

## Original Article

Delirium during Covid-19 pandemic: were we  
over-reporting an overlooked syndrome?

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## ABSTRACT

**Objective:** To compare incidence of delirium in Emergency Department in elderly patients admitted for SARS-CoV-2 infection and sepsis for other etiologies. **Methods:** This observational study analyzed elderly patients (>65 years) from two cohort studies that recruited patients in an urban and academic Emergency Department. The first cohort studied septic patients before Covid-19 pandemic and was conducted between September 30, 2019, and March 17, 2020. The second cohort studied Covid-19 patients between April 8, 2021, and May 28, 2021. Our primary outcome was the incidence of delirium at admission in Emergency Department, which we defined using the Confusion Assessment Method. **Results:** We included 141 patients in our final analysis, with a median age of 72 (interquartile range: 68 to 79) years and a predominance of the male sex (58%). We identified delirium at admission in 31 participants (21%) in septic non-Covid group and 11 (24%) in Covid-19 group ( $p=0.70$ ). **Conclusion:** This present study does not support that elderly patients with Covid-19 have higher risk for delirium at admission in Emergency Department when compared to patients hospitalized with sepsis for other etiologies. Although sepsis for Covid-19 have had more than 28% mortality, Covid-19 was not associated with higher mortality in elderly than sepsis for other etiologies. The study protocol was approved by the local Research Ethics Committee (CAPESq, protocol number 30417520.0.0000.0068).

**Keywords:** Delirium; Emergency medicine; Emergency service, hospital; Covid-19

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## INTRODUCTION

Delirium is a common, life-threatening, and often preventable neuropsychiatric emergency mostly characterized by a disturbance in attention and awareness.<sup>1,2</sup> Delirium indicates acute and severe brain dysfunction, and it is associated with worse outcomes including increased hospital and intensive care unit (ICU) length of stay, persistent cognitive decline, and mortality.<sup>3</sup>

The prevalence estimates of delirium in older Emergency Department (ED) patients prior to the coronavirus disease 2019 (Covid-19) pandemic ranged from 7% to 24%.<sup>2</sup> Despite such high occurrence, ED providers can miss the diagnosis of delirium in up to 70% of cases, mostly because most episodes are hypoactive, and patients are quiet and withdrawn rather than agitated.<sup>3,4</sup>

Neurological symptoms (including delirium) are the most common extrapulmonary manifestation in Covid-19 patients, being present in 35 to 50%

of hospitalized patients on the wards and in up to 70% of ICU patients.<sup>5-7</sup> Several hypotheses have been raised to explain such high occurrence of neurological manifestations including inflammation, hypoxemia, thrombosis, sedation, social isolation, and a possible neurotropism of *severe* acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>8</sup> However, most studies about the relationship between delirium and Covid-19 were performed in the inpatient and ICU settings, where the rates of delirium are simply described but no comparison is made with other infectious etiologies. Moreover, sparse ED-specific data exist to clarify the impact of SARS-CoV-2 infections on ED delirium rates. In this context, it is not known whether Covid-19 ED patients have higher rates of delirium when compared to similarly ill patients presenting with other infectious diseases.

In this study, we aimed to evaluate whether geriatric ED patients who were hospitalized with Covid-19 have a higher rate of delirium when compared to similarly ill septic patients hospitalized with infections of other etiologies. Furthermore, we assessed the association between acute ED delirium and subsequent in-hospital mortality for geriatric patients with Covid-19.

## METHODS

This manuscript adheres to the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>9</sup> The local Ethics Committee in Research approved the study protocols and informed consent was obtained from patients or legal guardians prior to inclusion in either cohort (*Comissão de Ética para Análise de Projetos de Pesquisa* [CAPPesq] protocol number 77169716.2.0000.0068 for non-Covid-19 cohort and CAPPesq protocol number 30417520.0.0000.0068 for Covid-19 cohort). We adhered to the principles expressed in the Declaration of Helsinki. All patient-identifiable information was stored in secure electronic servers, with access restricted to our researchers.

### Study design, setting, and participants

This was an observational study that compared two cohorts of adults aged 65 years or older who presented to an academic tertiary ED in the city of São Paulo (SP), Brazil: one cohort of septic ED patients prior to the existence of Covid-19 (comparison group, cohort 1) and one cohort of ED patients with Covid-19

requiring hospitalization. As a tertiary referral hospital in the Brazilian public health care system, ED visits and admissions are regulated in order to prioritize transfers of severely ill patients from lower complexity acute care facilities to our hospital ED. For this reason, the acuity and severity of patients in our ED tend to be higher than an average non-tertiary ED. During the pandemic, for example, our hospital became a major treatment center for Covid-19 in São Paulo, the epicenter of the pandemic in Brazil. In late March 2020, one of our main buildings was converted into a Covid-19-only facility, with approximately one thousand beds dedicated to the care of patients infected with SARS-CoV-2.

Cohort 1 included a convenience sample of older adults (age  $\geq 65$  years) who presented to our ED between September 30, 2019, and March 17, 2020 (prior to the first case of SARS-CoV-2 in Brazil), and who were admitted within 24 hours of ED arrival for a diagnosis of sepsis. Sepsis was defined in this cohort as the presence of a suspected infection (as determined by the emergency physician in charge of the patient) along with two or more points in the Sequential Organ Failure Assessment (SOFA) score.<sup>10</sup> Patients who were hospitalized for more than 24 hours in previous hospitals, were in exclusive palliative care or who were hospitalized within 30 days prior to the ED visit were excluded. When we started the Covid-19 cohort study, we had already recruited 95 patients in the septic non-Covid-19 cohort study.

The second and main cohort (cohort 2) included a convenience sample of older adult patients (age  $\geq 65$  years) who presented to our ED between April 8, 2021, and May 28, 2021, and who were hospitalized within 24 hours of ED arrival for a diagnosis of Covid-19. The decision of hospitalization was left at the discretion of the attending provider, but it all involved the need for oxygen therapy to maintain adequate oxygenation. Patients who were intubated in the ED, however, were excluded as they were not assessable for delirium (our primary outcome). A diagnosis of Covid-19 was defined as the presence of suggestive signs and symptoms along with a positive test for SARS-CoV-2 using real-time polymerase chain reaction (RT-PCR) in nasopharyngeal smear or tracheal aspirate. These patients were also considered “septic” due to the presence of an infection (i.e., SARS-CoV-2) that was leading to an acute organ dysfunction, mostly pulmonary in which oxygen therapy was required. Nevertheless, patients did not have to meet the SOFA  $\geq 2$  criteria for sepsis to be

eligible for this cohort. Palliative care patients, those with a hospitalization within 30 days prior to the ED visit, and those without a confirmed SARS-CoV-2 infection were excluded. For this cohort, we expected difficulties in recruiting for two reasons: our center was reference for severe cases of Covid-19, and most patients came to our hospital after being hospitalized for more than 24 hours in an outside hospital (an exclusion criteria); and vaccination campaign against SARS-CoV-2 started in São Paulo in January 2021, and it reduced the number of older patients being hospitalized.

### Baseline characteristics

Several baseline characteristics were obtained from both cohorts including data on demographics (age, sex), comorbidities (presence of documented dementia in the electronic health records [EHR], hypertension, diabetes, and obesity), and the SOFA score.

SOFA score evaluates the following variables: need for respiratory support, partial pressure of oxygen ( $\text{PaO}_2$ ), fraction of inspired oxygen ( $\text{FiO}_2$ ), platelet count, Glasgow coma scale (GCS), bilirubin, mean arterial pressure (MAP), administration of vasoactive agents, and creatinine (or urine output). The score was calculated based on data from the first available results in the ED arrival.

All data were collected by trained research personnel through a chart review process using an electronic case report form with Research Electronic Data Capture resources.<sup>11</sup>

### Delirium measurement (primary outcome)

Our primary outcome was the presence of delirium in the ED. Delirium was ascertained by trained research personnel (mostly trained nurses) with the validated Portuguese version of the Confusion Assessment Method (CAM).<sup>12,13</sup>

Structured interviews were performed with patients and their parents during their ED length of stay. This diagnostic approach was the same during both cohort study periods.

### Secondary outcomes

Secondary outcomes included the proportion of ED patients admitted directly to the ICU (i.e., ICU admission rate) and in-hospital mortality. Patients were followed up throughout their entire hospitalization during both study periods.

### Sample size

Both cohorts were made of a convenience sample of patients during the study periods. Nevertheless, assuming that the prevalence of delirium in older ED adults with Covid-19 has been estimated at 28%<sup>8</sup> and the prevalence of delirium in otherwise undifferentiated older adults in the ED at approximately 7%,<sup>2</sup> a sample size of 114 patients would have power of 80% for detecting a difference in proportions of 21% between the two groups.

### Data analysis

We reported descriptive results for the total sample, comparing the variables of interest according to the overall of delirium. We used the Chi-squared test to compare categorical variables, and we used the Student *t* test (normal distribution) or the Wilcoxon rank-sum test (non-normal distribution) to compare numerical variables.

All statistical tests were two-tailed, and an alpha error of up to 5% was accepted to define the statistical significance of any results. Statistical analyses were performed using Stata MP 16.1 (StataCorp)

## RESULTS

We included 141 patients in our final analysis, with a median age of 72 (interquartile range [IQR] 68 to 79) years and a predominance of the male sex (82; 58%) (Table 1).

**Table 1.** Baseline characteristics of the two studied cohorts

Variable	Septic non-Covid cohort (n = 95)	Covid-19 cohort (n = 46)
Median age, years	73 (69-80)	70 (66-76)
Sex		
Male	56 (59)	26 (57)
Female	39 (41)	20 (43)
Dementia	3 (3)	1 (2)
Hypertension	64 (65)	33 (72)
Diabetes	41 (43)	23 (50)
Obesity	1 (1)	7 (15)
SOFA $\geq 2$	94 (100)	19 (41)
Delirium	20 (21)	11 (24)

Results expressed as mean (interquartile range) or n (%).

SOFA: Sequential Organ Failure Assessment.

We identified delirium at admission in 31 participants (22%). Only four (3%) participants had a previous diagnosis of dementia. Patients

with delirium also had a higher prevalence of other comorbidities.

Intensive care admission and in-hospital mortality were different across groups, with unfavorable outcomes in delirium group. Sepsis for Covid-19 had more than 28% mortality, and Delirium in Covid-19 patients was associated with higher mortality ( $p=0.02$ ) (Table 2).

## DISCUSSION

This present study does not support that elderly patients with sepsis for Covid-19 have a higher risk for delirium at admission in ED when compared to patients hospitalized with sepsis for other etiologies.

Before the Covid-19 pandemics, delirium was a common presenting condition for older adults in the ED; however, two-thirds of cases went undetected.<sup>14</sup> Early Covid-19 studies have estimated rates of delirium about 30% in elderly hospitalized patients.<sup>15</sup> In a multicenter retrospective cohort study, 28% of 817 older patients with SARS-CoV-2 infection had delirium on arrival to the ED.<sup>8</sup> The authors explained the high rate of delirium because they used a structured delirium assessment tool and the high prevalence of comorbid conditions in their study population. However, 30% of these patients had a prior diagnosis of cognitive impairment or dementia, the most critical risk factor for delirium.<sup>16,17</sup>

The possible mechanisms behind the association between Covid-19 and delirium are also intriguing. Previous evidence suggests that SARS-CoV-2 may be a neurotropic virus and can cause direct brain damage by increasing demyelination, interleukin release, and blood-brain barrier permeability.<sup>18,19</sup> The main question was whether delirium in Covid-19 patients is caused by these neuroinflammatory pathways or by the direct action of the SARS-CoV-2 virus.

It is known that central nervous system inflammation participates in the pathogenesis of delirium; therefore, we compared a condition where systemic inflammation is also present.<sup>19</sup>

Despite possible distinct pathophysiological processes, sepsis-associated encephalopathy is a diffuse brain dysfunction secondary to infection without overt central nervous system infection.<sup>20</sup> Sepsis-associated encephalopathy presents itself in several degrees of severity and includes delirium. Interestingly, in a prospective postmortem study of patients with sepsis, cerebral lesions were reported, which in one patient were compatible with multifocal necrotizing leukoencephalopathy and evidence of cerebral ischemia and hemorrhages.<sup>21</sup> Similar findings were observed in Covid-19 patients.<sup>22</sup> Therefore, until there is more evidence showing SARS-CoV-2-related neuronal injury, we believe that delirium associated with Covid-19 could be considered an sepsis-associated encephalopathy spectrum.

During the pandemics, many EDs are overcrowded, placing ED providers under enormous pressure to care for critically ill patients simultaneously.<sup>23</sup> Under these circumstances, we believe that demonstrating the association between delirium admission and in-hospital mortality remains important to aware ED providers to adopt and use delirium screening protocols. Nevertheless, this study showed vital data about delirium prevalence in elderly septic patients at admission to ED.

Our data also show the relevance of diagnosing delirium in these patients. In our cohort, delirium at admission in ED was significantly associated with mortality during hospitalization ( $p=0.007$ ), which agrees with other authors.

## Limitations

This present study has some limitations. First, our study was performed in a single center dedicated to high-complexity medical care, and our results should be read with parsimony before being generalized to different populations. On the other hand, it is a strength because we reproduced the same delirium assessment tool,<sup>14</sup> and patients with Covid-19 and sepsis were hospitalized in similar conditions and treated by the same staff in a

**Table 2.** Association between delirium and adverse outcomes in hospitalized older adults

Delirium	Septic non-Covid patients (n=95)		p-value	Covid-19 Cohort (n=46)		p-value
	Yes (n=20)	No (n=75)		Yes (n=11)	No (n=35)	
Death	6 (30)	11 (15)	0.11	6 (54)	7 (20)	0.02
ICU admission	5 (25)	21 (28)	0.79	4 (36)	16 (46)	0.92

Results expressed as n (%).

ICU: intensive care unit.



short time difference. Second, our delirium incidence in septic patients was high, which does not allow us to prove our hypothesis with our previous sample size. Unfortunately, our sample has important limitations. We had a convenience sampling, and the sample size was insufficient to imply a small difference in percentage of delirium between the groups. Lastly, this was an ED study, and we did not do assessments regarding delirium duration and severity.

Despite these limitations, our study addresses two fundamental questions regarding delirium in Covid-19 patients. First, it suggests that the pathophysiology of delirium in Covid-19 patients may be related more to systemic inflammation than to the direct action of the SARS-CoV-2 virus in the central nervous system. Second, it points out the fundamental role of diagnosing delirium in ED.<sup>24</sup>

## CONCLUSION

Infection by SARS-COV-2 was not associated with higher delirium at emergency department admission. Furthermore, the prompt recognition of delirium is critical to ensure appropriate clinical care and prevent adverse outcomes in the elderly.

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