that increases vulnerability and precipitating factors related to acute illnesses (9). Furthermore, delirium is associated with increased length of stay, rehospitalization, and death (10,11). Risk factors of delirium in advanced age are multiple including cognitive impairment, comorbidity burden, and severity of the acute illness, as well as social isolation, sensorial deficits, and depression (12–14).

We hypothesize that older patients with COVID-19 and delirium have different characteristics than those without delirium. Therefore, this study investigated the risk factors of delirium in older patients hospitalized with COVID-19, as well as its association with in-hospital mortality and length of stay in acute care.

Method

Design, Setting, and Study Population

This retrospective study included all patients aged 65 years and older, hospitalized in acute geriatric wards with COVID-19. Geneva University Hospitals served as the referral center for all acutely ill COVID-19 patients requiring medical inpatient care during the SARS-CoV-2 pandemic in the Geneva region, which has about five hundred thousand inhabitants. Only older patients ineligible to intensive care units according to goals of care determinations were oriented to acute geriatric wards. These wards are managed by medical staff trained in internal medicine and geriatrics and are equipped to provide general acute medical care, such as intravenous treatments and noninvasive oxygen support (nasal cannula and face mask, allowing an increase of the fraction of inspired oxygen from 24% to 65%). Discharge from acute care was decided according to clinical improvement with subsequent transfer to rehabilitation wards or discharge at home directly. For patients presenting a worsening of symptoms and evolution, end-of-life care was implemented in these acute geriatric wards. There was no transfer to intensive care wards in this study population.

A total of 235 patients were admitted from March 13th to April 14th, 2020, all of them included in the study. The diagnosis of COVID-19 was defined by a positive polymerase chain reaction test for the SARS-CoV-2 on nasopharyngeal swabs (N = 218/235; 92.8%). Patients with negative virus detection in the RT-PCR test, but with a high clinical suspicion (15) defined as the presence of suggestive clinical symptoms and consistent radiological features (chest radiograph with interstitial infiltrate: uni- or bilateral, peripheral, or central associated or not with airspace consolidations; or computed tomography showing ground-glass opacities and/or crazy paving), were also diagnosed with COVID-19 (N = 17/235; 7.2%).

Because of the urgent need to develop knowledge regarding COVID-19, patients and members of the public were not directly involved in the study conception. An Institutional Board in the University Hospitals of Geneva was created to validate and coordinate all COVID-19-related research protocols. Also, this project was accepted by Geneva's state ethical committee (Project-Id: 2020-00819).

Data Collection

Delirium was systematically screened at hospital admission by the interdisciplinary team using the Confusion Assessment Method (CAM) (16) and then further evaluated by the medical staff according to the established diagnosis criteria in the DSM-5 (17) and classified as hyperactive, hypoactive, or mixed. In this study, we report delirium presented at hospital admission or developed in the first 24 hours of hospitalization in acute wards. Cognitive diagnosis for each patients was documented by an exhaustive review of medical records, considering previous reports from the memory clinic, as well as neuroimaging features and documented medical assessment performed before hospitalization. All patients had their cognitive status categorized as cognitively normal, mild cognitive impairment, or dementia. Specifically, no suspicion of dementia during the acute phase was considered in the analysis. Etiologies included Alzheimer's disease, vascular dementia, and dementia with Lewy bodies. Clinical data from all included patients were retrospectively collected from the computerized medical records by the same research nurse. For each included patient, collected data were categorized according to the following domains: demographics, clinical history, clinical status, vital signs, comorbidities, routine laboratory analysis, and chest imaging. Acute stroke was defined as stroke occurring during the hospitalization in acute units with neuroimaging confirmation. Acute respiratory distress syndrome (ARDS) was defined as the presence of respiratory failure symptoms, with compatible chest X-ray findings and moderate-to-severe hypoxemia (18).

Additionally, we included elements from the comprehensive geriatric assessment performed at hospital admission such as the comorbidity burden evaluation according to the CIRS (Cumulative Illness Rating Scale) (19), and functional status by the Functional Independence Measure (FIM) (20) and frailty by the Clinical Frailty Scale (CFS) (21). The FIM was performed within the first 24 hours of hospitalization by the referent nurse in charge of the patient. It varies from 18 to 126 points, higher scores corresponding to better functional status (22). The CFS is a 9-point scale based on clinical judgment and performed by the physician, validated to predict death or need for institutional care. It varies from 1 "Very fit" to 9 "Terminally ill" (21). In-hospital mortality was defined as death occurring within hospitalization, while the length of stay refers to the number of days of hospitalization in acute care wards.

Statistical Analysis

Continuous variables were presented as means ± SD and categorical variables as absolute numbers and proportions. We computed 2-group comparisons between patients with and without delirium by Mann–Whitney–Wilcoxon rank-sum u test or chi-squared test, according to the variable type.

To investigate delirium risk factors, we performed logistic regression models to test the association between independent variables with a significant difference in the comparison of patients with and without delirium and the dependent one (delirium). Statistical significance was defined at a level of 95%, with p-values <.05. Cox proportional hazard models were used to assess the risk of dying according to delirium status. Finally, we tested for potential multicollinearity among the FIM score, CFS, and cognitive impairment using the variance inflation factor (VIF) as an indicator (23). Data analyses were performed with Stata, version 16.1 software (StataCorp 2019).

Results

Characteristics of Patients and the Prevalence of Delirium

A total of 235 Caucasian patients were admitted to acute care units during the period of the study. Forty-eight (20.4%) patients presented delirium on admission, which was hypoactive in 41.6% of cases, and hyperactive and mixed in 35.4% and 23.0% of cases, respectively. The mean age of the study population was 86.3 ± 6.5 years, 56.6% were women, with a length of stay of 12.8 ± 7.6 days in acute care. Cognitive impairment was present in 50.6% of cases, the majority of those in the dementia stage (97/235; 41.3%). A detailed description of the etiologies of cognitive impairment and their distribution in patients with and without delirium is available in the Supplementary Material. The other prevalent comorbidities were hypertension (168/235; 71.5%), dyslipidemia (84/235; 35.7%), heart failure (86/235; 37.9%), and diabetes (54/235; 23.0%). Frailty was diagnosed in 80.9% of patients, corroborated by an overall low functional status according to the FIM (72.0 ± 29.4) (Table 1).

Risk Factors for Delirium

The risk of delirium at hospital admission was more than 4 times higher in patients with cognitive impairment (odds ratio [OR] 4.3;

Table 1. Comparison Between Patients With and Without Delirium

	Delirium			
	Total	No	Yes	
Characteristics	*N* = 235	*N* = 187	*N* = 48	*p* Value
Age	86.3 ± 6.5	86.1 ± 6.7	86.9 ± 5.6	.408
Female sex	133 (56.6%)	109 (58.3%)	24 (50.0%)	.330
Previous hospitalization	103 (44.2%)	87 (47.0%)	16 (33.3%)	.104
Lives alone	102 (55.1%)	88 (57.5%)	14 (43.8%)	.138
Formal help	114 (48.5%)	94 (50.3%)	20 (41.7%)	.333
Place of living				.175
Home	172 (74.1%)	141 (76.6%)	31 (64.6%)	
Nursing home	49 (21.1%)	33 (17.9%)	16 (33.3%)	
Enriched home	11 (4.7%)	10 (5.4%)	1 (2.1%)	
Delay from first symptoms and hospitalization	4.4 ± 5.1	4.4 ± 4.7	4.7 ± 6.4	.722
N. medication	7.5 ± 4.1	7.6 ± 4.2	6.8 ± 3.6	.156
Cognitive impairment	119 (50.6%)	82 (43.8%)	37 (77.1%)	**<.001**
MCI	22 (9.4%)	16 (8.6%)	6 (12.5%)	.409
Dementia	97 (41.3%)	66 (35.3%)	31 (64.6%)	**<.001**
Heart failure	86 (37.9%)	75 (41.7%)	11 (23.4%)	**.028**
Diabetes	54 (23.0%)	45 (24.1%)	9 (18.8%)	.564
Stroke	46 (19.8%)	33 (17.8%)	13 (27.7%)	.152
Swallowing disorders	23 (9.8%)	15 (8.1%)	8 (16.7%)	.099
Coronary syndrome	34 (14.5%)	28 (15.0%)	6 (12.5%)	.819
Atrial fibrillation	58 (24.7%)	51 (27.3%)	7 (14.6%)	.090
Hypertension	168 (71.5%)	137 (73.3%)	31 (64.6%)	.282
Dyslipidemia	84 (35.7%)	65 (34.8%)	19 (39.6%)	.613
BMI	24.7 ± 6.3	24.7 ± 6.7	24.8 ± 4.8	.244
Cough	144 (61.3%)	114 (61.0%)	30 (62.5%)	.870
Tiredness	104 (44.3%)	87 (46.5%)	17 (35.4%)	.194
Dyspnea	10 (4.3%)	9 (4.8%)	1 (2.2%)	.613
Abdominal pain	17 (7.3%)	15 (8.1%)	2 (4.2%)	.535
Diarrhea	28 (11.9%)	22 (11.8%)	6 (12.5%)	.808
Falls	26 (11.1%)	18 (9.6%)	8 (16.7%)	.196
CIRS	17.1 ± 5.8	17.3 ± 5.9	16.4 ± 5.4	.307
FIM	72.0 ± 29.4	74.5 ± 29.0	62.4 ± 29.2	.027
CFS	5.8 ± 1.6	5.7 ± 1.7	6.4 ± 1.1	**.001**
CFS ≥ 5	190 (80.9%)	143 (76.5%)	47 (97.7%)	**<.001**
Lymphocytes, g/L	2.5 ± 4.5	2.8 ± 5.0	1.3 ± 1.8	**.002**
CRP, mg/L	66.3 ± 69.9	62.2 ± 66.7	81.6 ± 80.0	.129
PaO_2, kPa	9.6 ± 5.9	9.8 ± 6.4	9.0 ± 3.5	.355
eGFR, mL/min/1.73m^2	55.6 ± 21.6	54.5 ± 22.1	60.1 ± 19.1	.086
Infiltrate on chest radiograph	131 (58.2%)	110 (61.5%)	21 (45.7%)	.065
FiO_2	26.3 ± 9.5	25.9 ± 8.6	27.9 ± 12.1	.298
Temp	38.1 ± 0.8	38.1 ± 0.8	38.2 ± 0.8	.485
HR	93.1 ± 17.1	92.7 ± 17.6	94.6 ± 15.4	.464
RR	26.2 ± 8.9	25.6 ± 7.4	28.1 ± 13.1	.208
ARDS	74 (31.76%)	60 (32.43%)	14 (29.17%)	.730
Ischemic stroke	5 (2.2%)	3 (1.6%)	2 (4.2%)	.276
Hemorrhagic stroke	1 (0.43%)	0	1 (2.08%)	.207

Note: ARDS = acute respiratory distress syndrome; BMI = body mass index; CFS = Clinical Frailty Score; CIRS = Cumulative Illness Rating Scale; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; FIM = Functional Independence Measure; FiO_2 = fraction of inspired oxygen; HR = heart rate; MCI = mild cognitive impairment; RR = respiratory rate. Data are expressed as *n* (%) or mean ± *SD*.

95% CI: 2.1–8.9, $p < .001$). Similarly, each higher level on the frailty scale from 0 to 8 increased by 35% the risk of having delirium (OR 1.3; 95% CI: 1.1–1.7, $p = .004$), while better functionality was protective against delirium as each additional point in the FIM scale (range 0–126) lowered the risk of delirium by 2% (OR 0.9; 95% CI: 0.97–0.99, $p = .029$) (Table 2).

Additionally, in order to test for multicollinearity among FIM, CFS, and cognitive impairment, we computed VIF in our model and obtained a value of 1.42, which is acceptable as a statistical indicator against multicollinearity.

Delirium, In-Hospital Mortality, and Length of Stay

Seventy-six patients died during hospitalization (76/235; 32.3%), 20 patients with delirium (20/48; 41.6%) and 56 patients without delirium (56/187; 29.9%) at hospital admission. Patients with delirium stayed on average 12.2 ± 6.7 days in acute wards, while those without delirium

Table 2. Logistic Regression Models for Delirium Prediction

Characteristics	Model 1—Univariate				Model 2—Stepwise Forward*				Model 3—Multiple Variable*			
N = 235	OR	95% CI	*p* Value	Pseudo-R^2	OR	95% CI	*p* Value	Pseudo-R^2 = 11.3%	OR	95% CI	*p* Value	Pseudo-R^2 = 12.6%
Age	1.0	0.9–1.1	.449	0.2%	—	—	—		1.03	0.9–1.1	.305	
Male sex	1.4	0.7–2.6	.303	0.5%	—	—	—		1.7	0.83–3.36	.150	
Cognitive impairment	4.3	2.1–8.9	**<.001**	7.4%	3.71	1.7–7.9	**.001**		3.7	1.7–7.9	**.001**	
Heart failure	0.4	0.2–0.9	**.023**	2.2%	0.39	0.2–0.8	**.016**		0.3	0.1–0.7	**.006**	
Frailty	1.3	1.1–1.7	**.004**	3.4%	1.25	0.9–1.6	**.063**		1.3	0.9–1.6	.059	
FIM	0.9	0.97–0.99	**.029**	2.6%	—	—	—		—	—	—	
Lymphocytes	0.9	0.7–1.2	.602	0.1%	—	—	—		—	—	—	

Note: FIM = Functional Independence Measure; OR = odds ratio. Bold values correspond to statistically significant results.
*p of the model < .001.

stayed on average 13.0 ± 7.9 days (p = .491). Moreover, patients were hospitalized on average 4.4 days after the onset of COVID-19 symptoms, which was similar in both groups (with and without delirium), suggesting that the presence of delirium did not delay hospital admission. Although lengths of stay were similar, delirium diagnosis at hospital admission increased by more than 2 times the risk of dying after adjustment for sex (hazard ratio 2.1; 95% CI: 1.2–3.7, p = .0105).

Discussion

This study showed that older patients with COVID-19 had a prevalence of delirium of 20.4% on admission to acute medical wards, with the main risk factor being cognitive impairment previous to SARS-CoV-2 infection. Importantly, delirium at admission was associated with higher mortality despite a similar length of stay and complications' incidence in both patient groups. In our cohort, patients with delirium had a higher functional decline and prevalence of frailty. Usually, delirium is also an indicator of the severity of the underlying acute illness, but in this case, risk factors were essentially related to the substrate (frailty, prior dementia) but not to the severity of the disease itself (no relation to FiO_2, complications of COVID-19 such as ARDS), which all had a similar prevalence and incidence in patients with and without delirium.

Our results show that although COVID-19 is not associated with a higher prevalence of delirium than other acute illnesses, it is strongly associated with higher mortality (8,24). A meta-analysis reported that older patients hospitalized in acute care with delirium had up to 2 times increased risk of dying in the 2-year follow-up after hospital discharge, whereas in our study, patients with COVID-19 and delirium had a doubled risk of dying only during the acute phase (10). Recent emerging studies also showed the association of delirium in the course of COVID-19 with increased mortality and worse physical function after hospital discharge (25,26).

Another study described a prevalence of delirium of 67.9% in 82 older patients, all with dementia and COVID-19, raising the question of whether atypical symptoms of COVID-19, such as hypoactive delirium, could impact the quality of care (27). This study showed that patients with and without delirium had similar length of stay and number of days from the onset of symptoms to the hospitalization, which speaks against a possible effect of delirium on prompt diagnosis and adequate care in this population. On the other hand, we also showed that preexisting cognitive impairment was the strongest independent risk factor for incident delirium. Other risk factors included functional decline and frailty, while age and sex were not relevant in this age group. The bidirectional interaction between delirium and dementia is well reported by previous studies as dementia is a risk factor of delirium, while the latter may accelerate subsequent cognitive impairment progression after the acute phase (28,29). In this study, most of the patients presented delirium superimposed on dementia, which further increases the risk of worse outcomes (30,31). Our results are in agreement with previous studies that showed that patients with dementia, independently of its etiology, had increased pneumonia-associated mortality and the presence of delirium reported as an aggravating factor (32). Similarly, frailty is a recognized predisposing factor of delirium in older patients (33), which was confirmed by this study and particularly relevant as frailty assessment has been increasingly incorporated in different settings and used as a predictor of poor outcomes, especially mortality (34,35).

Our study has several limitations, as we describe a population of old patients who were ineligible for intensive care and thus caution should be exercised when extrapolating these results to other populations. Moreover, this study was performed in a geriatric acute care setting with teams that are trained in the detection and management of delirium. It is possible that the described prevalence and complication rate may differ in other settings. Also, data were collected from routine measurements documented in medical records, representing a potential bias in this observational study.

Conclusion

The presence of preexisting cognitive impairment was the main risk factor of incident delirium in older patients with COVID-19. Delirium was associated with increased in-hospital mortality, but not with the length of stay. These results highlight the importance of early detection of cognitive comorbidities and delirium in this population. Furthermore, as delirium is a preventable condition, whether specific strategies targeting significant risk factors will positively impact its occurrence and outcomes after COVID-19 remains to be investigated.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Author Contribution

All authors provided a significant contribution to this study.

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