Predictors and impact on disability of delirium in Covid-19:
an observational study on 2288 consecutive hospitalized patients

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Running Title: Predictors of delirium in Covid-19 patients.

Search terms: COVID-19; delirium; predictors; mortality.

Impact Statement: We certify that this work is confirmatory of recent novel clinical research.

Key Points:
Age, premorbid disability and Covid-19 severity were the strongest predictors of both delirium and poor outcomes

Why does this paper matter:
The study helps to identify older and frail Covid-19 patients at higher risk of delirium, which is an important predictor of in hospital mortality and poor outcomes, independently from COVID-19 severity.
Abstract

Backgrounds

Delirium is a common event among Covid-19 hospitalized patients. In this work, we aim at evaluate the predictors of delirium and its impact on mortality and disability in Covid-19 patients.

Methods

Two thousand two hundred eighty-eight Covid-19 patients were admitted to Brescia hospital from 2020 to 2022. Clinical and laboratory features were extracted from digital medical records. Statistical analysis was implemented to evaluate predictive factors of delirium, mortality and disability at discharge.

Results

Out of 2288 patients, 223 (9.7%) experienced delirium (Del+). Compared to patients without delirium (Del-), Del+ subjects were older, exhibited worse premorbid conditions and disease severity, higher mortality rates and discharge outcomes. Age, premorbid disability and Covid-19 severity were the strongest predictors of both delirium and poor outcomes.

Conclusion

Older and frail Covid-19 patients are at higher risk of delirium, which is an important predictor of in hospital mortality and poor outcomes, independently from disease severity.
Introduction

Delirium is an acute syndrome characterized by change in attention, awareness and cognition, caused by a medical condition that cannot be better explained by a pre-existing neurocognitive disorder\(^1\).

Since the outbreak of SARS-CoV2 pandemic, delirium has been described both as an atypical initial presentation\(^2\) and a common complication among older Covid-19 patients\(^3\), \(^4\), \(^5\), \(^6\).

Several studies suggested that older age, premorbid vulnerability and COVID-19 disease severity impact on the risk of developing delirium in COVID-19. However, the interaction between these different factors and the impact of delirium on mortality rates are still open issue for clinicians in acute setting. Furthermore, only few studies evaluate the impact of delirium on disability independently from COVID-19 disease severity\(^7\), \(^8\), \(^9\), \(^10\), \(^11\).

In this single-center observational study, we aim at evaluate the risk factors associated with severe delirium and its impact on in-hospital mortality and disability at discharge in a large population of Covid-19 hospitalized patients.

Methods

This retrospective cohort study included 2288 adult inpatients (\(\geq 18\) years old) consecutively admitted to single COVID-19 tertiary hub in four different Covid-19 Units in the ASST Spedali Civili Hospital of Brescia, from March 2020 to May 2022. Demographic, clinical and laboratory data were extracted from both printed and electronic medical records, using standardized anonymized data collection forms.

Delirium diagnosis was performed using the Confusion Assessment Method (CAM) delirium severity scale\(^12\). Delirium was thus defined by an acute change or fluctuations in mental status, associated with attention deficits, and either disorganized thinking or altered level of consciousness. Only patients with persistent delirium were included in the analyses- defined by a
CAM score >2 for more than 12 consecutive hours. This restrictive definition was implemented in order to exclude cases with transient confusion/altered level of consciousness due to prominent hypoxia/respiratory impairment due to COVID-19 disease.

Differences between patients with and without delirium were compared by t-test and x² test, as appropriate. The variables independently associated with COVID-19 severity were analyzed by Pearson correlation test in order to evaluate the risk of an overfitting model, and highly correlated factors (R > 0.5) were excluded from further analyses. Logistic regression analysis was performed to evaluate predictive factors associated to severe delirium. Cox-regression (using days of hospitalization as time-dependent variable) and logistic regression models were implemented in order to evaluate the predictive factors of in hospital mortality and poor outcomes, expressed by the differences between modified Rankin Scale at discharge and pre-admission (∆mRS) >1, respectively.

This study received approval from the ethical standards committee on human experimentation (local ethics committee of the ASST Spedali Civili Hospital, Brescia: NP 4067, approved in this last version on the 16.12.2021).

**Results**

Out of 2288 hospitalized patients with COVID-19 disease, 223 (9.7%) experienced delirium (Del+). Del+ patients were older (80.9±12.6 vs 67.2±16.2, p <0.001), exhibited worse pre-morbid conditions, according to Cumulative Illness Rating Scale (CIRS) (1.16±0.9 vs 1.05±0.9, p<0.001) and modified Rankin Scale (mRS) (1.62±0.4 vs 1.44±0.4, p<0.001) compared to patients without delirium (Del−) (table 1).
Table 1. Demographic, clinical, laboratory characteristics of all included patients.

<table>
<thead>
<tr>
<th></th>
<th>Covid-19 patients with delirium (n=223)</th>
<th>Covid-19 patients without delirium (n=2065)</th>
<th>*p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>80.9±12.6</td>
<td>67.2±16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>108 (48.4%)</td>
<td>900 (43.5%)</td>
<td>0.155</td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>20.7±16.4</td>
<td>15.2±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vaccination status (% of full-dose vax)</td>
<td>44 (19.7%)</td>
<td>330 (15.9%)</td>
<td>0.145</td>
</tr>
<tr>
<td>qSOFA score</td>
<td>2.34±1.4</td>
<td>1.7±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO clinical progression scale</td>
<td>5.30±0.8</td>
<td>4.93±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Rankin Scale premorbid</td>
<td>1.62±0.4</td>
<td>1.44±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIRS pre-admission</td>
<td>1.16±0.9</td>
<td>1.05±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>71.9±68.4</td>
<td>60.8±62.7</td>
<td>0.133</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>50.5±67.4</td>
<td>31.96±54.2</td>
<td>0.025</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>2535.8±186.4</td>
<td>1900.7±4036.8</td>
<td>0.053</td>
</tr>
<tr>
<td><strong>Therapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-flow oxygen therapy</td>
<td>95 (42.6%)</td>
<td>826 (40.0%)</td>
<td>0.952</td>
</tr>
<tr>
<td>High-flow oxygen therapy/NIV</td>
<td>93 (41.7%)</td>
<td>425 (20.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroid Treatment</td>
<td>132 (59.1%)</td>
<td>1018 (49.3%)</td>
<td>0.998</td>
</tr>
<tr>
<td><strong>Outcomes measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Rankin Scale at discharge (with death)</td>
<td>3.92±1.8</td>
<td>2.30±2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Rankin Scale at discharge (without death)</td>
<td>2.78±1.3</td>
<td>1.57±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In Hospital mortality</td>
<td>70 (31.4%)</td>
<td>266 (12.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p values were calculated by t-test and χ² test, as appropriate; BCRSS: Brescia-COVID Respiratory Severity Scale; CIRS: Cumulative Illness Rating Scale; qSOFA: quick sequential organ failure assessment; NIV: non-invasive ventilation.
Compared to Del-, Del+ patients showed higher quick sequential organ failure assessment (qSOFA) (2.34 ± 1.4 vs 1.7 ± 1.2, p < 0.001), worse inflammatory blood parameters, a higher rate of patients needing high-flow/non-invasive ventilation (41.7% vs 20.6%, p < 0.001) and WHO Clinical Progression Scale 13 (5.30 ± 0.8 vs 4.93 ± 0.7, p < 0.001) score. Logistic regression analysis identified age (p < 0.001), pre-morbid mRS (p < 0.001) and Covid-19 severity as the strongest predictive factors for delirium, independently from gender, pre-morbid comorbidity severity index, and inflammatory blood parameters (Table 2).
Table 2: Logistic regression evaluating predictors of delirium.

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>Exp(B)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>1.062</td>
<td>1.044-1.081</td>
</tr>
<tr>
<td>Gender</td>
<td>0.117</td>
<td>1.326</td>
<td>0.932-1.885</td>
</tr>
<tr>
<td>pre-morbid mRS</td>
<td>&lt;0.001</td>
<td>1.507</td>
<td>1.304-1.742</td>
</tr>
<tr>
<td>Pre-morbid CIRS (mean value)</td>
<td>0.113</td>
<td>0.683</td>
<td>0.426-1.095</td>
</tr>
<tr>
<td>WHO clinical progression scale</td>
<td>&lt;0.001</td>
<td>1.780</td>
<td>1.378-2.298</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.581</td>
<td>0.999</td>
<td>0.996-1.002</td>
</tr>
</tbody>
</table>

Additionally, the odds of delirium increase by 6.2% (95% CI 1.04 - 1.08) for every additional year of age, and by 51% (95% CI 1.30 - 1.74) for every unit added to pre-morbid mRS value.

Multivariate analyses showed that mortality rates were significantly related to age (p <0.001; Exp(B) 1.057, CI 1.041-1.072), pre-morbid mRS (p <0.001; Exp(B) 1.407, CI 1.257-1.575), delirium (p=0.04; Exp(B) 1.386, CI 1.014-1.895), clinical severity of Covid-19, namely WHO clinical severity scale (p=0.035; Exp(B) 1.537, CI 1.056-2.237) and PCR (p<0.001; Exp(B) 1.004, CI 1.002-1.006), independently from gender (Figure 1).

Disability at discharge was associated with age (p<0.001), pre-morbid disability (p<0.001), and severity of Covid-19 in multivariate analyses (Table 3).
Table 3.: Logistic regression evaluating predictors of poor outcomes, expressed by ΔmRS>1 in the total sample.

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>Exp(B)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>1.017</td>
<td>1.007-1.026</td>
</tr>
<tr>
<td>Gender</td>
<td>0.727</td>
<td>1.045</td>
<td>0.817-1.336</td>
</tr>
<tr>
<td>Pre-morbid mRS</td>
<td>&lt;0.001</td>
<td>0.723</td>
<td>0.636-0.823</td>
</tr>
<tr>
<td>Pre-morbid CIRS (mean value)</td>
<td>0.113</td>
<td>0.720</td>
<td>0.479-1.081</td>
</tr>
<tr>
<td>WHO clinical progression scale</td>
<td>&lt;0.001</td>
<td>1.750</td>
<td>1.456-2.103</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.550</td>
<td>1.001</td>
<td>0.999-1.003</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.687</td>
<td>0.914</td>
<td>0.590-1.416</td>
</tr>
</tbody>
</table>

The analyses focused on delirium thus showed a higher risk of mortality (p=0.001; OR 3.102, CI 2.273-4.234) but not disability (p=0.691; OR 1.077, CI 0.746-1.555) when adjusting for age, gender, premorbid conditions and COVID-19 severity.

Finally, logistic models implemented separately in patients with and without delirium, showed that mortality rates is strongly related to age (p=0.002, Exp(B) 1.056, CI 1.021-1.092 and p<0.001, Exp(B) 1.055, CI 1.038-1.072, respectively) in both groups, whereas only for Del – group there was a significant impact due to pre-morbid conditions (p<0.001, Exp(B) 1.429, CI 1.260-1.620) and Covid-19 severity (p<0.001, Exp(B) 2.085, CI 1.697-2.563). With regard to poor outcome, in Del+ and Del- groups age (p=0.003, Exp(B) 1.052, CI 1.017-1.088 and p<0.001, Exp(B) 1.022, CI 1.013-1.032, respectively) and Covid-19 severity (p=0.018, Exp(B) 1.820, CI 1.107-2.992 and p<0.001, Exp(B) 2.289, CI 1.911-2.742, respectively) are the strongest predictors of disability at discharge, independently from gender and pre-morbid conditions (Supplementary Tables 1,2,3,4).

Discussion

This single-center retrospective study identified predictive factors and impact of delirium in a large cohort of consecutive hospitalized Covid-19 patients. Findings showed that age- premorbid
conditions and severity of COVID-19 predicted both delirium and poor outcomes in the cohort.

The multivariate analyses also confirm that delirium is an independent predictor of mortality and highlighted that premorbid conditions themselves - instead of severity of COVID-19 were highly associated with poor outcomes in patients with delirium. This highly vulnerable population is thus associated with an increased risk of mortality and disability regardless the severity of COVID-19 - a very important finding still debated in the literature.

As expected, subjects diagnosed with delirium were older, showed worse pre-morbid conditions and exhibited a worse COVID-19 related clinical severity, resulting in higher rate of patients needing non-invasive ventilation (NIV), comparing to patients without delirium. The outcome measures, expressed by mRS and mortality rates, were worse in the delirium group, corroborating previous studies conducted on hospitalized Covid-19 patients. In multivariate model including premorbid conditions and covid-19 severity, delirium was associated with higher mortality risk but not disability at discharge – which is an important finding still neglected from previous literature.

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 occurring during hospitalization.

To the best of our knowledge, inflammation is one of the possible pathophysiological mechanisms for delirium; specifically, inflammatory response to systemic infection may alter blood brain barrier, allowing a central inflammatory activation, leading to neuronal dysfunction. Indeed, in this consecutive series, we found that patients with delirium exhibited higher inflammatory parameters at admission, despite this association was not confirmed in multivariate analyses adjusting for premorbid conditions.
In line with this, the strongest predictors of delirium were age, pre-morbid disability and Covid-19 related clinical severity, independently from gender and inflammatory blood parameters in both univariate and multiple analyses, according to previous studies. Notwithstanding, cox-regression analysis identified delirium, age, pre-morbid disability and Covid-19 related clinical severity as the variables significantly related to mortality rate. Our study also evaluated the different role on mortality and disability of premorbid condition and disease severity in patients with and without delirium in multivariate analyses. Findings showed an interesting lower impact of COVID-19 severity of mortality in patients with delirium, thus indicating that even milder pulmonary disease might cause severe consequences in highly vulnerable subjects.

Our study went a step further, indicating a larger effect size of age and premorbid vulnerability compared to COVID-19 severity in determining the final outcome of patients at discharge-of note, this was evaluated in two different models with and without considering the mortality rates during hospitalization. Again, the impact of COVID-19 severity and inflammatory parameters was definitively higher in patients without delirium, whereas Del+ patients exhibited higher risk of disability independently from primary COVID-19 disease. These findings corroborate the hypothesis that frailer and more vulnerable subjects represent a high-risk population for both delirium and worse outcomes, deserving preventive strategies to improve an early management of this condition with possible impact on short and long-term prognosis.

This study entails some limitations, namely the exclusion of patients admitted in the intensive care settings and the lack of data regarding transient forms of delirium. To date, we reported all the COVID-19 patients diagnosed with persistent delirium. In order to exclude transient forms of altered consciousness possibly related to hypoxia during acute phase of COVID-19, encephalopathy, psychiatric conditions or mild behavior abnormalities were also excluded; this
might contribute to the higher prevalence of delirium observed in other large consecutive series. Nevertheless, our study showed that delirium represents an important condition in non-neurological patients with COVID-19 and is a major predictor of mortality in patients hospitalized for an acute SARS-COV-2 infection.

Further studies are warranted to confirm and extend these findings, in order to identify Covid-19 patients with extreme vulnerability and a higher risk of poor outcomes. In this scenario, it will be critical to evaluate the preventable nature of delirium in COVID-19 and to identify intervention strategies to reduce the severity and duration of delirium.

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Conflict of interest regarding the research related to the manuscript:

All authors have no conflict of interest regarding the research related to the manuscript.

Authors Contributions: VC, AP and AP designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content. ML, SG, EC had a major role in the acquisition of data and revised the manuscript for intellectual content. CR, FC and MM revised the manuscript for intellectual content.

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Sponsor’s Role: The study was not sponsor supported.

References

1. Association AP. Diagnostic and Statistical Manual of Mental Disorders (5th ed.). 2013


**Figure 1.** Predictors of mortality in Cox regression analysis between Covid-19 patients with and without delirium.

**Supplementary Table S1.** Cox regression analysis between Covid-19 patients with delirium.

**Supplementary Table S2.** Cox regression analysis between Covid-19 patients without delirium.

**Supplementary Table S3.** Logistic regression evaluating predictors of poor outcomes, expressed by ΔmRS>1 in Covid-19 patients with delirium.
Supplementary Table S4.: Logistic regression evaluating predictors of poor outcomes, expressed by ∆mRS≥1 in Covid-19 patients without delirium.