SHORT REPORT

The impact of delirium on outcomes for older adults hospitalised with COVID-19

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Abstract

Introduction: Delirium is a frequent condition in hospitalized older patients and it usually has a negative prognostic value. A direct effect of SARS-COV-2 on the central nervous system (CNS) has been hypothesized.
Objective: To evaluate the presence of delirium in older patients admitted for a suspected diagnosis of COVID-19 and its impact on in-hospital mortality.
Setting and subjects: 91 patients, aged 70-years and older, admitted to an acute geriatric ward in Northern Italy from March 8th to April 17th, 2020.
Methods: COVID-19 cases were confirmed by reverse transcriptase-polymerase chain reaction assay for SARS-Cov-2 RNA from nasal and pharyngeal swabs. Delirium was diagnosed by two geriatricians according to the Diagnostic and Statistical Manual of Mental Disorders V (DMS V) criteria. The number of chronic diseases was calculated among a pre-defined list of 60. The pre-disease Clinical Frailty Scale (CFS) was assessed at hospital admission.
Results: Of the total sample, 39 patients died, 49 were discharged and 3 were transferred to ICU. Twenty-five patients (27.5%) had delirium. Seventy-two percent of patients with delirium died during hospitalization compared to 31.8% of those without delirium. In a multivariate logistic regression model adjusted for potential confounders, patients with delirium were four times more likely to die during hospital stay compared to those without delirium (OR = 3.98;95%CI = 1.05–17.28; p = 0.047).
Conclusions: Delirium is common in older patients with COVID-19 and strongly associated with in-hospital mortality. Regardless of causation, either due to a direct effect of SARS-COV-2 on the CNS or to a multifactorial cause, delirium should be interpreted as an alarming prognostic indicator in older people.

Keywords: COVID-19, delirium, older people

Key points

- Delirium is a common condition in medical wards and it usually has a negative prognostic impact in hospitalized older patients.
- Almost one third of older patients with COVID-19 have delirium and 70% of them die during hospital stay.
- Delirium could be directly caused by SARS-COV-2 or it can be the result of multifactorial causes.
- Regardless of the pathophysiology underlying delirium, it should be regarded as an alarming prognostic indicator in older people.

Introduction

Delirium has recently been acknowledged as "the missing piece in the coronavirus disease 2019 (COVID-19) pandemic puzzle" [1]. Reasons for this include: the absence of systematic assessment for delirium in current COVID-19 management guidelines, the lack of recognition of delirium as an atypical sign of the disease, and the failure to account for delirium's impact on mortality in older people [1].

It is well-known that delirium is a frequent condition in medical wards and has a strong negative prognostic impact among hospitalized older patients [2]. In persons affected by COVID-19, delirium may be due to direct central nervous system (CNS) effect, hypoxaemia, cytokine response and hypercoagulability, or other common causes of delirium in context of brain vulnerability and predisposing factors [3,4]. A systematic review of the literature on psychiatric symptoms in paediatric and adult patients with coronavirus infections showed a high prevalence of delirium in those patients with severe COVID-19 admitted to intensive care units (ICU) [5]. Mao et al. showed that 36% of patients admitted to hospital for COVID-19 had neurological manifestations, such as cerebrovascular diseases, impaired consciousness and skeletal muscle injury, but the mean age of patients was 52 years [6]. Helms and colleagues evaluated patients admitted to intensive care unit (ICU), finding that 26 of 40 patients (median age 63 years) had confusion according to the Confusion Assessment Method for the ICU [7]. An Italian study found that delirium was the most frequent symptom of onset among patients with dementia diagnosed with COVID-19 [8]. Finally, a national French survey shows that adults 70-year-old and older with COVID-19 presented delirium in 26.6% of cases among with other symptoms [9].

The aim of this study is to evaluate the presence of delirium in older patients admitted for a suspected diagnosis of COVID-19 and its impact on in-hospital mortality.

Methods

This is a retrospective analysis of 91 patients, aged 70-years and older, with a suspected diagnosis of COVID-19 consecutively admitted to an acute geriatric ward in a designated hospital in Montichiari (Brescia, Northern Italy) from March 8th to April 17th, 2020. Nasal and pharyngeal swab samples were collected at hospital admission. COVID-19 cases were confirmed by reverse transcriptase-polymerase chain reaction assay for SARS-Cov-2 RNA.

Assessment of delirium

In non-emergency situation, delirium is usually assessed by both nurses and physicians according to the 4-AT screening tool [10] and confirmed by a geriatrician according to the DSM-V criteria [11]. During the emergency of the COVID-19 pandemic, delirium was directly assessed by two geriatricians of the hospital ward who visited the patients at least twice per day, by means of the Diagnostic and Statistical Manual of Mental Disorders V (DSM V) criteria [11]. Possible precipitating factors for delirium were assessed and managed daily including, but not limited to, bacterial infection, hypoxaemia, dehydration, fever, prescribed drugs, immobility, electrolyte disorders, and sensory impairments. Peripheral arterial blood oxygen saturation was recorded in all patients at hospital admission.

Measures to treat delirium were taken according to each specific case; patients were mobilized if possible; any infection other than COVID-19 was treated with specific drugs, oxygen requirement was checked several times per day, videocalls with relatives were organized, the revision of therapy was performed every day; only 2 patients were prescribed with very low doses of trazodone and 6 with haloperidol. As possible predisposing factors, the number of chronic diseases was calculated among a pre-defined list of 60 [12] and the pre-disease Clinical Frailty Scale (CFS) was assessed at hospital admission; patients were scored from 1 "very fit" to 9 "terminally ill". In the CFS the degree of frailty corresponds to the degree of dementia if the latter is present [13]. The study was notified to the Ethical Committee of the Brescia County.

Statistical analysis

Patients' characteristics were described using mean and standard deviation, median and inter quartile range (IQR) or count and proportion, as appropriate. The differences between individuals who experienced delirium and those who did not develop delirium were investigated through t-test, Mann–Whitney test or chi-squared test, as appropriate. Logistic regression models adjusted for major confounders were employed to investigate the independent association between delirium and in-hospital mortality.

Results

Of the total sample (n = 91), 39 (42.9%) patients died, 49 (53.8%) were discharged and 3 were transferred to ICU. All patients died due to COVID-19 pneumonia, sepsis and related severe complications. Twenty-five patients (27.5%) had delirium (one at admission and 24 during the hospital stay). Seventy-two percent of patients with delirium died during hospitalization compared to 31.8% of those without delirium (p = 0.001). Table 1 displays demographic and clinical characteristics of the study population in the whole sample and by delirium diagnosis. Patients with delirium were older and more likely to be frail.

In a multivariate logistic regression model adjusted for age, sex, number of chronic diseases, frailty, and arterial blood oxygen saturation at admission, patients with delirium were four times more likely to die during hospital stay compared to those without delirium (OR = 3.98; 95%CI = 1.05–17.28, p = 0.047) (Table 2).

Table 1. Demographic and clinical characteristics of the whole sample study population and by delirium diagnosis

	All (N = 91)	Delirium YES (N = 25)	Delirium NO (N = 66)	p
Age, y, mean (SD)	79.5 (6.1)	81.7 (5.5)	78.6 (6.1)	0.026
Males, number (%)	55 (60.4%)	16 (64.0%)	39 (59.1%)	0.851
Number of chronic diseases, median (IQR)	3 (2–4)	3 (2–6)	3 (2–4)	0.123
CFS, median (IQR)	3 (2–5)	5 (3–6)	3 (2–4)	0.001
Symptoms				
Fever, number (%)	82 (90.1)	22 (88.0)	60 (90.9)	0.983
Dyspnoea, number (%)	38 (41.8)	11 (44.0)	27 (40.9)	0.977
Cough, number (%)	40 (44.0)	9 (36.0)	31 (47.0)	0.481
Arterial Oxygen Saturation < 90%, number (%)	33 (38.4)	10 (43.5)	23 (36.5)	0.735
Non-invasive ventilation, number (%)	12 (13.2)	4 (16.0)	8 (12.1)	0.888
Mortality, number (%)	39 (42.9)	18 (72.0)	21 (31.8)	0.001

CFS=Clinical Frailty Scale; SD = Standard Deviation; IQR = Interquartile Range Missing: 2 for CFS, 3 for number of diseases, 4 for arterial oxygen saturation

Table 2. Odds ratios (OR) and 95% Confidence Intervals (95%CI) for in-hospital mortality

	OR (95%CI)
Delirium	3.98 (1.05–17.28)
Age	1.09 (0.98–1.21)
Male sex	3.08 (0.87–12.80)
CFS	1.31 (0.85–2.08)
Number of chronic diseases	1.14 (0.84–1.58)
Peripheral arterial oxygen saturation < 90% at admission	6.96 (2.12–26.57)

CFS=Clinical Frailty Scale

Discussion

Delirium is a common condition in older people admitted for COVID-19 and is strongly associated with in-hospital mortality independently of pre-existing individual characteristics and measures of infectious disease severity.

The comparison with other studies on prevalence of delirium during hospital stay, for instance the Italian Delirium Day study, shows that the prevalence of delirium in older patients admitted in acute medical wards for other morbidities is slightly lower compared to the one of patients affected by COVID-19 [14]. This can be explained by the fact that several well-known precipitating factors of delirium can co-exist during hospitalization for COVID-19, for example prolonged hypoxia, fever, dehydration, acute inflammation and the prescription of specific medications. Patient's isolation during hospital stay may be another trigger of delirium in patients hospitalized for COVID-19. Further, SARS-COVID-19 may have a direct effect on the nervous system. A recent review of the literature suggested that COVID-19 is associated with many neurological manifestations, including confusion, and a possible CNS involvement in the COVID-19 pathophysiology, but further investigation is needed [15]. The mechanisms suggested for explaining the possible direct CNS involvement of the SARS-COV-2 include the invasion of the virus via disruption of the brain blood barrier, possible nerves injuries mediated by the immune system, and hypoxia [16]. Steardo et al. indicated that coronaviruses infect brain stem neurons, which are responsible for the cardio-respiratory regulation, resulting in the respiratory failure and hypoxia [17]. On the other hand, severe hypoxia may exacerbate the neural damage triggering neurological manifestations. Finally, in support of a direct CNS effect are imaging findings; patients with severe COVID-19 have been diagnosed with a wide range of abnormalities at brain MRIs, such as white matter hyperintense lesions, and extensive and isolated white matter microhaemorrhages [18].

Whether or not delirium is directly caused by SARS-COV-2, its impact on in-hospital mortality was very high in our study and, as such, it should be interpreted as an alarming sign and used as prognostic indicator. In hospital mortality in non-COVID-19 older people with delirium has been reported to vary between 8–9% [19] to 32% in patients with delirium superimposed to dementia [20]. In our study in-hospital mortality was extremely high in patients with SARS-COV-2 with (72%) and without delirium (31.8%), but the odd of dying in patients with COVID-19 and delirium was four times higher compared to those without delirium, even after adjusting for possible predisposing factors, such as multimorbidity and frailty, and the severity of the infectious disease at hospital admission, measured by means of peripheral oxygen saturation.

Given these findings and those of other recent studies on delirium in older people with COVID-19, guidelines on this specific infectious disease should include a focus on older persons' clinical manifestations such as assessment and management of delirium [21], with the aim to raise the awareness of health care providers on this frequent and dramatic geriatric syndrome.

References

1. O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. Age Ageing 2020 May 6pii: afaa094. doi: 10.1093/ageing/afaa094.

2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014; 383: 911–922.3.

3. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. J Alzheimers Dis 2020; 76: 3–19.

4. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med 2017; 377: 1456–66.

5. Rogers JP, Chesney E, Oliver D *et al.* Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020 May; 18: 2020. doi: https://doi.org/10.1016/S2215-0366(20)30203-0.

6. Mao L, Jin H, Wang M *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77: 1.

7. Helms J, Kremer S, Merdji H *et al.* Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020; 382: 2268–70.

8. Bianchetti A, Rozzini R, Guerini F *et al.* Clinical presentation of COVID19 in dementia patients. J Nutr Health Aging 2020; 24: 560–2.

9. Annweiler C, Sacco G, Salles N *et al.* National French survey of COVID-19 symptoms in people aged 70 and over. Clin Infect Dis, ciaa792 . https://doi.org/10.1093/cid/ciaa792.

10. Bellelli G, Morandi A, Davis D *et al.* Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 2015; 44: 175.

11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th ed. Washington, DC: American Psychiatric Association, 2013.

12. Calderón-Larrañaga A, Vetrano DL, Onder G *et al.* Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. J Gerontol A Biol Sci Med Sci 2017; 72: 1417–142.

13. Rockwood K, Song X, MacKnight C *et al.* A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489–95.

14. Bellelli G, Morandi A, Di Santo SG *et al.* "Delirium day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. BMC Med 2016; 14: 106.

15. Orsucci D, Ienco EC, Nocita G, Napolitano A, Vista M. Neurological features of COVID-19 and their treatment: a review. Drugs Context 2020; 9: 2020-5-1.

16. Wu Y, Xu X, Chen Z *et al.* Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020. doi: 10.1016/j.bbi.2020.03.031.

17. Steardo L, Zorec R, Verkhratsky A. Neuroinfection may potentially contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol 2020. doi: 10.1111/apha.13473.

18. Kremer S, Lersy F, de Sèze J *et al.* Brain MRI findings in severe COVID-19: a retrospective observational study. Radiology 2020 Jun; 202222: 16. doi: 10.1148/radiol.2020202222.

19. Morandi A, Di Santo SG, Zambon A *et al.* Delirium, dementia, and in-hospital mortality: the results from the Italian delirium day 2016, a National Multicenter Study. J Gerontol A Biol Sci Med Sci 2019; 74: 910–6.

20. Avelino-Silva TJ, Campora F, Curiati JA, Jacob-Filho W. Association between delirium superimposed on dementia and mortality in hospitalized older adults: a prospective cohort study. PLoS Med 2017; 14: e1002264.

21. LaHue SC, James TC, Newman JC, Esmaili AM, Ormseth CH, Ely EW. Collaborative delirium prevention in the age of COVID-19. J Am Geriatr Soc 2020; 68: 947–9.