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Review article

# Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia☆

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## Cerebral Performance Categories Scale

### CPC Scale

| |
|---|
| Note: If patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate scores. |
| **CPC 1.** Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit. |
| **CPC 2.** Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment. |
| **CPC 3.** Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis. |
| **CPC 4.** Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness. |
| **CPC 5.** Brain death: apnea, areflexia, EEG silence, etc. |

Safar P. Resuscitation after Brain Ischemia, in Grenvik A and Safar P Eds: Brain Failure and Resuscitation, Churchill Livingstone, New York, 1981; 155-184.

## Introduction

- Mortality after resuscitation from cardiac ar… ment)
- A…
- C…

1. Myoclonus status epilepticus on day 1
2. Bilateral absence of the N20 wave of somatosensory evoked potentials (SSEPs)
3. Blood concentration of neuron specific enolase (NSE) above 33 mcg/L at days 1–3
4. Absent pupillary and corneal reflexes or a motor response no better than extension (M1 -2) at day 3.

…on

## Materials and methods

- **PICOS**
- **P:**In adult patients who are comatose following resuscitation from cardiac arrest and who have been treated with TH.
- **I:**Predictors based on clinical examination, electro-physiology, serum biomarkers or neuro-imaging (within 7 days)
- **O:**Allow accurate prediction of poor outcome ? (CPC by dichotomized)

- **S:**Given the review question, the only eligible study design
- **C:** observational prognostic accuracy study in which a comparison is made between the respective proportions of poor outcome among the patients having a positive test result and those having a negative test result.

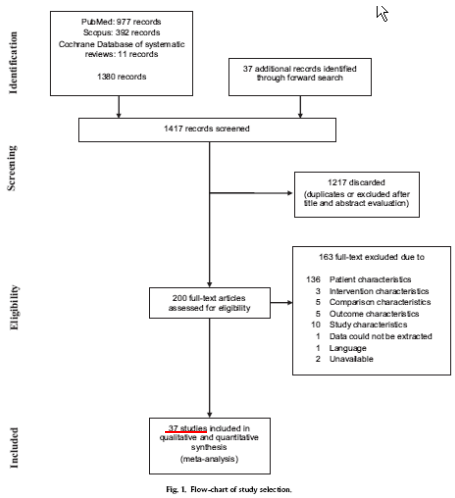


Fig. 1. Flow-chart of study selection.

Table 1
Characteristics of the included studies.

CPC4~5: 11
CPC3~5:26

| Author, year reference | IHCA or OHCA | No. of patients | Males, % | VF/VT % | Mean age, years [±SD] or median (range) | Definition of poor outcome (CPC) | Timing of outcome assessment |
|---|---|---|---|---|---|---|---|
| *Clinical examination* | | | | | | | |
| Al Thenayan, 2008[53] | N/A | 37 | N/A | N/A | N/A[a] | PLR, CR, MR | 3–5 vs. 1–3 | 3 mo |
| Bouwes, 2012a[40,b] | Mixed | 79 | 73 | 66 | 67 [±13] | Myoclonus | 3–5 vs. 1–2 | 6 mo |
| Okada, 2012[17] | OHCA | 66 | 80 | 79 | 59 | PLR, MR | 3–5 vs. 1–2 | Hospital discharge |
| Schefold, 2009[18] | Mixed | 72 | 75 | 68 | 58 (47–68) | GCS | 3–5 vs. 1–2 | ICU discharge |
| *Electrophysiology* | | | | | | | |
| Bouwes, 2009[39] | N/A | 77 | 71.4 | 66.2 | 65 (50–77) | N20 | 4–5 vs. 1–3 | 1 mo |
| Choosterman, 2012[20] | Mixed | 56 | 68 | 73 | 68 [± 11.5] | EEG, N20 | 3–5 vs. 1–2 | 6 mo |
| Kawai, 2011[21] | Mixed | 26 | 53.8 | 38.5 | 60 [±17.5] | EEG | 4–5 vs. 1–3 | 6 mo |
| Leary, 2010[22] | Mixed | 62 | 58.1 | 40.3 | 55 [±16] | BIS | 3–5 vs. 1–2 | Hospital discharge |
| Leithner, 2010[23] | N/A | 112 | 67.9 | 64.3 | 62 | N20 | 4–5 vs. 1–3 | Hospital discharge |
| Mani, 2012[24] | N/A | 38 | 52.6 | 44 | 50 (45–65) | cEEG | 3–5 vs. 1–2 | Hospital discharge |
| Oh, 2012[25] | N/A | 55 | 60 | 36.4 | 50 [±17] | aEEG | 3–5 vs. 1–2 | Hospital discharge |
| Rittenberger, 2012[26] | Mixed | 101 | 54.5 | 71.3 | 57 [±15] | EEG | 3–5 vs. 1–2 | Hospital discharge |
| Rundgren, 2010[27] | Mixed | 95 | 71.6 | 73.8 | 65 (50–74) | aEEG | 4–5 vs. 1–3 | 6 mo |
| Sakurai, 2006[28] | OHCA | 26 | 76.9 | 42.3 | (22–68) | BAEPs | 3–5 vs. 1–2 | 2 mo |
| Seder, 2010[29] | N/A | 82 | 65.9 | 87.8 | 62 (48–72) | BIS, SR | 3–5 vs. 1–2 | Hospital discharge |
| Stammet, 2000[30] | Mixed | 45 | 68.7 | 49 | 56 [±17] | BIS | 3–5 vs. 1–2 | 6 mo |
| Tiainen, 2005[31] | OHCA | 30 | 86.7 | 100 | 60 (23–75) | N20 | 4–5 vs. 1–3 | 6 mo |
| Zanatta, 2012[32] | N/A | 11 | 58.6 | 88.2 | 60 [±13] | EEG, N20 | 3–5 vs. 1–2 | 3 mo |
| *Biomarkers* | | | | | | | |
| Meeuwsen, 2011[33] | Mixed | 11 | 68 | 51.6 | 62 (22–84) | S-100, NSE | 3–5 vs. 1–2 | 6 mo |
| Oksanen, 2009[34] | OHCA | 90 | 79 | 100 | 63 (53–71) | NSE | 3–5 vs. 1–2 | 6 mo |
| Steffen, 2010[35] | Mixed | 97 | 78.4 | 67 | 60 (52–70) | NSE | 3–5 vs. 1–2 | ICU discharge |
| Storm, 2012[36] | Mixed | 25 | 66 | 42.8 | 62 (51–71) | NSE | 3–5 vs. 1–2 | ICU discharge |
| Tiainen, 2003[37] | OHCA | 26 | 89 | 100 | 60 (23–75) | NSE, S-100B | 3–5 vs. 1–2 | 6 mo |
| *Neuroimaging* | | | | | | | |
| Mlynash, 2010[38] | Mixed | 21 | N/A | N/A | 57 [±17] | MRI | 4–5 vs. 1–3 | 6 mo |
| Wijman, 2009[39] | Mixed | 22 | N/A | N/A | 59 [±17] | MRI | 4–5 vs. 1–3 | 6 mo |
| *Multimodal neuroprognostication* | | | | | | | |
| Bisschops, 2011[40] | N/A | 103 | 73.8 | 70 | 63 (53.8–76) | PLR, MR, myoclonus, SSEP, EEG | 3–5 vs. 1–2 | 3 mo |
| Bouwes, 2012b[41] | Mixed | 393 | 73.1 | 76 | 64 [±13.4] | PLR, CR, MR, NSE, SSEP | 3–5 vs. 1–2 | 6 mo |
| Choi, 2012[42] | OHCA | 19 | 36.8 | 0 | 48 [±13.3] | MRI, SSEP | 3–5 vs. 1–2 | Hospital discharge |
| Crepeau, 2013[43] | OHCA | 54 | 63 | N/A | 61 (33–81) | Myoclonus, cEEG | 3–5 vs. 1–2 | Hospital discharge |
| Cronberg, 2011[44] | Mixed | 24 | 65 | 53 | 71 (51–76) | PLR, CR, NSE, SSEP, EEG, MRI | 4–5 vs. 1–3 | 6 mo |
| Kim, 2012[45] | OHCA | 43 | 67.4 | 32.6 | 57 [±17.6] | NSE, MRI | 3–5 vs. 1–2 | 6 mo |
| Legriel, 2013[46] | Mixed | 106 | 69.8 | 51 | 65 (54–75) | Myoclonus, SE | 3–5 vs. 1–2 | 12 mo |
| Rossetti, 2010[47] | OHCA | 111 | 80.2 | 50.5 | 59 (17–85) | BR MR, myoclonus, EEG, SSEP | 3–5 vs. 1–2 | 6 mo |
| Rossetti, 2012[48] | N/A | 61 | 70.5 | 65.6 | 63.7 [±12.2] | BR MR, myoclonus, EEG, N20, NSE | 3–5 vs. 1–2 | 3 mo |
| Samaniego, 2011[49] | Mixed | 53 | 73.5 | 62 | 58 (19–84) | PLR, CR, MR, myoclonus, NSE, SSEP | 4–5 vs. 1–3 | 3 mo |
| Stammet, 2013[50] | Mixed | 75 | 76 | 65.3 | 65 (29–83) | BIS, S-100B | 3–5 vs. 1–2 | 6 mo |
| Wennervirta, 2009[51] | OHCA | 30 | 80 | 100 | 57 (24–77) | NSE, EEG | 3–5 vs. 1–2 | 6 mo |

1.Brainstem reflexes
2.Motor response
3.Myoclonus

clinical examination

| Timing | Index | Cutoff | Reference | Sensitivity % [95% CI] | FPR % [95% CI] | No. of patients | Quality of evidence |
|---|---|---|---|---|---|---|---|
| | | | | | 0 [0–15] | 44 | Very low |
| | | | | | PPV 86 [57–98] | 14 | Very low |
| | | | | | PPV 100 [61–100] | 6 | Very low |
| | | | | | PPV 100 [61–100] | 6 | Very low |
| | | | | | PPV 100 [69–100] | 8 | Very low |
| | | | Cronberg, 2011[44] | | 12 [3–31] | 78 | Very low |
| | Absent PLR | | Samaniego, 2011[49] | 17 [8–30] | 0 [0–13] | 74 | Very low |
| | Absent CR | | Cronberg, 2011[44] Samaniego, 2011[49] Cronberg, 2011[44] | 27 [15–41] | 5 [0–25] | 69 | Very low |
| CPC 1–5 vs. 1–2 | | | | | | | |
| On admission | Absent PLR | | Okada, 2012[17] Choi, 2012[42] | 86 [71–95] | 32 [19–48] | 86 | Very low |
| | M ≤ 2 | | Okada, 2012[17] | 92 [75–99] | 53 [36–68] | 66 | Very low |
| At 36–72 h | ≥1 BR absent[a] | | Rossetti, 2010[48] Rossetti, 2012[47] | 56 [47–66] | 9 [3–21] | 170 | Very low |
| | M ≤ 2 | | Rossetti, 2010[48] Rossetti, 2012[47] | 75 [66–83] | 11 [4–23] | 170 | Very low |
| ≤72 h | Myoclonus or status myoclonus | | Bouwes, 2012[41] Crepeau, 2013[43] Legriel, 2013[46] Rittenberger, 2012[26] Rossetti, 2010[48] Rossetti, 2012[47] | 37 [23–41] | 5 [3–9] | 812 | Very low |
| At 72 h | Absent PLR | | Bouwes, 2012[41] Choi, 2012[42] | 20 [13–28] | 1 [0–7] | 207 | Very low |
| | Absent CR | | Bouwes, 2012[41] | 26 [17–37] | 4 [1–14] | 130 | Very low |
| | M ≤ 2 | | Bouwes, 2012[41] Bisschops, 2011[40] | 60 [53–67] | 11 [7–16] | 387 | Very low |
| | M ≤ 2 or no PLR or no CR | | Bisschops, 2011[40] | 81 [69–89] | 11 [3–26] | 103 | Very low |
| | M ≤ 2 and no PLR and no CR | | Bisschops, 2011[40] | 15 [7–26] | 0 [0–8] | 103 | Very low |
| At 96 h | GCS ≤ 4 | | Schefold, 2009[18] | 46 [28–66] | 5 [1–15] | 72 | Very low |
| At <7 days | Myoclonus | | Bisschops, 2011[40] | 54 [41–66] | 11 [3–26] | 103 | Very low |

Table 2b
GRADE summary of findings for predictors based on electrophysiology.

Electrophysiology
1.Burst-suppression
2.Seizures and status epilepticus
3. Flat or low-amplitude EEG
4. Nonreactive EEG
5. EEG grading

| Timing | Index | Reference | Sensitivity % [95% CI] | FPR % [95% CI] | No. of patients | Quality of evidence |
|---|---|---|---|---|---|---|
| CPC 4–5 vs. 1–3 | | | | | | |
| During TH | EEG: Burst-suppression | Rundgren, 2010[27] | 37 [22–54] | 0 [0–15] | 44 | Very low |
| | EEG: Flat <10 μV | Rundgren, 2010[27] | 55 [38–71] | 0 [0–15] | 44 | Very low |
| After RW | EEG: Flat <10 μV[a] | Rundgren, 2010[27] | 10 [6–31] | 5 [1–15] | 95 | Very low |
| | EEG: Burst-suppression | Rundgren, 2010[27] | 18 [8–34] | 0 [0–5] | 95 | Very low |
| | SSEP: Bilaterally absent N20 | Choi, 2012[42] Cronberg, 2011[44] Leithner, 2010[23] Samaniego, 2011[49] | 63 [53–72] | 2 [0–8] | 180 | Very low |
| Any time | aEEG: CAEE | Rundgren, 2010[27] | 21 [10–37] | 0 [0–5] | 95 | Very low |
| | aEEG: SB-ESE | Rundgren, 2010[27] | 42 [26–59] | 0 [0–5] | 95 | Very low |
| CPC 3–5 vs. 1–2 | | | | | | |
| During TH induction | BAEP: Absence of wave V | Sakurai, 2006[28] | 56 [31–78] | 0 [0–31] | 26 | Very low |
| During TH | EEG: Burst-suppression | Choosterman, 2012[20] Kawai, 2011[21] Rossetti, 2012[47] | 35 [43–67] | 5 [1–14] | 133 | Very low |
| | EEG: BSR ≥ 21:60 | Wennervirta, 2009[51] | 11 [0–48] | 0 [0–13] | 30 | Very low |
| | EEG: Flat or low-voltage[a] | Choosterman, 2012[20] | 40 [19–64] | 0 [0–11] | 40 | Low |
| | EEG: Epileptiform discharges | Mani, 2012[24] | 62 [45–80] | 9 [0–19] | 39 | Very low |
| | EEG: Electrographic seizures | Mani, 2012[24] Rossetti, 2012[47] | 35 [17–56] | 0 [0–22] | 38 | Very low |
| | EEG: Status epilepticus | | 30 [16–49] | 0 [0–10] | 83 | Very low |
| | EEG: Nonreactive background | Rossetti, 2012[47] Crepeau, 2013[43] | 43 [30–55] | 5 [1–25] | 198 | Very low |
| | EEG: Grade 3 EEG[a] | Crepeau, 2013[43] | 76 [53–92] | 4 [1–20] | 54 | Very low |
| | BIS: ≤ 21:60 | Stammet, 2000[30] | 86 [71–95] | 10 [3–29] | 62 | Very low |
| | BIS: > 30 | Leary, 2010[22] | 40 [26–57] | 0 [0–25] | 62 | Very low |
| | BIS: ≤ 22 | Seder, 2010[29] | 86 [73–94] | 6 [1–20] | 83 | Very low |
| | BIS: ≤ 6 | Seder, 2010[29] | 49 [37–60] | 0 [0–4] | 128 | Low |
| | SSEP: N20 ≤ 48 | Stammet, 2000[30] | 84 [71–93] | 6 [1–20] | 83 | Very low |
| | SSEP: Bilaterally absent N20 | Bouwes, 2012[41] Choosterman, 2012[20] Tiainen, 2005[31] | 28 [22–34] | 0 [0–2] | 421 | Moderate |
| After RW | EEG: Epileptiform activity[a] | Rossetti, 2010[48] | 43 [33–55] | 12 [3–31] | 108 | Very low |
| | EEG: Status epilepticus | Wennervirta, 2009[51] | 44 [14–79] | 0 [0–13] | 30 | Low |
| | EEG: Burst-suppression background | Crepeau, 2013[43] | 62 [53–70] | 0 [0–3] | 223 | Low |
| | EEG: Grade 3 EEG[a] | Rossetti, 2010[48] Rossetti, 2012[47] | | | | |
| | SSEP: Bilaterally absent N20 | Crepeau, 2013[43] Bisschops, 2011[40] Bouwes, 2012[41] Rossetti, 2010[48] Rossetti, 2012[47] Zanatta, 2012[32] | 89 [65–99] 42 [26–48] | 0 [0–9] 0 [0–4] | 51 339 | Low Low |
| | MLCEPs: MLCEPs absent | Zanatta, 2012[32] | 88 [47–100] | 0 [0–63] | 11 | Very low |
| Any time | EEG: Burst-suppression[a] | Oh, 2012[25] | 63 [42–81] | 4 [0–18] | 55 | Very low |
| | EEG: Electrographic seizures | Crepeau, 2013[43] | 24 [8–47] | 0 [0–9] | 54 | Very low |
| | EEG: Status epilepticus | Rittenberger, 2012[26] | 12 [6–20] | 0 [0–78] | 101 | Very low |
| | EEG: No continuous normal voltage | Oh, 2012[25] | 78 [58–91] | 0 [0–10] | 55 | Very low |
| | EEG: Nonreactive background[a] | Crepeau, 2013[43] | 52 [30–74] | 6 [1–20] | 54 | Very low |
| | BIS: <5.5[a] | Stammet, 2013[50] | 65 [69–95] | 17 [7–32] | 75 | Very low |

Biomarker
1.NSE:neuron specific enloase
2.S-100B

Table 2c
GRADE summary of findings for predictors based on biomarkers.

| Timing | Index | Cutoff (μg l⁻¹) | Reference | Sensitivity % [95% CI] | FPR% [95% CI] | No. of patients | Quality of evidence |
|---|---|---|---|---|---|---|---|
| CPC 4–5 vs. 1–3 | | | | | | | |
| At 48 h | NSE | 33.0 | Cronberg, 2011[44] | 61 [41–79] | 0 [0–39] | 34 | Very low |
| CPC 3–5 vs. 1–2 | | | | | | | |
| At ROSC | NSE | 41.5 | Kim, 2012[45] | 32 [15–53] | 0 [0–29] | 35 | Very low |
| At 12 h | NSE | 33.0 | Bouwes, 2012[41] | 32 [25–39] | 10 [6–15] | 358 | Very low |
| At 24 h | NSE | 31.2 | Tiainen, 2003[37] | 20 [3–56] | 4 [0–20] | 35 | Very low |
| | | 41.0 | Oksanen, 2009[34] | 18 [8–34] | 4 [0–14] | 89 | Very low |
| | | 49.6 | Kim, 2012[45] | 80 [59–93] | 0 [0–29] | 34 | Very low |
| | | 52.4 | Wennervirta, 2009[51] | 10 [0–45] | 0 [0–14] | 30 | Very low |
| | S-100B | 0.18–0.21 | Moriberg, 2011[50] Tiainen, 2003[37] | 65 [44–83] | 0 [0–7] | 66 | Very low |
| At 24–48 h | NSE | 33.0 | Bouwes, 2012[41] Rossetti, 2012[47] | 50 [43–57] | 9 [5–14] | 395 | Very low |
| At 48 h | NSE | 4.97 | Moriberg, 2011[50] | 50 [25–75] | 7 [0–32] | 31 | Very low |
| | | 25.0 | Tiainen, 2003[37] | 22 [3–60] | 0 [0–12] | 33 | Very low |
| | | 33.0 | Bouwes, 2012[41] Oksanen, 2009[34] | 53 [46–60] | 6 [3–10] | 397 | Very low |
| | | 44.3 | Kim, 2012[45] | 86 [64–97] | 0 [0–34] | 29 | Very low |
| | | 54.5–59.3 | Bouwes, 2012[41] Storm, 2012[36] Wennervirta, 2009[51] | 30 [24–37] | 6 [3–11] | 373 | Very low |
| | | 81.8 | Bouwes, 2012[41] | 18 [13–25] | 0 [0–2] | 310 | Moderate |
| | S-100B | 0.23 | Tiainen, 2003[37] | 22 [3–60] | 4 [0–20] | 34 | Very low |
| | | 0.30 | Stammet, 2013[50] | 21 [9–38] | 0 [0–7] | 75 | Very low |
| At ≤72 h | NSE | 33.0 | Samaniego, 2011[49] | 75 [53–90] | 22 [6–48] | 42 | Very low |
| | | 57.2 | Storm, 2012[36] | 46 [26–67] | 0 [0–28] | 33 | Very low |
| | | 78.9 | Steffen, 2010[35] | 48 [32–63] | 0 [0–6] | 97 | Very low |

Imaging

Table 2d
GRADE summary of findings for predictors based on imaging.

| Timing | | Index | Reference | Sensitivity % [95% CI] | FPR % [95% CI] | No. of patients | Quality of evidence |
|---|---|---|---|---|---|---|---|
| CPC 4–5 vs. 1–3 | | | | | | | |
| Median 80 h (IQR 55–117) | MRI DWI or FLAIR | Extensive cortical lesion pattern | Mlynash, 2010[38] | 90 [55–100] | 9 [0–41] | 21 | Very low |
| | | Abnormalities in basal ganglia | Mlynash, 2010[38] | 80 [44–97] | 9 [0–41] | 21 | Very low |
| | | Abnormalities in brainstem | Mlynash, 2010[38] | 30 [7–65] | 0 [0–24] | 21 | Very low |
| At 49–108 h | MRI DWI (ADC) | ADC < 650 × $10^{-6}$ $mm^2/s$ in >10% of brain volume | Wijman, 2009[39] | 77 [46–95] | 0 [0–28] | 22 | Very low |
| CPC 3–5 vs. 1–2 | | | | | | | |
| On admission | CT | Lost grey/white matter interface (CT) | Choi, 2012[42] | 100 [55–100] | 0 [0–63] | 8 | Very low |
| Median 46 h (IQR 37–52) | MRI | ADC occipital cortex < 616 × $10^{-6}$ $mm^2/s$ | Kim, 2012[45] | 91 [75–98] | 0 [0–24] | 43 | Very low |
| Median 74 h (IQR 61–86) | MRI DWI | Abnormalities in both cortex and basal ganglia | Cronberg, 2011[44] | 58 [33–80] | 0 [0–63] | 22 | Very low |
| At <5 days | MRI DWI | Abnormalities in both cortex and basal ganglia | Choi, 2012[42] | 100 [55–100] | 0 [0–63] | 8 | Very low |

Predictors

Table 3
Predictors of poor outcome with 0% FPR and upper 95% CI limit <10% (for comments see text).

| Timing | Index | Sensitivity % [95% CI] | FPR % [95% CI] | LR+ [95% CI] | No. of patients with positive test | No. of studies | Used in WLST | Quality of evidence | |
|---|---|---|---|---|---|---|---|---|---|
| CPC 4–5 vs. 1–3 | | | | | | | | | |
| During TH | Burst-suppression | 37 [22–54] | 0 [0–5] | 42 [3–678] | 14 | 1 | No | Low | 27 |
| After RW | Burst-suppression | 18 [8–34] | 0 [0–5] | 22 [1–379] | 7 | 1 | No | Low | 27 |
| Any time | SB-ESE[a] | 42 [26–59] | 0 [0–5] | 49 [3–794] | 16 | 1 | No | Low | 27 |
| CPC 3–5 vs. 1–2 | | | | | | | | | |
| During TH | Bilaterally absent N20 | 28 [22–34] | 0 [0–2] | 13 [5–32] | 63 | 4 | Yes (2/4) | Moderate | 19,20,31,41 |
| During TH (at 24 h) | S-100B ≥ 0.18–0.21 mcg/L | 65 [44–83] | 0 [0–7] | 22 [3–156] | 17 | 2 | N/A | Very low | 33,37 |
| After RW | Bilaterally absent N20[b] | 42 [36–48] | 0 [0–4] | 15 [5–44] | 109 | 5 | Yes (4/5)[c] | Low | 32,40,41,47,48 |
| After RW | Nonreactive background | 62 [53–70] | 0 [0–3] | 33 [7–163] | 76 | 3 | Yes (1/3) | Low | 43,47,48 |
| After RW (at 48 h) | NSE ≥ 81.8 μg l⁻¹ | 18 [13–25] | 0 [0–2] | 56 [3–909] | 29 | 1 | No | Moderate | 41 |
| | S-100B > 0.3 μg l⁻¹ | 21 [9–38] | 0 [0–7] | 18 [1–304] | 7 | 1 | N/A | Very low | 50 |
| After RW (at 72 h) | NSE ≥ 78.9 μg l⁻¹ M ≤ 2 and no PLR and no CR | 48 [32–63] 15 [7–26] | 0 [0–6] 0 [0–8] | 52 [3–828] 11 [1–190] | 21 10 | 1 1 | Yes Yes | Very low Very low | 35 40 |

# Discussion

- Clinical examination
  - Brainstem reflexes and motor response
    1. Still affected by sedation.
    2. hypothermia reduces drug clearance.
    3. absence of PLR after rewarming was the **most accurate** predictor.
    4. CR and motor response **were less reliable** predictors , be likely to be affected by the residual effects of neuromuscular blocking drugs.
  - Myoclonus
    1. Clinical and electrophysiological characteristics of myoclonus varied widely
    2. no specific definition

- Electrophysiology
  - EEG is prone to interference from **both sedation and hypothermia** itself in patients treated with TH after cardiac arrest.
  - Predictive value of EEG can be influenced **by timing of recording.**
  - Burst suppression
    1. In patients with favourable outcome,burst suppression may **occur during TH as a transient pattern** , which usually disappears shortly after rewarming.
    2. The definition of burst-suppression was inconsistent among studies.

  - Low-amplitude or flat EEG
    1. Low EEG amplitudecan be observed in the first hours after resuscitation .
    2. The presence of a flat or low-amplitude EEG during TH or after rewarming is not consistently associated to a poor out-come. Its predictive value may be affected by factors like timing of recording and interference from sedatives and body temperature.
  - Epileptiform activity and status epilepticus
    1. Spikes, polyspikes or sharp waves / independently and randomly or periodically.
    2. A prolonged (>30 min) continuous or recurrent series of electrographic seizures :electrographic status epilepticus (ESE)
    3. invariably associated to poor outcome .

  - EEG reactivity
    1.tactile or nociceptive stimulation, auditory stimuli(clapping, voice sounds) or eye opening.
    2. Absence of EEG reactivity both during TH and after rewarming predicted poor outcome with 100% specificity in two studies from the same group.
  - N20 SSEP wave
    1. absenceof N20 SSEP wave was the one most commonly used for treatment decisions.

- Biomarkers
  - important theoretical advantages.
  - independence from the effects of sedative drugs.
  - NSE values are markedly increased in the presence of haemolysis because red blood cells contain NSE.
  - S-100B is contained in muscle and adipose tissue.
  - increased by a thoracic trauma caused by prolonged CPR.
- Imaging
  - CT finding/ MRI / ADC (absolute diffusion coefficient)
  - diffuse brain cytotoxic oedema

- Self-fulfilling prophecy
  - Prevention of self-fulfilling prophecy bias would require blind-ing of test results to the treating team and providing sufficiently prolonged life support in patients who do not recover conscious-ness after resuscitation and rewarming.
  - indefinite supportive care in potentially hopeless patients raises both ethical and financial concerns.
- Study limitations
  - the lack of specific GRADE guidelines for evaluation of prognostic accuracy studies.
  - did not have a consistent timing of out-come measurement.
  - most predictors were documented in only one or two studies and their reproducibility needs to be verified in further studies.

# Conclusion

- These predictors were described in a small number of patients in a single study, inconsistent definitions.
- The most important being the lack of blinding in included studies and the frequent use of the investigated predictor to support decisions.
- Bilateral absence of the N20 SSEP wave appears as the most reproducible predictor with 0% FPR.
- An integrated approach using a combination of predictors along with a careful evaluation of all available clinical information at present is probably the best strategy for early prognostication after cardiac arrest.