Incidence and long-term functional outcome of neurological disorders in hospitalized COVID-19 patients infected with pre-Omicron variants

From the Neuro-COVID Italy Investigators

Supplemental material

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Clusters of neuro-COVID disorders.

Cluster heat map of selected neuro-COVID disorders. The color scale indicates the percent of association between two disorders.
eFigure 2
Recovery curves for headache and dizziness
eFigure 3
Survival curves for Guillain Barrè syndrome, seizures and status epilepticus, encephalitis and hemorrhagic stroke
eFigure 4
Recovery and survival curves of the most common Neuro-COVID disorders, with and without severe respiratory failure during the acute phase

- **Hyposmia-hypogeusia**
  - Respiratory failure = severe respiratory failure requiring continuous positive airway pressure (CPAP) or mechanical ventilation.

- **Cognitive impairment**

- **Acute encephalopathy**

- **Acute ischemic stroke**

Logrank p values: 0.0546, 0.0562, 0.003, 0.003.
**eTable 1. Complete list of neuro-COVID disorders**

<table>
<thead>
<tr>
<th>Disorders</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute encephalopathy</td>
<td>470</td>
<td>16.3</td>
</tr>
<tr>
<td>Hyposmia-hypogeusia</td>
<td>377</td>
<td>13.1</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>343</td>
<td>11.9</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>256</td>
<td>8.9</td>
</tr>
<tr>
<td>Peripheral neuropathy* (any, including focal neuropathy and critical illness neuropathy; excluding GBS)</td>
<td>248</td>
<td>8.6</td>
</tr>
<tr>
<td>Headache</td>
<td>220</td>
<td>7.6</td>
</tr>
<tr>
<td>Myalgia*</td>
<td>201</td>
<td>7.0</td>
</tr>
<tr>
<td>Seizures and status epilepticus</td>
<td>135</td>
<td>4.7</td>
</tr>
<tr>
<td>Guillain Barré syndrome (GBS)</td>
<td>135</td>
<td>4.7</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>56</td>
<td>1.9</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>56</td>
<td>1.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>49</td>
<td>1.7</td>
</tr>
<tr>
<td>Transient ischemic attack (TIA)**</td>
<td>42</td>
<td>1.5</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>36</td>
<td>1.2</td>
</tr>
<tr>
<td>Postural instability and gait disturbance</td>
<td>34</td>
<td>1.2</td>
</tr>
<tr>
<td>Syncope</td>
<td>29</td>
<td>1.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27</td>
<td>0.9</td>
</tr>
<tr>
<td>Catatonia, mutism, bradykinesia</td>
<td>26</td>
<td>0.9</td>
</tr>
<tr>
<td>Upper cranial nerve palsy (diplopia, facial nerve, facial sensation)</td>
<td>23</td>
<td>0.8</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Tremor</td>
<td>21</td>
<td>0.7</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Subjective sensory symptoms</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Unvoluntary muscle contractions, muscle cramps, subcortical myoclonic jerks</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Lower cranial nerve palsy (dysphonia, dysphagia, dysarthria)</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Myelitis</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Auditory symptoms, including tinnitus</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome (PRES)</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperosmia</td>
<td>1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Corea</td>
<td>1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2881</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Analysis was patient-centered and focused on 10 major neuro-COVID disorders (on grey background). * not considered as major neuro-COVID disorders, since these disorders commonly occur as consequence of prolonged hospitalization or ICU admissions. ** not considered as a major neuro-COVID disorder, since diagnostic accuracy for TIA is low.
### eTable 2. Major diagnostic tests of selected neuro-COVID disorders (clinical neurological syndromes)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Brain imaging (CT or MRI)</th>
<th>EEG</th>
<th>CSF</th>
<th>EMG &amp; NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>new focal lesion n/n (%)</td>
<td>new multifocal lesions n/n (%)</td>
<td>generalized or focal slowing n/n (%)</td>
<td>epileptiform discharges n/n (%)</td>
</tr>
<tr>
<td>Subsyndromal delirium*</td>
<td>5/71 (7.0)</td>
<td>9/71 (12.7)</td>
<td>15/38 (39.5)</td>
<td>5/38 (13.2)</td>
</tr>
<tr>
<td>Delirium*</td>
<td>22/121 (18.2)</td>
<td>13/121 (10.7)</td>
<td>32/62 (51.6)</td>
<td>11/62 (17.7)</td>
</tr>
<tr>
<td>Coma*</td>
<td>10/49 (20.4)</td>
<td>12/49 (24.5)</td>
<td>19/32 (59.4)</td>
<td>2/32 (6.2)</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>160/259 (61.8)</td>
<td>71/259 (27.4)</td>
<td>26/44 (59.1)</td>
<td>6/44 (13.6)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seizures and status epilepticus</td>
<td>22/110 (20.0)</td>
<td>15/110 (13.6)</td>
<td>31/103 (30.1)</td>
<td>35/103 (33.9)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>30/41 (73.2)</td>
<td>9/41 (21.9)</td>
<td>6/16 (37.5)</td>
<td>3/16 (18.7)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>4/31 (12.9)</td>
<td>9/31 (29.0)</td>
<td>15/29 (51.7)</td>
<td>4/29 (13.8)</td>
</tr>
</tbody>
</table>

* pre-defined subtypes of acute encephalopathy. CT = computerized tomography. MRI = magnetic resonance imaging. EEG = electroencephalography. CSF = cerebrospinal fluid. EMG & NCS = electromyography and nerve conduction studies. n/n = number of patients with the indicated diagnostic finding divided by the number of patients with the indicated diagnostic test reported in the study dataset.
### eTable 3. Outcome of neuro-COVID disorders in the working age population

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Total n (%)</th>
<th>Full recovery n (%)</th>
<th>Mild symptoms n (%)</th>
<th>Disabling symptoms n (%)</th>
<th>Unknown n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All neuro-COVID cases aged 18 to 64</td>
<td>781 (100)</td>
<td>244 (31.4)</td>
<td>321 (41.1)</td>
<td>101 (12.9)</td>
<td>115 (14.7)</td>
</tr>
<tr>
<td>Selected disorders, participants aged 18 to 64:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute encephalopathy</td>
<td>141 (100)</td>
<td>60 (42.5)</td>
<td>38 (27.0)</td>
<td>22 (15.6)</td>
<td>21 (14.9)</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>90 (100)</td>
<td>23 (25.6)</td>
<td>40 (44.4)</td>
<td>24 (26.7)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>71 (100)</td>
<td>11 (15.5)</td>
<td>39 (54.9)</td>
<td>12 (16.9)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>Seizures and status epilepticus</td>
<td>47 (100)</td>
<td>37 (78.7)</td>
<td>3 (6.4)</td>
<td>2 (4.3)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>21 (100)</td>
<td>9 (42.9)</td>
<td>4 (19.0)</td>
<td>7 (33.3)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>19 (100)</td>
<td>12 (63.2)</td>
<td>1 (5.3)</td>
<td>2 (10.5)</td>
<td>4 (21.0)</td>
</tr>
<tr>
<td>Hyposmia/hypogeusia</td>
<td>228 (100)</td>
<td>122 (53.5)</td>
<td>57 (25)</td>
<td>13 (5.7)</td>
<td>36 (15.8)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>109 (100)</td>
<td>24 (22.0)</td>
<td>64 (58.7)</td>
<td>6 (5.5)</td>
<td>15 (13.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>171 (100)</td>
<td>107 (62.6)</td>
<td>36 (21.0)</td>
<td>2 (1.2)</td>
<td>26 (15.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28 (100)</td>
<td>9 (32.1)</td>
<td>14 (50)</td>
<td>0 (0)</td>
<td>5 (17.9)</td>
</tr>
</tbody>
</table>
### Table 4. Outcome predictors for selected neuro-COVID disorders

<table>
<thead>
<tr>
<th></th>
<th>unit</th>
<th>good functional outcome</th>
<th>poor functional outcome</th>
<th>crude OR (95% CI)</th>
<th>p value</th>
<th>adjusted OR (95% CI)</th>
<th>adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute encephalopathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. = 299</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>71 (61-79)</td>
<td>78 (67-84)</td>
<td>1.03 (1.01-1.04)</td>
<td><em>p &lt; 0.001</em></td>
<td>1.03</td>
<td>(1.01-1.05)</td>
<td><em>p = 0.003</em></td>
</tr>
<tr>
<td>Sex male (%)/female</td>
<td>173 (57.8)</td>
<td>74 (64.3)</td>
<td>1.31 (0.84-2.05)</td>
<td><em>p = 0.228</em></td>
<td>1.30</td>
<td>(0.81-2.09)</td>
<td><em>p = 0.273</em></td>
</tr>
<tr>
<td>Pre-existing neurological comorbidity n (%)</td>
<td>87 (29.1)</td>
<td>47 (40.8)</td>
<td>1.68 (1.07-2.63)</td>
<td><em>p = 0.022</em></td>
<td>1.47</td>
<td>(0.87-2.49)</td>
<td><em>p = 0.146</em></td>
</tr>
<tr>
<td>Severe respiratory failure b n (%)</td>
<td>139 (46.5)</td>
<td>73 (63.5)</td>
<td>2.00 (1.28-3.11)</td>
<td><em>p = 0.002</em></td>
<td>2.61</td>
<td>(1.57-4.33)</td>
<td><em>p &lt; 0.001</em></td>
</tr>
<tr>
<td>Anticoagulants n (%)</td>
<td>158 (52.3)</td>
<td>64 (55.6)</td>
<td>1.12 (0.72-1.72)</td>
<td><em>p = 0.607</em></td>
<td>0.68</td>
<td>(0.40-1.13)</td>
<td><em>p = 0.143</em></td>
</tr>
<tr>
<td>Steroids n (%)</td>
<td>152 (50.1)</td>
<td>71 (61.2)</td>
<td>1.56 (1.00-2.42)</td>
<td><em>p = 0.047</em></td>
<td>1.31</td>
<td>(0.77-2.22)</td>
<td><em>p = 0.315</em></td>
</tr>
<tr>
<td>Remdesivir n (%)</td>
<td>72 (24.1)</td>
<td>16 (13.9)</td>
<td>0.51 (0.28-0.92)</td>
<td><em>p = 0.025</em></td>
<td>0.60</td>
<td>(0.31-1.14)</td>
<td><em>p = 0.121</em></td>
</tr>
<tr>
<td><strong>Acute ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. = 178</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>71 (60-79)</td>
<td>79 (69-86)</td>
<td>1.05 (1.03-1.06)</td>
<td><em>p &lt; 0.001</em></td>
<td>1.05</td>
<td>(1.03-1.07)</td>
<td><em>p &lt; 0.001</em></td>
</tr>
<tr>
<td>Sex male (%)/female</td>
<td>106 (58.8)</td>
<td>90 (62.9)</td>
<td>1.13 (0.72-1.79)</td>
<td><em>p = 0.577</em></td>
<td>1.25</td>
<td>(0.75-2.08)</td>
<td><em>p = 0.387</em></td>
</tr>
<tr>
<td>Pre-existing neurological comorbidity n (%)</td>
<td>40 (22.4)</td>
<td>42 (29.4)</td>
<td>1.43 (0.86-2.37)</td>
<td><em>p = 0.159</em></td>
<td>0.97</td>
<td>(0.55-1.69)</td>
<td><em>p = 0.922</em></td>
</tr>
<tr>
<td>Severe respiratory failure b n (%)</td>
<td>25 (14.0)</td>
<td>46 (32.2)</td>
<td>2.92 (1.67-5.02)</td>
<td><em>p &lt; 0.001</em></td>
<td>3.01</td>
<td>(1.63-5.51)</td>
<td><em>p &lt; 0.001</em></td>
</tr>
<tr>
<td>Anticoagulants n (%)</td>
<td>67 (37.6)</td>
<td>70 (48.9)</td>
<td>1.58 (1.01-2.48)</td>
<td><em>p = 0.042</em></td>
<td>1.29</td>
<td>(0.74-2.25)</td>
<td><em>p = 0.359</em></td>
</tr>
<tr>
<td>Steroids n (%)</td>
<td>47 (26.4)</td>
<td>44 (30.8)</td>
<td>1.24 (0.76-2.01)</td>
<td><em>p = 0.388</em></td>
<td>0.78</td>
<td>(0.41-1.47)</td>
<td><em>p = 0.450</em></td>
</tr>
<tr>
<td>Remdesivir n (%)</td>
<td>33 (18.5)</td>
<td>23 (16.1)</td>
<td>0.84 (0.46-1.51)</td>
<td><em>p = 0.564</em></td>
<td>0.78</td>
<td>(0.41-1.48)</td>
<td><em>p = 0.454</em></td>
</tr>
<tr>
<td><strong>Hyposmia-hypogeusia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. = 278</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>58 (50-69)</td>
<td>59 (49-73)</td>
<td>1.00 (0.97-1.04)</td>
<td><em>p = 0.572</em></td>
<td>1.07</td>
<td>(0.97-1.04)</td>
<td><em>p = 0.707</em></td>
</tr>
<tr>
<td>Sex male (%)/female</td>
<td>155 (55.7)</td>
<td>8 (38.1)</td>
<td>0.488 (0.19-1.2)</td>
<td><em>p = 0.123</em></td>
<td>0.49</td>
<td>(0.18-1.33)</td>
<td><em>p = 0.165</em></td>
</tr>
<tr>
<td>Pre-existing neurological comorbidity n (%)</td>
<td>18 (6.5)</td>
<td>4 (19.0)</td>
<td>3.39 (1.03-11.16)</td>
<td><em>p = 0.043</em></td>
<td>2.57</td>
<td>(0.72-9.17)</td>
<td><em>p = 0.144</em></td>
</tr>
<tr>
<td>Severe respiratory failure b n (%)</td>
<td>93 (33.4)</td>
<td>6 (28.6)</td>
<td>0.79 (0.29-2.11)</td>
<td><em>p = 0.647</em></td>
<td>1.08</td>
<td>(0.36-3.24)</td>
<td><em>p = 0.889</em></td>
</tr>
<tr>
<td>Anticoagulants n (%)</td>
<td>127 (45.7)</td>
<td>12 (57.1)</td>
<td>1.58 (0.64-3.88)</td>
<td><em>p = 0.313</em></td>
<td>1.09</td>
<td>(0.34-3.46)</td>
<td><em>p = 0.878</em></td>
</tr>
<tr>
<td>Steroids n (%)</td>
<td>112 (40.3)</td>
<td>12 (57.1)</td>
<td>1.97 (0.80-4.84)</td>
<td><em>p = 0.136</em></td>
<td>1.19</td>
<td>(0.36-3.93)</td>
<td><em>p = 0.775</em></td>
</tr>
<tr>
<td>Remdesivir n (%)</td>
<td>94 (33.8)</td>
<td>2 (9.5)</td>
<td>0.20 (0.04-0.90)</td>
<td><em>p = 0.036</em></td>
<td>0.26</td>
<td>(0.05-1.23)</td>
<td><em>p = 0.090</em></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>No. = 187</td>
<td>No. = 27</td>
<td>OR</td>
<td>CI</td>
<td>OR</td>
<td>CI</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Age(^a) years</td>
<td>66 (54-73)</td>
<td>75 (67-81)</td>
<td>1.07</td>
<td>(1.03-1.11)</td>
<td><strong>p &lt; 0.001</strong></td>
<td>1.06</td>
<td>(1.01-1.10)</td>
</tr>
<tr>
<td>Sex</td>
<td>113 (60.4)</td>
<td>17 (62.9)</td>
<td>1.11</td>
<td>(0.48-2.56)</td>
<td><strong>p = 0.801</strong></td>
<td>0.95</td>
<td>(0.38-2.34)</td>
</tr>
<tr>
<td>Pre-existing neurological comorbidity n (%)</td>
<td>25 (13.4)</td>
<td>11 (40.7)</td>
<td>4.45</td>
<td>(1.85-10.69)</td>
<td><strong>p &lt; 0.001</strong></td>
<td>2.48</td>
<td>(0.92-6.67)</td>
</tr>
<tr>
<td>Severe respiratory failure(^b) n (%)</td>
<td>75 (40.1)</td>
<td>13 (48.1)</td>
<td>1.38</td>
<td>(0.61-3.11)</td>
<td><strong>p = 0.428</strong></td>
<td>1.45</td>
<td>(0.60-3.49)</td>
</tr>
<tr>
<td>Anticoagulants n (%)</td>
<td>111 (59.3)</td>
<td>14 (51.8)</td>
<td>0.73</td>
<td>(0.32-1.65)</td>
<td><strong>p = 0.460</strong></td>
<td>0.61</td>
<td>(0.23-1.56)</td>
</tr>
<tr>
<td>Steroids n (%)</td>
<td>105 (56.1)</td>
<td>17 (62.9)</td>
<td>1.32</td>
<td>(0.57-3.05)</td>
<td><strong>p = 0.504</strong></td>
<td>1.03</td>
<td>(0.37-2.87)</td>
</tr>
<tr>
<td>Remdesivir n (%)</td>
<td>44 (23.5)</td>
<td>3 (11.1)</td>
<td>0.40</td>
<td>(0.11-1.41)</td>
<td><strong>p = 0.156</strong></td>
<td>0.50</td>
<td>(0.12-1.97)</td>
</tr>
</tbody>
</table>

OR = odds ratio. CI = confidence intervals. OR > 1 indicates higher probability of poor functional outcome. \(^a\) per year of age; \(^b\) requiring CPAP or mechanical ventilation.