Electronic supplementary Material Intensive Care Medicine

Performance of a guideline recommended algorithm for prognostication of neurological outcome after cardiac arrest

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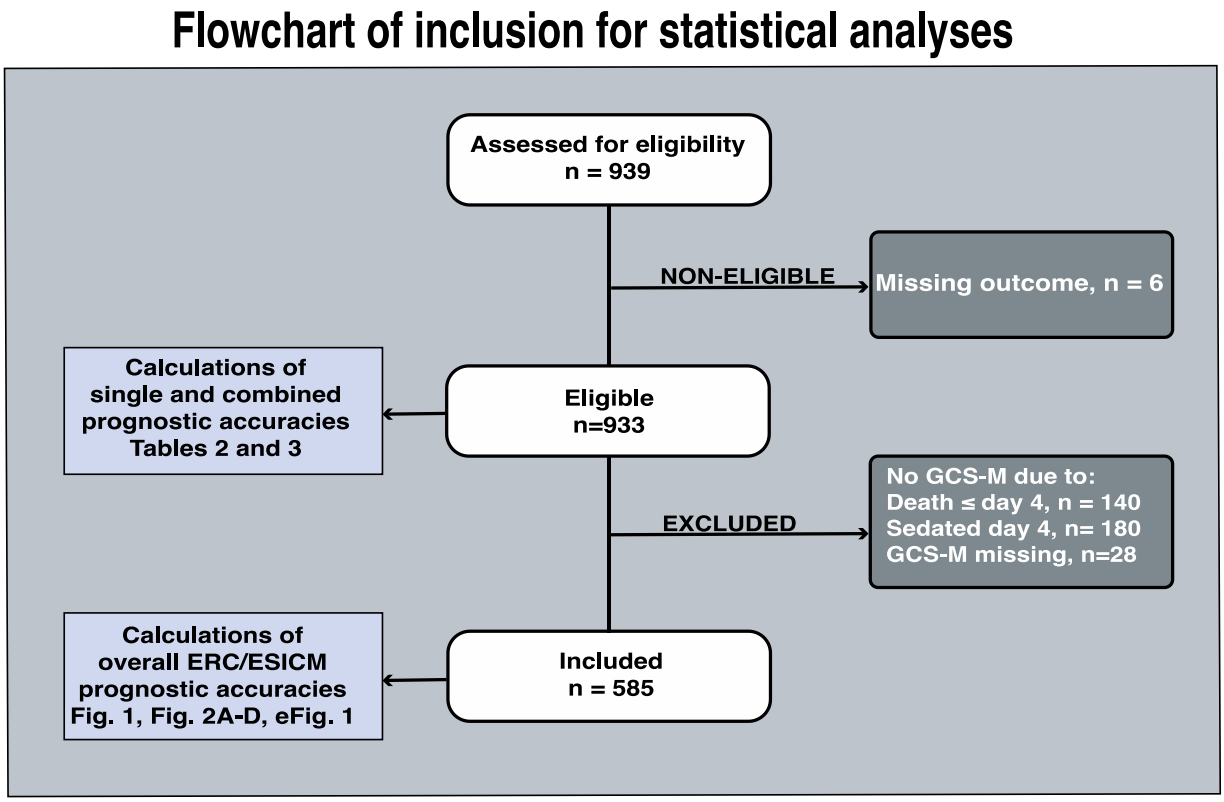
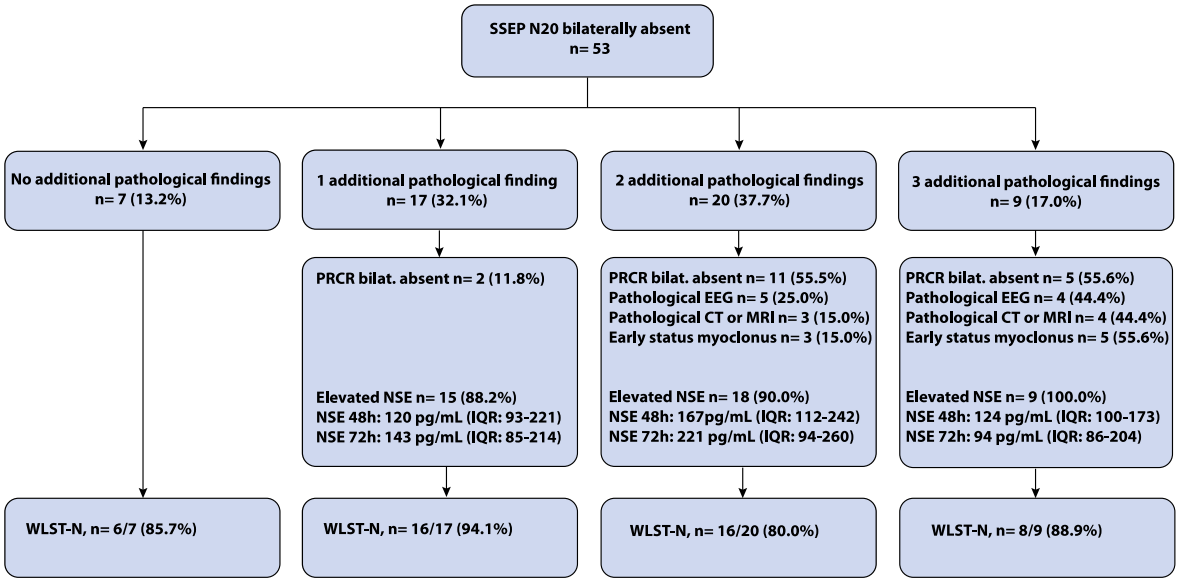
eFigure 1 Flow-chart of patient inclusion



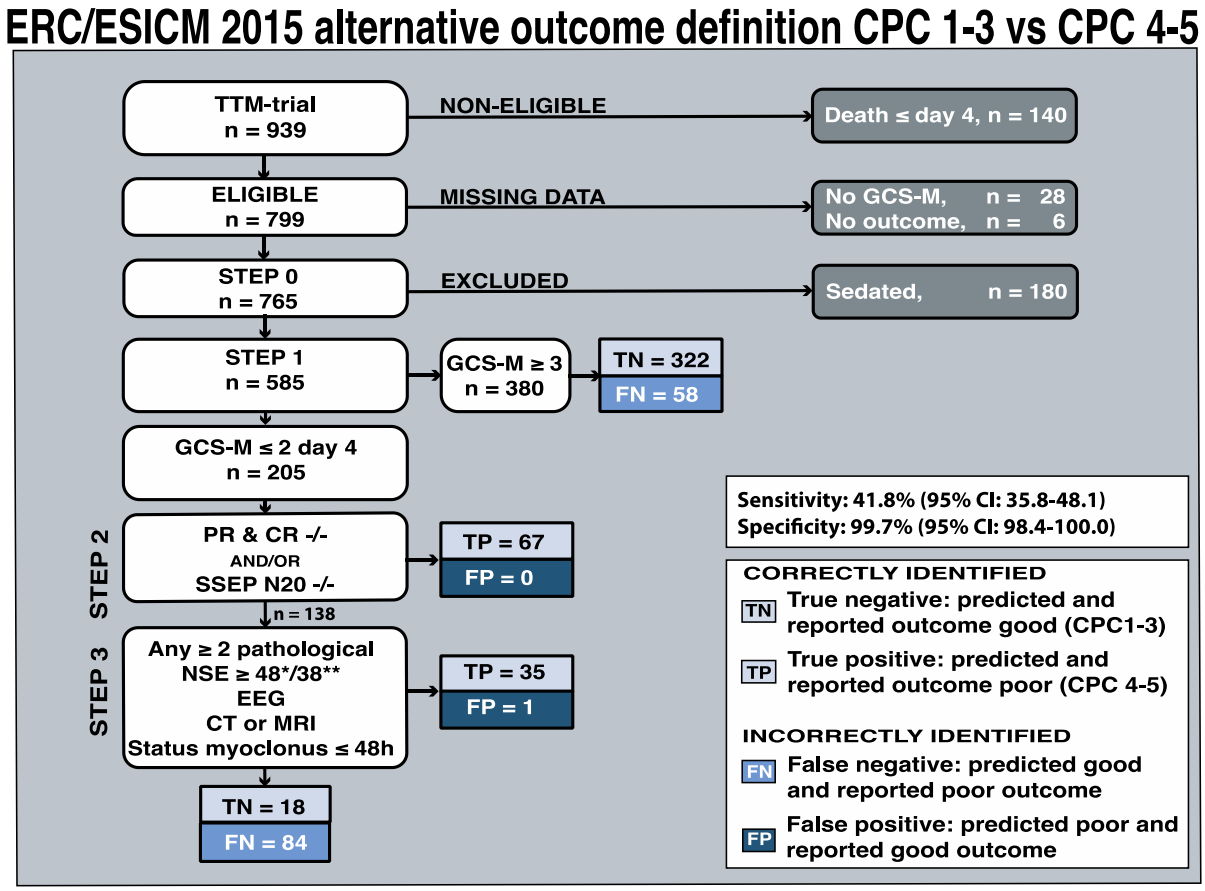
Numbers of patients assessed for eligibility, excluded and included patients. The blue boxes to the left indicate the two different cohorts used for statistical analyses. Missing outcome refers to patients where 6-month Cerebral Performance Category Scale was unavailable. GCS-M; Glasgow Coma Scale Motor Score on day 4 post-arrest.

eFigure 2 Overview of additional pathological prognostic findings in patients with bilaterally absent N20 potentials on SSEP in Step 2



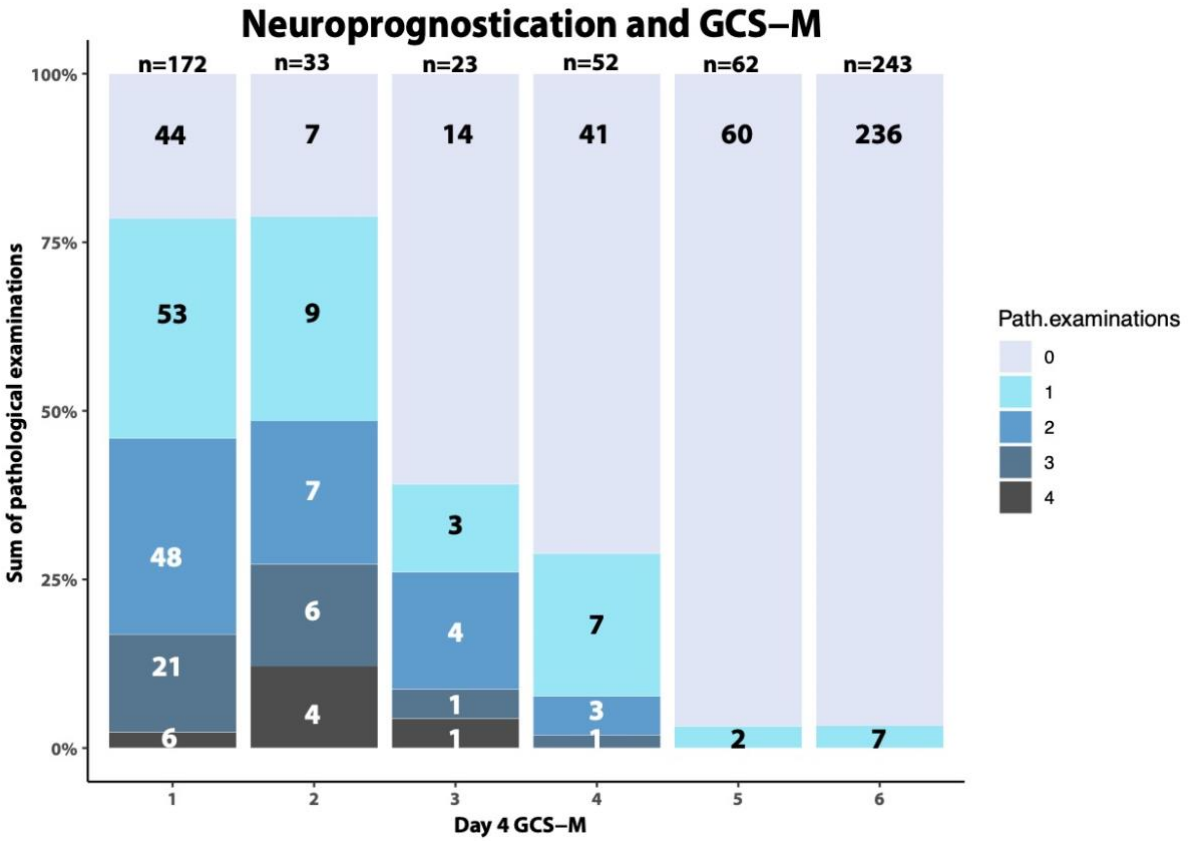
Number (percentages) of additional pathological prognostic findings in patients fulfilling the Step 2 criterion of bilaterally absent N20 potentials on SSEP. For example, only 7/53 (13.2%) of patients with bilaterally absent N20 had no other pathological Step 2 or Step 3 criteria. 32.1% of patients with bilaterally absent N20 had 1 other finding, mostly elevated serum Neuron-specific enolase (NSE). NSE serum concentrations are presented as median (interquartile range) in those patients with NSE elevated ≥48 pg/mL at 48 hours or ≥38 pg/mL at 72 hours post-arrest. PRCR: bilaterally absent pupillary and bilaterally absent corneal reflexes; pathological EEG according to ERC/ESICM criteria, early status myoclonus <48 hours post-arrest; pathological CT or MRI: generalized oedema according to local radiologists; WLST-N: withdrawal of life-sustaining therapy due to presumed neurological futility. Please note that serum NSE concentrations were analyzed after trial completion and result were not available when deciding on WLST.

eFigure 3 Flowchart ERC/ESICM algorithm with alternative definitions of outcome (CPC 1-3 versus CPC 4-5).



Flowchart using an alternative definition of good (CPC 1-3) versus poor (CPC 4-5) neurological outcome at 6 months post-arrest. In this analysis, 1 patient with CPC 3 fulfilled criteria for "poor outcome likely" in Step 3 and was classified as false positive (FP). Pathological findings of the CPC 3 patient were generalized oedema on CT 159 hours post-arrest, pathological EEG after 54 h according to ERC/ESICM criteria and elevated NSE at 48 and 72 hours (68.4 and 66.6 pg/mL, respectively). This patient was classified as modified Rankin Scale 4 at 6 months. The definitions of pathological prognostic examinations used to predict poor outcome are identical to those used in Figure 1.

eFigure 4 Number of pathological findings in relation to Glasgow Coma Scale Motor Score on day 4



The stacked bar chart displays Glasgow Coma Scale Motor Score (GCS-M) level on day 4 post-arrest, numbers (number on bar chart) and percentages (on the y-axis) of corresponding pathological neuroprognostic findings according to the ERC/ESICM algorithm (Step 2 and/or Step 3). The findings of this bar chart is the sum of eTable 5A (good outcome patients) and eTable 5B (poor outcome patients).

eTable 1 McNemar´s Test for comparison of prognostic accuracies of single methods in combined models predicting poor outcome

A. Comparing single sensitivities within combined models

Sensitivities compared A / B	Poor outcome and examined n=	Pathological test A n=	Pathological test B n=	Pathological test A+ B n=	Both tests normal n=	P-value
SSEP / PRCR	137	SSEP = 34	PRCR = 4	SSEP & PRCR = 23	76	<0.001***
SSEP / NSE	129	SSEP = 4	NSE = 39	SSEP & NSE = 53	33	<0.001***
SSEP / EEG	134	SSEP = 44	EEG = 34	SSEP & EEG = 14	42	0.31
SSEP / CT	91	SSEP = 25	CT = 15	SSEP & CT = 14	37	0.15
SSEP / S. myoclonus	161	SSEP = 59	S.M. = 3	SSEP & S.M.= 14	85	<0.001***
SSEP / MRI	19	SSEP = 1	MRI = 2	SSEP & MRI = 1	15	1
PRCR/ NSE	188	PRCR = 4	NSE = 102	PRCR & NSE = 31	51	<0.001***
PRCR/ EEG	171	PRCR = 24	EEG = 51	PRCR & EEG = 8	88	0.003**
PRCR / CT	150	PRCR = 19	CT = 40	PRCR & CT = 15	76	0.009**
PRCR / S. myoclonus	254	PRCR = 46	S.M. = 14	PRCR & S.M. = 5	189	<0.001***
PRCR / MRI	20	PRCR = 0	MRI = 2	PRCR & MRI = 1	17	0.48
NSE / EEG	176	NSE = 79	EEG = 14	NSE & EEG = 41	42	<0.001***
NSE / CT	163	NSE = 57	CT = 7	NSE & CT = 47	52	<0.001***
NSE / S. myoclonus	309	NSE = 170	S.M. = 3	NSE & S.M. = 16	120	<0.001***
NSE / MRI	18	NSE = 6	MRI = 0	NSE & MRI = 3	9	0.04*
EEG / CT	133	EEG = 27	CT = 27	EEG & CT= 16	63	1
EEG / S. myoclonus	221	EEG = 63	S.M. = 10	EEG & S.M. = 7	141	<0.001***
EEG / MRI	16	EEG = 7	MRI = 3	EEG & MRI = 0	6	0.34
CT / S. myoclonus	235	CT = 71	S.M. = 11	CT & S.M. = 5	148	<0.001***
CT / MRI	13	CT = 1	MRI = 2	CT & MRI = 1	9	1
S. myoclonus / MRI	23	S.M. = 1	MRI = 3	S.M. & MRI = 0	19	0.62

This is a contingency table comparing sensitivities for prediction of poor outcome by combinations of tests using the McNemars´s Test for dependent variables. Significance levels are also indicated in Table 3 by asterisks (*).
Only poor outcome patients (CPC 3-5) examined with both methods of a given combination were included in the estimation of sensitivity, therefore sensitivities of single methods within combinations may differ from those reported for each method separately (Tables 2 and 3).The columns describe which pair of methods is examined and total number of poor outcome patients examined with this combination (n), number of patients with pathological findings of method A, B and A+B respectively, and the number of poor outcome patients without pathological findings. *p<0.05, **p<0.01, ***p<0.001. A significant difference indicate that one method contributes more to the overall sensitivity of the combined model A/B.
PRCR; bilaterally absent pupillary and bilaterally absent corneal reflexes, CT; head computed tomography, MRI; magnetic resonance imaging, NSE; serum neuron specific enolase, EEG; electroencephalogram, S. myoclonus; status myoclonus. The definitions of pathological findings according to ERC/ESICM used in this study is described in the methods section.

B. Comparing single specificities within combined models

Specificities compared A / B	Good outcome and examined n=	Pathological test A n=	Pathological test B n=	Pathological test A+ B n=	Both tests normal n=	P-value
SSEP / PRCR	27	SSEP = 1	PRCR = 0	SSEP & PRCR = 0	26	NA
SSEP / NSE	32	SSEP = 1	NSE = 2	SSEP & NSE = 0	29	1
SSEP / EEG	29	SSEP = 1	EEG = 0	SSEP & EEG = 0	28	NA
SSEP / CT	7	SSEP = 0	CT = 0	SSEP & CT = 0	7	NA
SSEP / S. myoclonus	39	SSEP = 1	S.M. = 0	SSEP & S.M.= 0	38	NA
SSEP / MRI	3	SSEP = 0	MRI = 0	SSEP & MRI = 0	3	NA
PRCR/ NSE	36	PRCR = 0	NSE = 2	PRCR & NSE = 0	34	NA
PRCR/ EEG	31	PRCR = 0	EEG = 0	PRCR & EEG = 0	31	NA
PRCR / CT	15	PRCR = 0	CT = 0	PRCR & CT = 0	15	NA
PRCR / S. myoclonus	47	PRCR = 0	S.M. = 1	PRCR & S.M. = 0	46	NA
PRCR / MRI	4	PRCR = 0	MRI = 0	PRCR & MRI = 0	4	NA
NSE / EEG	65	NSE = 4	EEG = 1	NSE & EEG = 0	60	0.37
NSE / CT	91	NSE = 3	CT = 2	NSE & CT = 0	86	1
NSE / S. myoclonus	337	NSE = 12	S.M. = 0	NSE & S.M. = 0	325	NA
NSE / MRI	6	NSE = 1	MRI = 0	NSE & MRI = 0	5	NA
EEG / CT	31	EEG = 1	CT = 0	EEG & CT= 0	31	NA
EEG / S. myoclonus	84	EEG = 1	S.M. = 1	EEG & S.M. = 0	82	1
EEG / MRI	9	EEG = 0	MRI = 0	EEG & MRI = 0	9	NA
CT / S. myoclonus	121	CT = 2	S.M. = 0	CT & S.M. = 0	119	NA
CT / MRI	5	CT = 0	MRI = 0	CT & MRI = 0	5	NA
S. myoclonus / MRI	12	S.M. = 0	MRI = 0	S.M. & MRI = 0	12	NA

This is a contingency table comparing specificities for prediction of poor outcome by combinations of tests using the McNemars´s Test for dependent variables. Only good outcome patients (CPC 1-2) examined with both methods of a given combination were included in the estimation of specificity, therefore specificities of single methods within combinations may differ from those reported for each method separately (Tables 2 and 3).The columns describe which pair of methods is examined and total number of good outcome patients examined with this combination (n), number of patients with pathological findings of method A, B and A+B respectively, and the number of good outcome patients without pathological findings. $p<0.05$ was considered statistically significant. NA indicates that no p-value could be calculated because at least one of the prognostic methods had 0 pathological findings. PRCR; bilaterally absent pupillary and bilaterally absent corneal reflexes, CT; head computed tomography, MRI; magnetic resonance imaging, NSE; serum neuron specific enolase, EEG; electroencephalogram, S. myoclonus; status myoclonus. The definitions of pathological findings according to ERC/ESICM used in this study is described in the methods section.

eTable 2 Number of WLST due to neurological futility for TP patients for each prognostic method

Pathological findings	n=	Poor outcome (%)	WLST-N in poor outcome patients (%)
Glasgow Coma Scale-Motor ≤2	205	191 (93.2)	113/191 (59.2)
PR/CR	51	51 (100.0)	38/51 (74.5)
SSEP	74	73 (98.6)	64/73 (87.7)
Status myoclonus	35	34 (97.1)	23/34 (67.6)
Elevated NSE	198	186 (93.9)	116/186 (62.4)
EEG	71	70 (98.6)	55/70 (78.6)
CT	78	76 (97.4)	54/76 (71.1)
MRI	3	3 (100.0)	2 (66.7)

This table describes number of patients with pathological findings for each prognostic examination in Steps 1-3 of the ERC/ESICM algorithm, number and percentage of poor outcome patients (CPC 3-5 at 6 months post-arrest), and number and percentage of patients with withdrawal of life-sustaining therapy due to presumed neurological futility (WLST-N). PR/CR; bilaterally absent pupillary and bilaterally absent corneal reflexes. Please see methods section for definitions of pathological findings used in this study.

eTable 3 Baseline data for good and poor outcome patients with GCS-M≥3 in Step 1 of the ERC/ESICM algorithm

Findings	TN Step 1 (n=305)	FN Step 1 (n=75)	p-value
Age (years)	62 (52-60)	71 (64-71)	<0.001
Sex male	256 (83.9)	58 (77.3)	0.24
Time to ROSC (min.)	20 (13-24)	23 (15-29)	0.036
Initial rhythm shockable	286 (93.8)	58 (77.3)	<0.001

Baseline data of patients with Glasgow Coma Scale Motor Score (GCS-M) ≥3 on day 4 in Step 1 of the ERC/ESICM algorithm. Good outcome patients (CPC 1-2 at 6 months post-arrest) were classified as true negative (TN) and poor outcome patients (CPC 3-5) were classified as false negative (FN). Continuous variables are presented as median (interquartile range) and p-values were calculated with the Mann-Whitney-Test. Binary variables are presented in numbers (percentages) and p-values were calculated using Chi-Square-Test.

eTable 4 Good outcome patients (CPC 1-2) with GCS-M≤2 on day 4 (n=14)

#	Day 4 GCS-M	Age (years) /sex	Minutes to ROSC	Initial rhythm	Time to awakening	NSE 24 (pg/mL)	NSE 48 (pg/mL)	NSE 72 (pg/mL)	CPC ICU discharge	Hours from CA to ICU discharge	CPC at 6 months	Length of hospital stay (h)
1	1	57, male	16	VF	Day 7: GCS-M 1	NA	NA	NA	4	149	2	1682
2	1	80, male	25	VF	Day 6: obeys commands	14.5	15.1	6.9	1	282	1	556
3	1	62, male	51	VF	Day 7: GCS-M 4	22.0	19.5	15.7	3	690	1	975
4	1	74, male	45	VF	Day 5: obeys commands	NA	NA	NA	2	117	1	269
5	1	61, male	20	VF	Day 6: obeys commands	7.3	5.7	3.4	1	911	1	1199
6	1	43, male	25	VF	Day 7: GCS-M 4	24.9	10.8	7.6	2	311	1	411
7	1	80, male	13	VF	Day 7: GCS-M 4	34.3	26.2	15.7	3	850	2	1826
8	1	63, male	23	Asystole	Day 7: obeys commands	6.8	8.8	6.4	3	313	1	1595
9	1	56, male	12	VF	Day 5: obeys commands	13.2	18.1	6.4	2	140	1	389
10	1	61, male	35	VF	Day 7: obeys commands	NA	NA	NA	2	454	1	882
11	1	39, male	30	VF	Day 6: obeys commands	37.9	27.6	16.2	1	158	1	206
12	2	57, male	37	VF	Missing data	NA	NA	NA	4	89	2	Unknown
13	1	73, male	25	VF	Day 6: obeys commands	43.3	48.2	46.3	2	124	2	340
14	2	75, male	22	VF	Day 3 and day 7: GCS-M 5	11.8	12.6	8.1	3	175	2	242

This table informs about the fourteen patients with Glasgow Coma Scale Motor (GCS-M) 1 (no reaction) or 2 (extension posture) on day 4 post-arrest. All patients were male, 13/14 had ventricular fibrillation (VF) on ECG. Time to awakening describes the first day when patient is awake and obeys commands (GCS-M 6) or best GCS-M on day 7 post-arrest. ROSC, return of spontaneous circulation; VF, ventricular fibrillation; NSE, serum neuron specific enolase; mRS, modified Rankin Scale 6 months post-arrest; CPC, Cerebral Performance Category Scale 6 months post-arrest; CA, cardiac arrest.

eTable 5 Good outcome patients with single pathological findings (n=9)

Baseline data						Prognostic data					Outcome		
#	**Pathological examination**	**Age (years) /sex**	**Minutes to ROSC**	**Initial rhythm**	**Bystander CPR**	**Day 4 GCS-M**	**NSE 24 (pg/mL)**	**NSE 48 (pg/mL)**	**NSE 72 (pg/mL)**	**Comment:**	**mRS at 6 months**	**CPC at 6 months**	**Length of hospital stay (h)**
1	NSE 48	46, male	35	PEA	YES	6 (obeys commands)	11.54	49.54	35.85	Awake on day 4	0	1	413
2	NSE 48	67, male	20	VF	NO	4 (withdrawal to painful stimulus)	52.54	49.16	22.42	EEG: benign Haemolysis? Decreasing NSE from 24 to 72h	0	1	1823
3	NSE 48	64, female	22	VF	NO	6 (obeys commands)	75.64	67.34	34.43	Haemolysis? Decreasing NSE from 24 to 72h. Awake on day 4	1	1	306
4	NSE 48/72	73, male	25	VF	YES	1 (no reaction)	43.25	48.21	46.34	CT 99 h, normal	0	1	340
5	NSE 48/72	73, male	11	VF	YES	6 (obeys commands)	106.3	74.92	47.97	Haemolysis? Decreasing NSE from 24 to 72h. Awake on day 4	2	1	461
6	NSE 72	65, male	7	VF	YES	6 (obeys commands)	7.84	13.06	40.47	Awake on day 4	0	1	256
7	NSE 72	80, male	40	Non-perfusing VT	YES	6 (obeys commands)	36.8	26.26	43.98	SSEP N20 bilat present. Awake on day 4	0	1	716
8	EEG: unreactive status epilepticus	65, male	15	VF	YES	5 (localizes to painful stimulus)	11.32	NA	9.97	EEG: generalized abundant periodic discharges >50%, continuous normal voltage background. Unreactive according to local investigators. CT 153 h: normal	1	1	368
9	Early status myoclonus ≤48h	63, male	12	VF	NO	6 (obeys commands)	NA	NA	NA	Awake on day 4	1	2	642

The table describes the nine good outcome patients with single pathological findings identified in Step 3 of the ERC/ESICM algorithm. ROSC, return of spontaneous circulation; PEA, pulseless electric activity; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; Day 4 GCS-M, Glasgow Coma Scale Motor Score on day 4 post-arrest; NSE, serum neuron specific enolase; mRS, modified Rankin Scale 6 months post-arrest; CPC, Cerebral Performance Category Scale 6 months post-arrest. Six of

these nine patients with single false pathological findings were awake on day 4 post arrest and obeying commands (GCS-M 6) (patients #1, #3, #5, #6, #7, and #9). Three of seven patients with elevated NSE had decreasing levels of NSE from 24 h to 72 h post-arrest (patients #2, #3 and #5).

eTables 6 A+B GCS-M and pathological neuroprognostic findings

A. Good outcome (CPC 1-2 at 6 months post-arrest)

Sum path. findings	GCS-M day 4						
	1 n=12 (3.8)	**2 n=2 (0.6)**	**3 n=9 (2.8)**	**4 n=29 (9.1)**	**5 n=46 (14.4)**	**6 n=221 (69.3)**	**All CPC 1-2 n=319 (100.0)**
0	11	2	9	28	45	215	310
1	1	0	0	1	1	6	9
≥2	0	0	0	0	0	0	0

B. Poor outcome (CPC 3-5 at 6 months post-arrest)

Sum path. findings	GCS-M day 4						
	1 n=160 (60.2)	**2 n=31 (11.7)**	**3 n=14 (5.3)**	**4 n=23 (8.6)**	**5 n=16 (6.0)**	**6 n=22 (8.2)**	**All CPC 3-5 n=266 (100.0)**
0	33	5	5	13	15	21	92
1	52	9	3	6	1	1	72
2	48	7	4	3	0	0	62
3	21	6	1	1	0	0	29
4	6	4	1	0	0	0	11

The tables describe numbers (%) of Glasgow Coma Scale Motor Score (GCS-M) on day 4 post-arrest and the sum of pathological neuroprognostic findings according to ERC/ESICM (step 2/3). The total sum of findings in eTable 6A (good outcome) and eTable 6B (poor outcome) are displayed in the stacked bar chart in eFigure 3. Pathological findings were defined as: bilaterally absent pupillary and corneal reflexes, bilaterally absent N20-potentials on SSEP, early status myoclonus ≤48 hours, generalized odema on CT or MRI, elevated Neuron specific enolase (NSE) ≥48 pg/mL at 48 hours and/or ≥38 pg/mL at 72 hours or pathological EEG according to ERC/ESICM criteria.

eTable 7 Sensitivities and specificities of single prognostic methods recalculated excluding patients with WLST due to neurological futility

Method	Sensitivity (95% CI)	Specificity (95% CI)	TP	TN	FP	FN	N=	Poor outcome
GCS-M ≤2	56.5 (48.2-64.5)	95.6 (92.8-97.4)	78	305	14	60	457	138 (30.2)
GCS-M ≤3	60.1 (51.8-67.9)	92.8 (89.4-95.2)	83	296	23	55	457	138 (30.2)
GCS-M ≤4	72.5 (64.5-79.2)	83.7 (79.3-87.4)	100	267	52	38	457	138 (30.2)
PR/CR	14.8 (8.8-23.7)	100.0 (92.4-100.0)	13	47	0	75	135	88 (65.2)
SSEP	18.8 (10.2-31.9)	97.4 (86.8-99.6)	9	38	1	39	87	48 (55.2)
NSE ≥ 33*/**	51.2 (43.6-58.8)	89.9 (86.2-92.7)	84	303	34	80	501	164 (32.7)
NSE ≥48*/≥38**	42.7 (35.4-50.3)	96.4 (93.9-98.0)	70	325	12	94	501	164 (32.7)
EEG ERC/ESICM	17.4 (10.9-26.8)	98.8 (93.6-99.8)	15	83	1	71	170	86 (50.6)
EEG "highly malignant"	27.9 (19.5-38.2)	98.8 (93.6-99.8)	24	83	1	62	170	86 (50.6)
Status Myoclonus ≤ 48h	3.9 (2.2-6.9)	99.8 (98.7-100.0)	11	439	1	271	722	282 (39.1)
CT	21.1 (14.4-30.0)	98.3 (94.2-99.6)	22	119	2	82	225	104 (46.2)
MRI	9.1 (1.6-37.7)	100.0 (75.8-100.0)	1	12	0	10	23	11 (47.8)

Recalculation of sensitivities and specificities of prognostic methods as demonstrated in Table 2 excluding all patients with withdrawal of life-sustaining therapy (WLST) due to presumed neurological futility (n=211). Results presented with 95% confidence intervals together with the number of correctly and incorrectly diagnosed patients with poor neurological outcome defined as Cerebral Performance Category Scale 3-5 at 6 months. Only patients with available results to be classified as pathological in the examined methods were included in the statistical analyses. All definitions of pathological findings are identical to those in Table 2 and are describes in the methods section of the article. TP, true positive (predicted and reported outcome CPC 3-5); TN, true negative (predicted and reported outcome CPC 1-2); FP, false positive (predicted CPC 3-5, reported outcome CPC 1-2), FN, false negative (predicted CPC 1-2, reported outcome CPC 3-5).