**SUPPLEMENTARY MATERIAL**

**Early clinical and electrophysiological brain dysfunction is associated with ICU outcomes in COVID-19 critically ill patients with ARDS: a prospective bicentric observational study**

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3. **SUPPLEMENTARY METHODS**
   1. **Sedation and analgesia management**

Sedatives and opioids were administered following a nurse-protocolized targeted sedation based on BPS and RASS levels, assessed at least every 4 hours and followed in both participating centers. Sedation targets varied according to the phase of ARDS resuscitation.Schematically, at the acute phase of the ARDS (PaO2/FiO2 ratio <150 in low tidal volume and PEEP >8cmH20), an initial titration of sedatives and opioids to maintain a BPS of 3 and target a deep sedation (RASS<-3) was performed before starting neuro-muscular blockers (NMB) if needed (23). Sedatives and opioids infusion rates were left unchanged during NMB infusion. Once the initial phase of the ARDS was over (PaO2/FiO2 ratio >150 without NMB infusion with PEEP ≤8cmH20), the objective was to target the lightest sedation necessary following the protocols, to maintain patient’s comfort and synchrony with the respirator, with discontinuation of sedation as soon as possible (BPS target of 3 and RASS target of 0) **(Supplementary Figure 1).**

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**Supplementary Figure 1. Sedation protocol**

BPS: Behavioral Pain Scale; RASS: Richmond Assessment Sedation Scale.

* 1. **Brainstem Response Assessment Sedation Score (BRASS)**

|  |  |
| --- | --- |
| **Variable** | **Point** |
| **Absence of cough reflex** | 1 |
| **Absence of photo-motor reflex** | 1 |
| **Absence of corneal reflex** | 2 |
| **Absence of grimacing to pain and horizontal oculocephalic reflexes** | 1 |
| **Absence grimacing to pain and preservation of horizontal oculocephalic reflexes** | 3 |

**Supplementary Table 1. BRASS score**

*The BRASS score corresponds to the sum of the tested items.*

The BRASS score ranges from 0 (all brainstem responses present, no BS-dys) to a theoretical maximum of 7. A BRASS of 7, corresponding to the most severe brainstem dysfunction, is obtained when a patient would combine the abolition of cough (1 point), photo-motor (1 point) and corneal reflex (2 points) and grimacing to pain with the preservation of horizontal oculocephalic reflexes (3 points). Since only 1/148 patients of this cohort obtained a score over 5, **authors set a maximum value for the BRASS at 5.**

1. **SUPPLEMENTARY RESULTS**
   1. **Flow chart**

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**Supplementary Figure 2. Flow chart**ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019.

* 1. **characteristics of the non-included patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Population** | **Included, N = 52** | **Not-included, N = 65** | **p-value** |
| **Demographic characteristics** | | | |
| **Age (years)** | 69 [56-75] | 65 [59-75] | 0.826 |
| **Gender** |  |  | 1.0 |
| F | 10 (19%) | 13 (20%) |  |
| M | 42 (81%) | 52 (80%) |  |
| **MacCabe score** |  |  | **0.043** |
| 1 - no chronic disease | 42(81%) | 43 (66%) |  |
| 2 - chronic disease with at least 5 years of expected survival | 10 (19%) | 16 (25%) |  |
| 3 - chronic disease with less than 5 years of expected survival | 0 (0%) | 6 (9%) |  |
| **Severity at admission** | | | |
| **SAPS-II at ICU admission** | 48 [35-69] | 53 [41-64] | 0.341 |
| **SOFA-total at ICU admission** | 5 [4-8] | 8 [5-10] | **0.008** |
| **Outcomes** | | | |
| **Mechanical ventilation duration***, days* | 18 [10-34] | 16 [9-28] | 0.293 |
| **In-ICU mortality** | 10 (23%) | 31 (49%) | **0.011** |

**Supplementary Table 2. Comparison of patients characteristics with non-included patients.**

Included patients were compared for baseline characteristics and outcomes with the 65 ARDS patients out of delay for assessement.

ICU : intensive care unit; SAPS-II: Simplified Acute Physiology Score-II ; SOFA: sequential organ failure assessment.

* 1. **Results of brain imaging and of cerebrospinal fluid analyses**

Among the 52 patients included in the study, 6 (12%) presented in the ICU with altered mental status with a median GCS at ICU admission of 15 [15-15] without any focal sign. Altered mental status was attributed to the acute respiratory failure and no brain imaging was performed at admission. However, during the hospitalization brain CT/MRI and cerebrospinal fluid (CSF) analyses were performed at the treating physician’s discretion based on clinical judgment, notably in case of focal neurological symptoms. In 20 (38%) patients, a brain imaging was performed during the ICU stay after ARDS development (12 patients had only a CT scan, 5 patients had only an MRI only and 3 patients had both imaging), with 4 (20%) finding brain lesions: one patient had cerebellar and supratentorial ischemic lesions, another had frontal and cerebellar hemorrhagic lesions, another had a frontal subarachnoid hemorrhage and the last one had an MRI compatible with limbic encephalitis. All patients with brain lesions on imaging presented a brainstem dysfunction, yet none of these lesions were in the brainstem. CSF analyses were performed in 2 cases, both without any abnormalities.

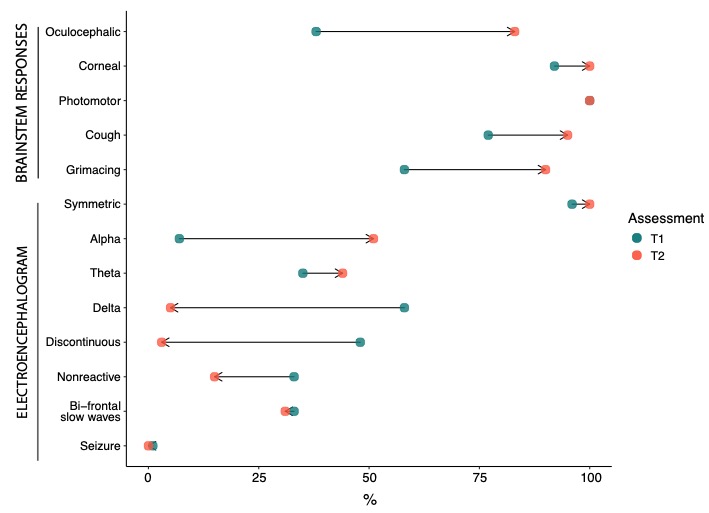
* 1. **Distribution of BRASS scores**



**Supplementary Figure 3. Distribution of BRASS score.**

Distribution of BRASS score at neurological assessment according to vital status at ICU discharge (alive in green and deceased in red). Dashed line separates patients without brainstem dysfunction (BRASS score of 0, left) from patients with brainstem dysfunction (BRASS≥1, right).

* 1. **Evolution of brainstem dysfunction and EEG between T1 and T2**



**Supplementary Figure 4. Clinical and neurophysiological assessment at T1 and T2**

T1: first assessment (under sedation); T2: second assessment (4-7 days after sedatives weaning).

* 1. **Laboratory findings and sedatives/opioids exposure according to the presence of brainstem dysfunction and continuity of EEG background at T1**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Brainstem dysfunction | |  | EEG background | |  |
| **Characteristics** | **Absent**  **N = 26** | **Present**  **N = 26** | **p-value** | **Discontinuous**  **N = 25** | **Continuous**  **N = 27** | **p-value** |
| **Laboratory findings** | | | | | | |
| **Sodium (mmol/L)** | 141 [137-142] | 139 [136-142] | 0.446 | 140 [137-142] | 140 [136-142] | 0.847 |
| **Creatinine (µmol/L)** | 86 [62-145] | 206 [89-361] | **0.042** | 159 [93-370] | 82 [60-152] | **0.016** |
| **Urea (mmol/L)** | 12 [10-20] | 17 [13-30] | 0.062 | 18 [14-30] | 13 [10-20] | **0.018** |
| **Blood glucose (mmol/L)** | 7.7 [7.0-8.8] | 8.5 [7.2-10.0] | 0.078 | 8.0 [7.2-10.0] | 8.0 [7.0-9.5] | 0.406 |
| **Ammonemia (µmol/L), n=47** | 34 [28-50] | 41 [36-59] | 0.105 | 50 [38-68] | 32 [27-39] | **<0.001** |
| **Bilirubin (µmol/L), n=50** | 8 [7-11] | 7 [6-11] | 0.785 | 10 [7-11] | 8 [5-11] | 0.227 |
| **PaO2/FiO2 ratio** | 208 [190-249] | 190 [161-236] | 0.187 | 188 [160-232] | 214 [190-250] | **0.034** |
| **PaCO2 (mmHg)** | 40 [38-43] | 45 [39-49] | 0.052 | 42 [39-48] | 41 [38-44] | 0.409 |
| **White blood cells (G/L), n=51** | 10 [8-12] | 12 [10-19] | 0.100 | 12 [10-18] | 10 [7-11] | 0.223 |
| **Platelets (G/L), n=51** | 289 [224-361] | 231 [177-314] | 0.247 | 252 [177-342] | 286 [224-357] | 0.309 |
| **D-dimers (ng/mL), n=35** | 1462  [866-1935] | 1962  [1632-3048] | **0.017** | 1908  [1508-2170] | 1283  [882-1975] | 0.113 |
| **Fibrinogen (g/L), n=43** | 6.3 [5.4-6.8] | 6.2 [5.2-7.0] | 0.922 | 6.3 [5.7-7.2] | 5.6 [4.7-6.7] | **0.044** |
| **CRP (mg/L), n=27** | 90 [44-169] | 152 [102-263] | 0.167 | 167 [135-252] | 78 [30-100] | **0.010** |
| **Sedatives and opioids exposure** | | | | | | |
| **Sedatives infusion rate (mg/kg/h of midazolam equivalent)** | 0.09 [0.06-0.17] | 0.17 [0.09-0.23] | 0.103 | 0.17 [0.10-0.22] | 0.08 [0.05-0.22] | 0.062 |
| **Opioids infusion rate (µg/kg/h)** | 0.11 [0.07-0.18] | 0.21 [0.14-0.26] | **0.004** | 0.17 [0.11-0.23] | 0.14 [0.07-0.21] | 0.223 |
| **Sedatives cumulative dose (mg/kg), n=50** | 10 [8-19] | 16 [9-21] | 0.311 | 12 [9-17] | 15 [7-26] | 0.617 |
| **Opioids cumulative dose (µg/kg), n=50** | 15 [9-28] | 19 [13-44] | 0.258 | 15 [11-20] | 21 [12-44] | 0.141 |
| **Sedatives and opioids duration (days)** | 4 [3-6] | 4 [3-10] | 0.641 | 3 [3-4] | 4 [3-10] | 0.301 |

**Supplementary Table 3. Laboratory findings and sedatives and opioids exposure according to EEG background and brainstem dysfunction at T1 assessment.**

* 1. **Association of brainstem dysfunction with outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall** | **Brainstem dysfunction** | |  |
| **Characteristics** | **N=52** | **Absent,**  **N = 26** | **Present,**  **N = 26** | **P** |
| **Outcomes at ICU discharge** | | | | |
| **ICU mortality** | 12 (23) | 4 (15) | 8 (31) | 0.323 |
| **ICU length of stay (days)** | 20 [12-36] | 18 [12-33] | 26 [13-38] | 0.197 |
| **IMV duration (days)** | 18 [10-34] | 15 [10-32] | 20 [11-36] | 0.223 |
| **Coma** |  |  |  |  |
| Awakening  Nb.  Delayed, *n=43*  Delay (days), *n=43* | 43 (83)  29 (67)  4 [1-13] | 25 (96)  14 (56)  2 [0-8] | 18 (69)  15 (83)  9 [2-19] | **0.024**  0.059  **0.019** |
| Duration (days)  All  Awoken, *n=43* | 13 [8-26]  13 [8-26] | 11 [6-24]  11 [6-22] | 17 [10-27]  24 [14-32] | 0.098  **0.022** |
| CF delay, days*, n=43* | 5 [2-17] | 3 [1-10] | 11 [4-22] | **0.014** |
| **Delirium, n=43** |  |  |  |  |
| Delirium | 32 (74) | 18 (72) | 14 (78) | 0.941 |
| Type of delirium, |  |  |  | >0.999 |
| *Hyperactive* | 4 (12) | 2 (11) | 2 (14) |  |
| *Hypoactive* | 8 (25) | 5 (28) | 3 (21) |  |
| *Mixed* | 20 (62) | 11 (61) | 9 (64) |  |
| Duration (days), n=32 | 5 [3-8] | 4 [3-7] | 7 [2-10] | 0.702 |
| **Outcomes at D28 from assessment** | | | | |
| **Mortality** | 11 (21) | 3 (12) | 8 (31) | 0.090 |
| **Ventilator-free days**, (days) | 6 [0-20] | 18 [0-24] | 0 [0-12] | **0.004** |
| **Coma-free days**, (days) | 14 [0-25] | 23 [6-25] | 6 [0-16] | **0.021** |
| **Delirium-free days**, (days) | 12 [0-22] | 18 [2-25] | 5 [0-14] | **0.015** |
| 1Statistics presented: Median [IQR]; n (%) | | | | | |
| 2Statistical tests performed: Mann-Whitney test; Fisher's exact test; chi-square test of independence  ✭ One missing data. | | | | | |

**Supplementary Table 4– ICU outcomes according to brainstem dysfunction at T1**

CF: command following; D28 : day 28; ICU : intensive care unit; IMV: invasive mechanical ventilation;

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**Supplementary Figure 5. Time-to-event analyses at day 28 from neurological assessment according to brainstem dysfunction**

Survival probability (A) and cumulative incidences of mechanical ventilation weaning (B), of coma (C) and of delirium (D) recovery according to brainstem dysfunction. Kaplan-Meier curves were used for visual presentation and Cox proportional hazards models were used to compute the crude and adjusted hazard ratio (HR) and corresponding 95% confidence intervals on the sedatives and opioids exposure between intubation and T1. Patients were followed for 28 days from the neurological assessment or up to ICU discharge, whichever came first.

* 1. **Crude hazard-ratios from the Cox proportional hazards estimates of outcomes at day 14 and 28 of T1 neurological assessment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Outcomes at D14 from T1** | | **Outcomes at D28 from T1** | |
| **Variables** | **Crude HR**  **[95% CI]** | **p-value** | **Crude HR**  **[95% CI]** | **p-value** |
| **Mortality** | | | | |
| **Brainstem dysfunction** | 3.4 [0.7-16.2] | 0.096 | 2.4 [0.63-9.1] | 0.176 |
| **Discontinuous EEG** | 9.1 [1.2-76.9] | **0.007** | 11.11[1.45-100] | **0.002** |
| **Nonreactive EEG** | 7.7 [1.6-3.7] | **0.004** | 3.85 [1.11-12.5] | **0.029** |
| **Bifrontal slow waves** | 0.25 [0.03-2.0] | 0.122 | 0.21 [0.03-1.63] | 0.066 |
| **Liberation from Mechanical Ventilation** | | | | |
| **Brainstem dysfunction** | 0.26 [0.09-0.71] | **0.004** | 0.33 [0.14-0.8] | **0.01** |
| **Discontinuous EEG** | 0.41 [0.16-1.05] | **0.05** | 0.5 [0.22-1.19] | 0.112 |
| **Nonreactive EEG** | 0.34 [0.1-1.14] | **0.048** | 0.54 [0.20-1.45] | 0.195 |
| **Bifrontal slow waves** | 2.09 [0.89-4.93] | 0.096 | 1.95 [0.87-4.35] | 0.11 |
| **Freedom from Coma** | | | | |
| **Brainstem dysfunction** | 0.28 [0.12-0.67] | **0.002** | 0.57 [0.3-1.08] | 0.082 |
| **Discontinuous EEG** | 0.29 [0.12-0.69] | **0.003** | 0.44 [0.23-0.85] | **0.013** |
| **Nonreactive EEG** | 0.41 [0.16-1.10] | 0.054 | 0.79 [0.39-1.61] | 0.518 |
| **Bifrontal slow waves** | 2.65 [1.22-5.74] | **0.017** | 2 [1.04-3.85] | **0.043** |
| **Freedom from Delirium** | | | | |
| **Brainstem dysfunction** | 0.27 [0.11-0.69] | **0.003** | 0.47 [0.23-0.97] | **0.036** |
| **Discontinuous EEG** | 0.30 [0.12-0.76] | **0.006** | 0.32 [0.15-0.71] | **0.002** |
| **Nonreactive EEG** | 0.38 [0.13-1.11] | 0.05 | 0.53 [0.23-1.23] | 0.12 |
| **Bifrontal slow waves** | 2.89 [1.29-6.43] | **0.011** | 2.69 [1.34-5.4] | **0.007** |

**Supplementary Table 5. Crude hazard-ratios from the Cox proportional hazards estimates of outcomes at day 14 and 28 of T1 neurological assessment.**

CI : Confidence interval; HR : Hazard-ratio.P-values from likelihood ratio test.

* 1. **Hazard-ratios from the Cox proportional hazards estimates of outcomes at day 28 of T1 neurological assessment adjusted on each sedatives/opioids exposure (infusion rates, cumulative doses and duration).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes at D28 from T1 assessment** | | | | | | |
| **Adjustment variables** | **sed./op. infusion rates** | | **sed./op. cumulative doses** | | **sed./op. duration** | |
| **Independent variable** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** |
| **Mortality** | | | | | | |
| **Brainstem dysfunction** | 2.61 [0.61-11.1] | 0.19 | 2.47 [0.63-9.72] | 0.20 | 2.51 [0.66-9.56] | 0.18 |
| **Discontinuous EEG** | 10.88 [1.37-86.56] | **0.024** | 17.7 [1.65-189.88] | **0.018** | 17.07 [1.65-176.48] | **0.017** |
| **Nonreactive EEG** | 3.61 [1.05-12.37] | **0.041** | 3.8 [1.03-14.01] | **0.045** | 3.82 [1.08-13.49] | **0.037** |
| **Bifrontal slow waves** | 0.17 [0.02-1.52] | 0.112 | 0.19 [0.02-1.55] | 0.12 | 0.21 [0.03-1.66] | 0.14 |
| **Liberation from Mechanical Ventilation** | | | | | | |
| **Brainstem dysfunction** | 0.35 [0.13-0.93] | **0.035** | 0.33 [0.13-0.82] | **0.017** | 0.36 [0.15-0.87] | **0.023** |
| **Discontinuous EEG** | 0.5 [0.21-1.18] | 0.12 | 0.44 [0.18-1.06] | 0.067 | 0.41 [0.17-0.97] | **0.042** |
| **Nonreactive EEG** | 0.52 [0.19-1.41] | 0.20 | 0.5 [0.18-1.38] | 0.18 | 0.49 [0.18-1.33] | 0.16 |
| **Bifrontal slow waves** | 1.82 [0.8-4.14] | 0.15 | 1.79 [0.78-4.12] | 0.17 | 2.04 [0.91-4.56] | 0.082 |
| **Freedom from Coma** | | | | | | |
| **Brainstem dysfunction** | 0.56 [0.27-1.14] | 0.11 | 0.55 [0.28-1.1] | 0.091 | 0.54 [0.28-1.05] | 0.067 |
| **Discontinuous EEG** | 0.44 [0.23-0.86] | **0.016** | 0.43 [0.22-0.85] | **0.015** | 0.45 [0.23-0.89] | **0.022** |
| **Nonreactive EEG** | 0.8 [0.39-1.63] | 0.54 | 0.79 [0.38-1.65] | 0.54 | 0.81 [0.4-1.65] | 0.56 |
| **Bifrontal slow waves** | 1.98 [1.03-3.81] | **0.041** | 1.92 [0.98-3.77] | 0.059 | 2 [1.03-3.9] | **0.042** |
| **Freedom from Delirium** | | | | | | |
| **Brainstem dysfunction** | 0.41 [0.19-0.92] | **0.031** | 0.43 [0.2-0.95] | **0.036** | 0.42 [0.2-0.9] | **0.026** |
| **Discontinuous EEG** | 0.32 [0.15-0.7] | **0.004** | 0.32 [0.15-0.72] | **0.006** | 0.31 [0.14-0.69] | **0.004** |
| **Nonreactive EEG** | 0.53 [0.23-1.24] | 0.14 | 0.55 [0.23-1.3] | 0.17 | 0.54 [0.23-1.26] | 0.16 |
| **Bifrontal slow waves** | 2.69 [1.33-5.44] | **0.006** | 2.67 [1.3-5.49] | **0.008** | 2.66 [1.32-5.38] | **0.006** |

**Supplementary Table 6. Adjusted hazard-ratios from the Cox proportional hazards estimates of outcomes at day 28 of T1 neurological assessment.**

Adjusted hazard-ratio were adjusted on sedatives and opioids infusion rates (left), or cumulative dose (middle) or sedatives and opioids duration (right) at T1 assessment.

sed./op.: sedatives/opioids; CI : Confidence interval; HR : Hazard-ratio.

* 1. **Hazard-ratios from the Cox proportional hazards estimates of outcomes at day 28 of T1 neurological assessment adjusted on all sedatives/opioids exposure (infusion rates, cumulative doses and duration).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Outcomes at D14 from T1** | | **Outcomes at D28 from T1** | |
|  | **Adjusted HR on**  **sedatives/opioids exposure**  **[95% CI]** | **p-value** | **Adjusted HR on sedatives/opioids exposure**  **[95% CI]** | **p-value** |
| **Mortality** | | | | |
| **Brainstem dysfunction** | 4.62 [0.8-26.64] | 0.087 | 2.6 [0.6-11.16] | 0.24 |
| **Discontinuous EEG** | 15.33 [1.19-196.85] | **0.036** | 14.95 [1.37-163.16] | **0.027** |
| **Nonreactive EEG** | 0.09 [0.01-0.65] | **0.016** | 3.74 [1.06-13.17] | **0.04** |
| **Bifrontal slow waves** | 0.14 [0.01-1.61] | 0.11 | 0.17 [0.02-1.58] | 0.12 |
| **Liberation from Mechanical Ventilation** | | | | |
| **Brainstem dysfunction** | 0.27 [0.09-0.82] | **0.021** | 0.38 [0.14-1.02] | 0.054 |
| **Discontinuous EEG** | 0.35 [0.13-0.94] | **0.037** | 0.45 [0.18-1.09] | 0.075 |
| **Nonreactive EEG** | 0.34 [0.1-1.17] | 0.086 | 0.54 [0.2-1.49] | 0.24 |
| **Bifrontal slow waves** | 1.86 [0.75-4.65] | 0.182 | 1.73 [0.74-4.07] | 0.207 |
| **Freedom from Coma** | | | | |
| **Brainstem dysfunction** | 0.26 [0.1-0.72] | **0.009** | 0.56 [0.26-1.18] | 0.12 |
| **Discontinuous EEG** | 0.28 [0.11-0.7] | **0.006** | 0.44 [0.22-0.89] | **0.021** |
| **Nonreactive EEG** | 0.4 [0.14-1.1] | 0.077 | 0.78 [0.37-1.65] | 0.52 |
| **Bifrontal slow waves** | 2.71 [1.18-6.19] | **0.018** | 1.98 [1-3.92] | 0.051 |
| **Freedom from Delirium** | | | | |
| **Brainstem dysfunction** | 0.22 [0.07-0.67] | **0.007** | 0.37 [0.15-0.89] | **0.026** |
| **Discontinuous EEG** | 0.26 [0.1-0.68] | **0.006** | 0.32 [0.14-0.71] | **0.005** |
| **Nonreactive EEG** | 0.38 [0.13-1.14] | 0.083 | 0.53 [0.22-1.28] | 0.16 |
| **Bifrontal slow waves** | 3.07 [1.3-7.26] | **0.011** | 2.84 [1.35-5.96] | **0.006** |

**Supplementary Table 7. Adjusted hazard-ratios from the Cox proportional hazards estimates of outcomes at day 14 and 28 of T1 neurological assessment. Adjustment on sedative/opioids exposure (infusion rates, cumulative doses and duration).**

CI : Confidence interval; HR : Hazard-ratio.

* 1. **Hazard-ratios from the Cox proportional hazards estimates of outcomes at day 28 of T1 neurological assessment adjusted on each sedatives/opioids exposure (infusion rates, cumulative doses and duration) and non-neurological SOFA.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes at D14 from T1 assessment** | | | | | | |
| **Adjustment variables** | **Non neurological SOFA & sed./op. infusion rates** | | **Non neurological SOFA & sed./op. cumulative doses** | | **Non neurological SOFA & sed./op. duration** | |
| **Independent variable** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** |
| **Mortality** | | | | | | |
| **Brainstem dysfunction** | 1.86 [0.26-13.34] | 0.535 | 2.23 [0.39-12.72] | 0.37 | 2.55 [0.49-13.26] | 0.27 |
| **Discontinuous EEG** | 6.05 [0.67-54.72] | 0.109 | 11.19 [0.99-126.05] | 0.051 | 11.31 [1.06-120.19] | **0.044** |
| **Nonreactive EEG** | 6.26 [1.11-35.3] | **0.038** | 6.96 [1.25-38.75] | **0.027** | 7.16 [1.39-36.78] | **0.018** |
| **Bifrontal slow waves** | 0.39 [0.03-5.23] | 0.480 | 0.35 [0.04-3.2] | 0.35 | 0.36 [0.04-3.21] | 0.36 |
| **Liberation from Mechanical Ventilation** | | | | | | |
| **Brainstem dysfunction** | 0.4 [0.12-1.35] | 0.140 | 0.37 [0.13-1.1] | 0.074 | 0.38 [0.13-1.09] | 0.071 |
| **Discontinuous EEG** | 0.53 [0.2-1.44] | 0.214 | 0.45 [0.17-1.22] | 0.117 | 0.41 [0.15-1.08] | **0.072** |
| **Nonreactive EEG** | 0.4 [0.12-1.37] | 0.144 | 0.39 [0.11-1.41] | 0.151 | 0.37 [0.11-1.26] | 0.111 |
| **Bifrontal slow waves** | 1.25 [0.49-3.2] | 0.643 | 1.29 [0.51-3.26] | 0.586 | 1.53 [0.62-3.77] | 0.355 |
| **Freedom from Coma** | | | | | | |
| **Brainstem dysfunction** | 0.35 [0.12-0.97] | **0.043** | 0.35 [0.13-0.96] | **0.041** | 0.34 [0.13-0.86] | **0.022** |
| **Discontinuous EEG** | 0.34 [0.14-0.84] | **0.020** | 0.38 [0.15-0.96] | **0.040** | 0.32 [0.13-0.8] | **0.014** |
| **Nonreactive EEG** | 0.5 [0.18-1.35] | 0.172 | 0.48 [0.17-1.35] | 0.167 | 0.49 [0.18-1.33] | 0.162 |
| **Bifrontal slow waves** | 1.84 [0.79-4.29] | 0.159 | 1.8 [0.76-4.29] | 0.182 | 1.92 [0.83-4.44] | 0.13 |
| **Freedom from Delirium** | | | | | | |
| **Brainstem dysfunction** | 0.3 [0.1-0.89] | **0.030** | 0.42 [0.15-1.19] | 0.101 | 0.36 [0.14-0.98] | **0.045** |
| **Discontinuous EEG** | 0.35 [0.14-0.91] | **0.031** | 0.39 [0.15-1.03] | 0.056 | 0.33 [0.13-0.85] | **0.022** |
| **Nonreactive EEG** | 0.48 [0.16-1.44] | 0.190 | 0.52 [0.17-1.59] | 0.251 | 0.47 [0.16-1.41] | 0.178 |
| **Bifrontal slow waves** | 1.93 [0.79-4.7] | 0.149 | 1.78 [0.73-4.36] | 0.208 | 1.99 [0.83-4.74] | 0.122 |
| **Outcomes at D28 from T1 assessment** | | | | | | |
| **Adjustment variabless** | **Non neurological SOFA + sed./op infusion rates** | | **Non neurological SOFA + sed./op cumulative doses** | | **Non neurological SOFA + sed./op duration** | |
| **Independent variable** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** | **aHR [95% CI]** | **p** |
| **Mortality** | | | | | | |
| **Brainstem dysfunction** | 1.62 [0.34-7.88] | 0.547 | 1.97 [0.46-8.41] | 0.37 | 2.14 [0.53-8.59] | 0.28 |
| **Discontinuous EEG** | 9.02 [1.12-72.93] | **0.039** | 16.62 [1.48-186.15] | **0.023** | 15.95 [1.49-170.92] | **0.022** |
| **Nonreactive EEG** | 3.12 [0.89-10.91] | 0.076 | 3.44 [0.91-12.97] | 0.068 | 3.53 [0.99-12.62] | 0.052 |
| **Bifrontal slow waves** | 0.25 [0.02-2.57] | 0.243 | 0.23 [0.03-2.02] | 0.19 | 0.25 [0.03-2.09] | 0.20 |
| **Liberation from Mechanical Ventilation** | | | | | | |
| **Brainstem dysfunction** | 0.5 [0.17-1.46] | 0.21 | 0.43 [0.17-1.12] | 0.084 | 0.44 [0.18-1.12] | 0.087 |
| **Discontinuous EEG** | 0.66 [0.27-1.65] | 0.375 | 0.54 [0.22-1.33] | 0.180 | 0.49 [0.2-1.17] | 0.11 |
| **Nonreactive EEG** | 0.63 [0.23-1.72] | 0.368 | 0.62 [0.22-1.73] | 0.358 | 0.57 [0.21-1.55] | 0.27 |
| **Bifrontal slow waves** | 1.23 [0.5-3.01] | 0.654 | 1.3 [0.54-3.11] | 0.561 | 1.54 [0.66-3.6] | 0.321 |
| **Freedom from Coma** | | | | | | |
| **Brainstem dysfunction** | 0.64 [0.3-1.36] | 0.24 | 0.62 [0.3-1.26] | 0.18 | 0.58 [0.3-1.16] | 0.12 |
| **Discontinuous EEG** | 0.49 [0.24-0.99] | **0.046** | 0.5 [0.24-1.03] | 0.06 | 0.47 [0.23-0.95] | **0.037** |
| **Nonreactive EEG** | 0.9 [0.44-1.88] | 0.79 | 0.9 [0.43-1.91] | 0.78 | 0.89 [0.43-1.85] | 0.76 |
| **Bifrontal slow waves** | 1.68 [0.82-3.46] | 0.16 | 1.65 [0.78-3.48] | 0.19 | 1.74 [0.83-3.65] | 0.14 |
| **Freedom from Delirium** | | | | | | |
| **Brainstem dysfunction** | 0.52 [0.22-1.21] | 0.127 | 0.57 [0.25-1.28] | 0.172 | 0.51 [0.23-1.12] | 0.092 |
| **Discontinuous EEG** | 0.39 [0.18-0.87] | **0.021** | 0.42 [0.19-0.97] | **0.043** | 0.39 [0.17-0.88] | **0.024** |
| **Nonreactive EEG** | 0.68 [0.29-1.61] | 0.378 | 0.74 [0.3-1.79] | 0.502 | 0.69 [0.29-1.65] | 0.403 |
| **Bifrontal slow waves** | 1.95 [0.9-4.2] | 0.090 | 1.86 [0.85-4.1] | 0.123 | 1.92 [0.88-4.21] | 0.104 |

**Supplementary Table 8. Adjusted hazard-ratios from the Cox proportional hazards estimates of outcomes at day 14 and 28 of T1 neurological assessment.**

Adjusted hazard-ratio were adjusted on non-neurologic SOFA and sedative and opioids infusion rates (left), or cumulative dose (middle) or sedative and opioids duration (right) at T1 assessment. CI : Confidence interval; HR : Hazard-ratio; sed./op.: sedatives/opioids; SOFA: Sequential organ failure assessment.