SUPPLEMENTAL DIGITAL CONTENT

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* eTable 1 (page 1), eTable 2 (page 2), eTable 3 (page 3), eTable 4 (page 4), and eTable 5 (page 5).

|  |  |
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| CHUV | BWH |
| At least two of | At least two of |
| * Lack of return of pupillary/corneal reflexes * Bilateral lack of cortical somatosensory evoked potentials * Highly malignant EEG, lack of background reactivity * Treatment-refractory early myoclonus/SE * (Serum neuron-specific enolase>75 µg/l) * (Diffuse DWI changes on MRI) | * Lack of return of pupillary/corneal reflexes * Highly-malignant EEG * Diffuse DWI changes on MRI * (Bilateral lack of cortical somatosensory evoked potentials) * (Serum neuron-specific enolase >75 µg/l) |

**eTable 1. Criteria of withdrawal of life-sustaining treatment at 72hrs or later after cardiac arrest, at the time of recruitment (in parenthesis, items used in unclear cases).**

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| eTable 2. Demographic and Clinical Characteristics of the CHUV registry. | | | | |
| Variable | **CHUV registry**  **(n = 499)**  average (± SD) or n (%) | **CPC 1-2**  **(n = 191, 38.3%)**  average (± SD) or n (%) | **CPC 3-5**  **(n = 308, 61.7%)**  average (± SD) or n (%) | ***p* Value** (test) |
| Age, years | 62.3 (± 15,1) | 61.0 (± 14.4) | 63.1 (± 15.5) | 0.136 (*t*) |
| Female sex | 146/499 (29.3) | 50/191 (26.2) | 96/308 (31.2) | 0.234 (*X2*) |
| Noncardiac etiology | 167/499 (33.5) | 30/191 (15.7) | 137/308 (44.5) | **<0.001** (*X2*) |
| Shockable rhythm (VF,VT) | 239/499 (47.9) | 141/191 (73.8) | 98/308 (31.8) | **<0.001** (*X2*) |
| Time to ROSC, min | 23.9 (± 18.1) | 18.7 (± 16.8) | 27.1 (± 18.1) | **<0.001** (*t*) |
| Electroencephalography |  |  |  |  |
| EEG1 latency, h | 19.7 (± 6.1) | 19.8 (± 5.4) | 19.7 (± 6.5) | 0.854 (*t*) |
| EEG1 reactive | 296/474 (62.4) | 174/185 (94.1) | 122/289 (42.2) | **<0.001** *(X2)* |
| EEG1 continuous | 185/474 (39.0) | 128/185 (69.2) | 57/289 (19.7) |  |
| EEG1 discontinuous | 117/474 (24.7) | 50/185 (27.0) | 67/289 (23.2) |  |
| EEG1 burst-suppressed | 132/474 (27.8) | 7/185 (3.8) | 125/289 (43.3) |  |
| EEG1 suppressed | 40/474 (8.4) | 0/185 (0.0) | 40/289 (13.8) | **<0.001** (*Fisher*) |
| EEG1 non-epileptiform | 401/474 (84.6) | 182/185 (98.4) | 219/289 (75.8) | **<0.001** (*X2*) |
| EEG1 missing values | 25/499 (5.0) | 6/191 (3.1) | 19/308 (6.2) | 0.132 (*X2*) |
| Westhall category EEG1*a* |  |  |  |  |
| - highly malignant | 177/474 (37.3) | 9/185 (4.9) | 168/289 (58.1) |  |
| - malignant | 150/474 (31.6) | 65/185 (35.1) | 85/289 (29.4) |  |
| - benign | 147/474 (31.0) | 111/185 (60.0) | 36/289 (12.5) | **<0.001** (*X2*) |
| EEG2 latency, h | 48.4 (± 10.52) | 47.2 (± 11.8) | 49.1 (± 9.7) | 0.074 (*t*) |
| EEG2 reactive | 287/425 (67.5) | 153/155 (98.7) | 134/270 (49.6) | **<0.001** (*X2*) |
| EEG2 continuous | 266/425 (62.6) | 143/155 (92.3) | 123/270 (45.6) |  |
| EEG2 discontinuous | 72/425 (16.9) | 11/155 (7.1) | 61/270 (22.6) |  |
| EEG2 burst-suppressed | 40/425 (9.4) | 1/155 (0.7) | 39/270 (14.4) |  |
| EEG2 suppressed | 47/425 (11.1) | 0/155 (0.0) | 47/270 (17.4) | **<0.001** (*Fisher*) |
| EEG2 non-irritative | 353/425 (83.1) | 149/155 (96.1) | 204/270 (75.6) | **<0.001** (*X2*) |
| EEG2 missing values | 74/499 (14.8) | 36/191 (18.9) | 38/308 (12.34) | **0.047** (*X2*) |
| Westhall category EEG2*a* |  |  |  |  |
| - highly malignant | 90/425 (21.2) | 4/155 (2.6) | 86/270 (31.9) |  |
| - malignant | 132/425 (31.1) | 25/155 (16.1) | 107/270 (39.6) |  |
| - benign | 203/425 (47.8) | 126/155 (81.3) | 77/270 (28.5) | **<0.001** (*Fisher*) |
| Presence of SSEP (at least unilateral) | 331/446 (74.2) | 163/164 (99.4) | 168/282 (59.6) | **<0.001** (*X*2) |
| Clinical examination |  |  |  |  |
| FOUR score ≥ 5*b* | 285/445 (64.0) | 154/166 (92.7) | 131/279 (47.0) | **<0.001** (*X2*) |
| Presence of all brainstem reflexes*c* | 301/489 (61.6) | 170/187 (90.9) | 131/302 (43.4) | **<0.001** (*X2*) |
| Pupillary light reflexes bilaterally present | 385/492 (78.3) | 184/189 (97.4) | 201/303 (66.3) | **<0.001** (*X2*) |
| Corneal reflexes bilaterally present | 330/491 (67.2) | 176/188 (93.6) | 154/303 (50.8) | **<0.001** (*X2*) |
| Motor Glasgow Coma Score ≥ 3 | 235/492 (47.8) | 149/188 (79.3) | 86/304 (28.3) | **<0.001** (*X2*) |
| Absence of myoclonus | 425/497 (85.6) | 187/189 (98.9) | 238/306 (77.8) | **<0.001** (*X2*) |
| Quantified pupillometry (only for 110 patients) |  |  |  |  |
| q-PLR max within 48h, % reactivity | 24.48 (± 9.63) | 30.51 (± 1.16) | 21.67 (± 1.09) | **<0.001** (*t*) |
| q-PLR min on within 48h, % reactivity | 5.82 (± 4.74) | 8.09 (± 0.80) | 4.76 (± 0.51) | **0.001** (*t*) |
| Biomarkers |  |  |  |  |
| Peak NSE on 48 hours, 42 mv | 68.18 (± 99.62) | 24.55 (± 12.02) | 95.51 (± 118.85) | **<0.001** (*t*) |
| Abbreviations: CPC = Cerebral Performance Category; FOUR = Full Outline of UnResponsiveness; mv = missing values; NSE = neuro-specific enolase; q-PLR = quantified pupillary light reflex; ROSC = return of spontaneous circulation; SSEP = somatosensory evoked potential; VF = ventricular fibrillation; VT = ventricular tachycardia. EEG1 = 12 – 36 hours from CA and EEG2 = 36 – 72 hours from CA (see patients management for details). *a*Westhall EEG categories: highly malignant (suppression, suppression with periodic discharges, burst-suppression), malignant (periodic or rhythmic patterns, pathological or nonreactive background), benign (absence of malignant features). *b*See statistics section for explanation of how the threshold ≥5 was determined. *c*Presence of all brainstem reflexes: pupillary (bilat.), corneal (bilat.) and oculocephalic. Bold values are significant. | | | | |

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| eTable 3. Predictors of functional independence (Cerebral Performance Categories 1-2) at 3 months. | | | | | | | | | | | |
|  |  | Distribution | | | | Favorable Outcome (CPC 1-2, functional independence) | | | | | |
| Variable | Tested Patients | TP | FP | FN | TN | Sensitivity (%) | 95% CI (%) | PPV (%) | 95% CI (%%) | Specificity (%) | 95% CI (%) |
| Age < 65 | 499 | 103 | 140 | 88 | 168 | 53.93 | 49.55 - 58.30 | 42.39 | 38.05 - 46.72 | 54.55 | 50.18 - 58.91 |
| Cardiac etiology | 499 | 161 | 171 | 30 | 137 | 84.29 | 81.10 - 87.49 | 48.49 | 44.11 - 52.88 | 44.48 | 40.12 - 48.84 |
| Shockable rhythm (VF, VT) | 499 | 141 | 98 | 50 | 210 | 73.82 | 69.96 - 77.68 | 59.00 | 54.68 - 63.31 | 68.18 | 60.10 - 72.27 |
| Time to ROSC ≤ 54 min.a | 499 | 183 | 281 | 8 | 27 | 95.81 | 94.05 - 97.57 | 39.44 | 35.15 - 43.73 | 8.77 | 6.28 - 11.25 |
| EEG1 reactive | **474** | **174** | **122** | **11** | **167** | **94.05** | **91.93 - 96.18** | **58.78** | **54.35 - 63.21** | **57.79** | **53.34 - 62.23** |
| EEG1 continuous | 474 | 128 | 57 | 57 | 232 | 69.19 | 65.03 - 73.55 | 69.19 | 65.03 - 73.35 | 80.28 | 76.69 - 83.86 |
| EEG1 non-irritative | 474 | 182 | 219 | 3 | 70 | 98.38 | 97.24 - 99.52 | 45.39 | 40.90 - 49.87 | 24.22 | 20.36 - 28.08 |
| EEG1 benign\* | 474 | 111 | 36 | 74 | 253 | 60.00 | 55.59 - 64.41 | 75.51 | 71.64 - 79.38 | 87.54 | 84.57 - 90.52 |
| EEG1 not highly malignant\* | **474** | **176** | **121** | **9** | **168** | **95.14** | **93.20 - 97.07** | **59.26** | **54.84 - 63.68** | **58.13** | **53.69 - 62.57** |
| EEG2 reactive | **425** | **153** | **134** | **2** | **136** | **98.71** | **97.64 - 99.78** | **53.31** | **48.57 - 58.05** | **50.37** | **45.62 - 55.12** |
| EEG2 continuous | **425** | **143** | **123** | **12** | **147** | **92.26** | **89.72 - 94.80** | **53.76** | **49.02 - 58.50** | **54.44** | **49.71 - 59.18** |
| EEG2 non-irritative | 425 | 149 | 204 | 6 | 66 | 96.13 | 94.30 - 97.96 | 42.21 | 37.51 - 46.91 | 24.44 | 20.36 - 28.53 |
| EEG2 benign\* | 425 | 126 | 77 | 29 | 193 | 81.29 | 77.58 - 85.00 | 62.07 | 57.46 - 66.68 | 71.48 | 67.19 - 75.77 |
| EEG2 not highly malignant\* | 425 | 151 | 184 | 4 | 86 | 97.42 | 95.91 - 98.93 | 45.07 | 40.34 - 49.81 | 31.85 | 27.42 - 36.28 |
| Presence of all brainstem reflexesc | **489** | **187** | **131** | **17** | **171** | **90.91** | **88.36 - 93.46** | **56.48** | **52.08 - 60.87** | **56.62** | **52.23 - 61.02** |
| Presence of clinical pupillary reflexes | 492 | 184 | 201 | 5 | 102 | 97.35 | 95.94 - 98.77 | 47.79 | 43.38 - 52.21 | 33.66 | 29.49 - 37.84 |
| Presence of corneal reflexes | 491 | 176 | 154 | 12 | 149 | 93.62 | 91.45 - 95.78 | 53.33 | 48.92 - 57.75 | 49.17 | 44.75 - 53.60 |
| FOUR score ≥ 5a | **445** | **154** | **131** | **12** | **148** | **92.77** | **90.36 - 95.18** | **54.04** | **49.40 - 58.67** | **53.05** | **48.41 - 57.68** |
| Motor Glasgow Coma Score ≥ 3 | 492 | 149 | 86 | 39 | 218 | 79.26 | 75.67 - 82.84 | 63.40 | 59.15 - 67.66 | 71.71 | 67.73 - 75.69 |
| Absence of myoclonus | 495 | 187 | 238 | 2 | 68 | 98.94 | 98.04 - 99.84 | 44.00 | 39.63 - 48.37 | 22.22 | 18.56 - 25.88 |
| q-PLRmax on 48h  ≥ 21%a | 110 | 35 | 48 | 0 | 27 | 100.00 | 100.00 - 100.00 | 42.17 | 32.94 - 51.40 | 36.00 | 27.03 - 44.97 |
| q-PLRmin on 48h ≥ 2%a | 110 | 35 | 58 | 0 | 17 | 100.00 | 100.00 - 100.00 | 37.63 | 28.58 - 46.69 | 22.67 | 14.84 - 30.49 |
| Presence of SSEP (min. on 1 side) | 446 | 163 | 168 | 1 | 114 | 99.39 | 98.67 - 100.11 | 49.24 | 44.60 - 53.88 | 40.43 | 35.87 - 44.98 |
| Peak NSE on 48h ≤ 41 µg/La | **457** | **161** | **117** | **15** | **164** | **91.48** | **88.92 - 94.04** | **57.91** | **53.39 - 62.44** | **58.36** | **53.84 - 62.99** |
| NSE day 2 < NSE day 1 | 371 | 102 | 80 | 38 | 151 | 72.86 | 68.33 - 77.38 | 56.04 | 50.99 - 61.09 | 65.37 | 60.53 - 70.21 |
| NSE < 17 µg/Lb | 457 | 52 | 13 | 124 | 268 | 29.55 | 25.36 - 33.73 | 80.00 | 76.33 - 83.67 | 95.37 | 93.43 - 97.30 |
| Abbreviations: CPC = Cerebral Performance Category; EEG = electroencephalography, EEG1 = 12 – 36 hrs from CA and EEG2 = 36 – 72 hours from CA; FOUR = Full Outline of UnResponsiveness; NSE = neuron-specific enolase; PPV = positive predictive value; q-PLR = quantitative pupillometry; ROSC = return of spontaneous circulation; SSEP = somatosensory evoked potential; TP = true positive, FP = false positive, FN = false negative, TN = true negative; VF = ventricular fibrillation; VT = ventricular tachycardia. \*Please see text or table 1 for details on EEG Westhall categories. a Thresholds were selected through receiver operating characteristic (ROC) analysis to have a sensibility ≥ 90% with best specificity regarding to CPC 1-2. b NSE normal range according to the literature. c All brainstem reflexes: pupillary (bilat.), corneal (bilat.) and oculocephalic. Favorable outcome indicators offering a sensitivity ≥ 90% and a specificity ≥ 50% are given in bold. | | | | | | | | | | | |

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| eTable 4. Performance of the multimodal score to predict survival with contact to the environment (Cerebral Performance Categories 1-3) at 3 months, A. CHUV cohort (n = 346\*), and B. BWH cohort (n\* = 36). | | | |
| 1. CHUV | **Good Outcome CPC 1-3** | | |
| Score | Sensitivity (95% CI) | Specificity (95% CI) | Accuracy (95% CI) |
| ≥ 1/6 | 100.00 (97.87 - 100.00) | 29.14 (24.35 - 33.93) | 65.21 (59.93 - 70.22) |
| ≥ 2/6 | 100.00 (97.87 - 100.00) | 53.71 (46.03 - 61.27) | 77.27 (72.49 - 81.58) |
| ≥ 3/6 | **98.25 (94.96 - 99.64)** | **71.43 (64.12 - 77.99)** | **85.08 (80.88 - 88.66)** |
| ≥ 4/6 | 93.57 (88.78 - 96.75) | 79.43 (72.68 - 85.16) | 86.63 (82.58 - 90.03) |
| ≥ 5/6 | 85.96 (79.84 - 90.80) | 87.43 (81.59 - 91.95) | 86.68 (82.64 - 90.08) |
| 6/6 | 59.65 (51.89 - 67.07)) | 91.43 (86.26 - 95.12) | 75.25 (70.36 - 79.71) |
| 1. BWH | **Good Outcome CPC 1-3** | | |
| Score | Sensitivity (95% CI) | Specificity (95% CI) | Accuracy (95% CI) |
| ≥ 1/6 | 100.00 (66.37 - 100.00) | 18.52 (6.30 - 38.08) | 34.81 (19.76 - 52.47) |
| ≥ 2/6 | 100.00 (66.37 - 100.00) | 59.26 (38.80 - 77.61) | 67.41 (49.79 - 82.04) |
| ≥ 3/6 | **100.00 (66.37 - 100.00)** | **81.48 (61.92 - 93.70)** | **85.19 (69.39 - 94.78)** |
| ≥ 4/6 | 77.78 (39.99 - 97.19) | 85.19 (66.27 - 95.81) | 83.70 (67.62 - 93.86) |
| ≥ 5/6 | 55.56 (21.20 - 86.30) | 92.59 (75.71 - 99.09) | 85.19 (69.39 -94.78) |
| 6/6 | 22.22 (2.81 - 60.01) | 96.30 (81.03 - 99.91) | 81.48 (65.04 - 92.42) |
| Score made with 6 variables: not highly malignant Westhall category EEG1, EEG1 reactivity; EEG2 reactivity; EEG2 continuity; FOUR score ≥ 5; peak NSE on 48h ≤ 41 µg/l. Patients received 1 point for each positive element. Please see text for selection criteria of score items. \*346 of the 499 patients in CHUV registry (and 36 of the 50 patients in BWH registry) had data for each of the 6 score items. Score performance analysis on CHUV registry (up) and its external validation on BWH registry (down). Best score cut-offs are given in bold. | | | |

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| eTable 5.  A. Performance of the multimodal score to predict favorable neurological outcome (Cerebral Performance Categories 1-2) at 3 months on patients sedated with midazolam only (n = 83\*), CHUV cohort. | | | |
| Score | **Good Outcome CPC 1-2** | | |
| Sensitivity (95% CI) | Specificity (95% CI) | Accuracy (95% CI) |
| ≥ 1/6 | 100.0 (85.2 – 100.0) | 21.7 (12.1 – 34.2) | 43.4 (32.5 – 54.7) |
| ≥ 2/6 | 100.0 (85.2 – 100.0) | 33.3 (21.7 – 46.7) | 51.8 (40.6 – 62.9) |
| ≥ 3/6 | 100.0 (85.2 – 100.0) | 55.0 (41.6 – 67.9) | 67.4 (56.3 – 77.4) |
| ≥ 4/6 | **95.7 (78.1 – 99.9)** | **65.0 (51.6 – 76.9)** | **73.5 (62.7 – 82.6)** |
| ≥ 5/6 | 82.6 (61.2 – 95.0) | 80.0 (67.7 – 89.2) | 80.7 (70.6 – 88.7) |
| 6/6 | 43.5 (23.2 – 65.5) | 88.3 (77.4 – 95.2) | * 1. (65.3 – 84.6) |
| \* 83 patients in CHUV cohort, with data for each of the score variables, received only midazolam as a sedation; sedation assessed at the time of EEG1. | | | |

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| B. Performance of the multimodal score to predict favorable neurological outcome (Cerebral Performance Categories 1-2) at 3 months on patients sedated with propofol only (n = 137\*), CHUV cohort. | | | |
| Score | **Good Outcome CPC 1-2** | | |
| Sensitivity (95% CI) | Specificity (95% CI) | Accuracy (95% CI) |
| ≥ 1/6 | 100.0 (93.0 – 100.0) | 25.6 (16.8 – 36.1) | 53.3 (44.6 – 61.9) |
| ≥ 2/6 | 100.0 (93.0 – 100.0) | 45.3 (34.6 – 56.5) | 65.7 (57.1 – 73.6) |
| ≥ 3/6 | 100.0 (93.0 – 100.0) | 53.5 (42.4 – 64.3) | 70.8 (62.4 – 78.3) |
| ≥ 4/6 | **98.0 (89.6 – 100.0)** | **60.5 (49.3 – 70.8)** | **74.5 (66.3 – 81.5)** |
| ≥ 5/6 | 96.1 (86.5 – 99.5) | 66.3 (55.3 – 76.1) | 77.4 (69.5 – 84.1) |
| 6/6 | 80.4 (66.9 – 90.2) | 79.1 (69.0 – 87.1) | 79.6 (71.8 – 86.0) |
| \* 137 patients in CHUV cohort, with data for each of the score variables, received only propofol as a sedation; sedation assessed at the time of EEG1. | | | |