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Protein S100B as a reliable tool for early prognostication after cardiac arrest

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40 **Abstract**

41 **Purpose.** Early and reliable prognostication after cardiac arrest (CA) remains crucial. We
42 hypothesized that protein-S100B (PS100B) could predict more accurately outcome in the
43 early phase of CA compared with other current biomarkers.

44 **Methods.** This prospective single-center study included 330 adult comatose non-traumatic
45 successfully resuscitated CA patients, treated with targeted temperature management but not
46 extra-corporeal life support. Lactate, pH, creatinine, NSE, and PS100B were sampled in ICU
47 early after return of spontaneous circulation (ROSC) corresponding to admission (Adm).
48 Serial measurements were also performed at H24 and H48. PS100B was the sole biomarker
49 blinded to physicians.

50 **Measurements and Main Results.** The median delay between ROSC and first PS100B
51 sampling was 220 min. At admission, all biomarkers were significantly associated with good
52 outcome (CPC1-2; 109 patients) at 3-month follow-up ($P \leq 0.001$, except for NSE: $P = 0.03$).
53 PS100B-Adm showed the best AUC of ROC curves for outcome prediction at 3-month (AUC
54 0.83 [95%-CI: 0.78-0.88]), compared with other biomarkers ($P < 0.0001$), while AUC for
55 lactate-Adm was higher than for NSE-Adm. AUC for PS100B-H24 was significantly higher
56 than for other biomarkers except NSE-H24 ($P \leq 0.0001$), while AUC for NSE-H24 was higher
57 than for lactate-H24 and pH-H24. AUCs for PS100-H48 and NSE-H48 were significantly
58 higher than for all other biomarkers ($P < 0.001$). Compared to patients with decreased PS100B
59 values over time, an increasing PS100B value between admission and H24 was significantly
60 associated with poor outcome at 3 months ($P = 0.001$). No-flow, initial non-shockable rhythm,
61 PS100B-Adm, lactate-Adm, pH-Adm, clinical seizures, and absence of therapeutic
62 hypothermia were independent predictors associated with poor outcome at 3-month in
63 multivariate analysis. Net-Reclassification-Index was 70%, 64%, and 81% when PS100B-
64 Adm was added to the clinical model, to clinical model with NSE-Adm, and to clinical model
65 with standard biological parameters, respectively.

66 **Conclusions.** Early PS100B compared with other biomarkers was independently correlated
67 with outcome after CA, with an interesting added value.

68

69 **Keywords:** heart arrest; prognostication; outcome; Protein S100B; NSE; biomarker

70

71 **Introduction**

72 Favourable outcome after cardiac arrest (CA) remains poor.^{1,2} Early and reliable
73 prognostication in CA patients seems of major importance. It could avoid futile treatment in
74 patients with low chance of good outcome and could help clinicians to maximize treatment in
75 patients who have a high likelihood of good outcome. However, guidelines emphasize that
76 prognostication needs to be delayed, especially when targeted temperature management
77 (TTM) is applied, and that decisions to limit care should be supported by a multimodal
78 approach including clinical, biological, electrophysiological, and/or imaging parameters.^{2,3}

79 The usefulness of biomarkers to help clinicians in optimizing outcome prediction after CA is
80 described mainly for Neuron Specific Enolase (NSE).²⁻⁸ The initial NSE threshold validated
81 in 2006 did not remain 100%-predictive after a broader evaluation in TTM-treated
82 patients,^{2,4,5} while NSE accuracy seemed better at a delayed phase after return of spontaneous
83 circulation (ROSC).^{3,4,7-9} Other biomarkers, such as lactate, pH, and creatinine levels on
84 admission, have also been proposed to early predict outcome after CA.¹⁰⁻¹³ However,
85 specificity of these biomarkers is not 100%, leading to difficulties in assessing their precise
86 cut-off values and predictive accuracy.^{4,14} S100B protein (PS100B) is also presumed to be an
87 interesting prognostication tool besides NSE.^{3-8,14-22} S100 protein is an intracellular dimeric
88 protein with at least 4 sub-types, with S100A1B and S100BB being presently measured by
89 usual tests.¹⁸ Besides S100A1 protein, S100B protein (PS100B) is normally found in
90 astroglial and Schwann cells, and in neuroectodermal tumoral cells in pathological context,
91 while small amount of PS100 was also found in adipocytes, muscles and chondrocytes.
92 However, the large sub-TTM report by Stammet et al. showed that PS100B could be better
93 than NSE at H24 to predict poor outcome, but the added information was limited in all
94 prognosticating models with or without NSE.^{22,23} However, biomarkers were here only
95 sampled 24 hours after ROSC and thereafter. Therefore, NSE contrary to PS100B is preferred

96 in international guidelines as a validated and useful biomarker since it is superior at H48 and
97 H72.^{2,3} Considering the relative short half-life of PS100B compared to NSE, we hypothesized
98 that PS100B could more accurately predict the outcome of CA patients in the early phase after
99 ROSC compared to biomarkers such as lactate, pH, creatinine, and NSE. The aim of the
100 present study was to evaluate the usefulness of early PS100B sampling for prognostication in
101 a large cohort of successfully resuscitated CA patients.

102

103 **Methods**

104 This prospective single-center study was carried out between March 2010 and May 2016 in
105 the medical ICU of a university hospital (Lariboisiere Hospital, Assistance Publique des
106 Hôpitaux de Paris, France). The Ethics Committee of our institution approved the study
107 (Institutional Review Board of Paris North Hospital: CERB GHU Nord, N°00006477). All
108 surviving patients hospitalized for CA -or their next of kin if necessary- gave their written
109 informed consent. The study was declared at National Clinical Trial (NCT01374880).

110

111 Aims

112 Primary endpoint was to assess PS100B performance in discriminating patients with good
113 outcome versus those with poor outcome at 3-month follow-up as soon as the early phase
114 after CA (i.e. as early as possible and within the first 24 hours after ROSC). PS100B was
115 compared to other biomarkers (lactate, pH, creatinine, and NSE) in its ability to correctly
116 discriminate outcome.

117 Secondary endpoints were: 1/ to evaluate PS100B performance in the early phase after CA in
118 discriminating patients with good outcome versus those with poor outcome at hospital

119 discharge; 2/ to evaluate PS100B performance according to the timeframe serum sampling
120 after ROSC versus other biomarkers in its ability to discriminate patients with good outcome
121 versus those with poor outcome (i.e. when sampled within the first 72 hours after ROSC).

122 Patient selection

123 Were included all consecutive comatose adult patients ≥ 18 years old, suffering from non-
124 traumatic and successfully resuscitated CA (out-of-hospital or in-hospital CA: OH/IHCA),
125 with sustained ROSC (defined as possibility to maintain ROSC with palpable pulse for >20
126 min), hospitalized in ICU and TTM-treated. Conscious patients, with unsustained ROSC,
127 refractory CA or cardiogenic shock after CA necessitating an Extra-Corporeal Life Support
128 (ECLS) were excluded. Patients experiencing a do-not-resuscitate order and patients without
129 any PS100B values measured during the ICU course were excluded from this study.

130 Protocol

131 The protocol applied for all CA patients has been previously described and was in accordance
132 with international guidelines.^{2,3,24} Particularly, TTM was initiated as soon as possible for all
133 patients regardless of the initial cardiac rhythm and ranged from 32 to 36°C for 24 hours.
134 Prognostication and withdrawal of life sustaining therapies, if necessary, were performed
135 according to international guidelines.^{2,3}

136 Outcome assessment and data collection

137 Data collection followed the Utstein style recommendations.²⁵ Outcome was evaluated using
138 the Cerebral Performance Category (CPC) scoring, CPC 1-2 representing a good outcome
139 whereas CPC 3-4-5 a poor outcome. CPC was systematically collected at hospital discharge
140 and 3 months after CA, during a face-to-face appointment or by phone, by an independent
141 researcher unblinded to patient medical history.

142 Blood samples were obtained in ICU for all patients as early as possible after ROSC, and
143 hospital admission for OHCA (corresponding to admission: Adm.), at day 1 (H24:
144 corresponding to the day occurring between 6h00 AM the day following ROSC and the
145 following 24 hours), and at day 2 (H48: corresponding to the following 24 hours after H24).
146 Two serial blood samples were used to evaluate biomarker variations within the first 3 days
147 after CA. Physicians in charge of the patients were all blinded to PS100B measurements, but
148 not to other biomarkers. PS100B and NSE markers from serum were measured by the
149 sandwich electro-chemi-luminescent immuno-assay (ECLIA) methods using a Cobas E601
150 analyzer (Roche Diagnostics, Meylan, France), which is similar to those published in largest
151 studies.^{8,22}

152 Statistics

153 Results are expressed as median (IQR 25-75), unless expressed otherwise. Non-parametric
154 tests were used considering the non-Gaussian distribution of many parameters. Spearman tests
155 for correlations or Wilcoxon tests for serial measurements were used to compare quantitative
156 values. Kruskal-Wallis and Mann-Whitney tests with Bonferroni correction for multiple
157 comparisons were used to compare quantitative and qualitative parameters. Comparisons for
158 qualitative values were performed using chi-2 and the exact Fisher tests. To assess the
159 biomarker ability to correctly evaluate its prognostic value in terms of good outcome
160 predictions, receiver operating characteristic (ROC) curves with deriving sensitivities,
161 specificities, positive and negative predictive values, associated to different cut-off values
162 were performed. ROC curves and Area Under the Curve (AUC) were compared using the
163 Delong's test. These calculations were performed considering each parameter at admission
164 (Adm: primary endpoint), H24 and H48 on its own, as well as changes over admission to
165 H48. PS100B values at admission were compared versus other major prognostic clinical
166 parameters and biomarkers using univariate and multivariate analyses with backward

167 elimination for multiple linear regressions. Main significant clinical parameters and biological
168 values at admission were used in the multivariate analysis using logistic regression to evaluate
169 early predictors independently associated with good outcome at discharge. The Net
170 Reclassification Index (NRI) was used to assess biomarkers added value in the final model. P-
171 values were considered as significant when <0.01 . All statistics were performed using XL-stat
172 Biomed (version 2018.3, Addinsoft, Microsoft, USA), except the NRI performed using R
173 statistical software version 3.1.1 (The “R” Foundation for Statistical Computing, Vienna,
174 Austria).

175

176 **Results**

177 Among 370 CA without ECLS implementation, 351 patients without exclusion criteria were
178 included, of which 21 were lost to 3-month follow-up (Supplemental Figure S1). Patients’
179 general characteristics are described in Table 1 and Supplemental Table S1. The delay
180 between CA and the first blood sample measuring NSE and PS100B (Admission) was 245
181 min [180-338], the delay between ROSC and the first sample being 220 min [155-316]. The
182 delay between ROSC and the second sample (H24) was 23.5 hours [15.3-36.0], while it was
183 48.1 hours [39.2-61.2] between ROSC and the third sample (H48).

184 Biomarker values within the first 3 days are described in Table 2. At admission, all
185 biomarkers were significantly associated with good outcome at 3-month ($P \leq 0.001$), P-value
186 for NSE being 0.03. At H24, all biomarkers except pH were significantly associated with
187 good outcome at hospital discharge ($P < 0.0001$). At H48, PS100B, NSE, and creatinine values
188 were significantly associated with good outcome at hospital discharge ($P \leq 0.004$), but not pH
189 and lactate. Results were similar at hospital discharge (Supplemental Table S2). PS100B and
190 NSE values according to CPC at 3-month are detailed in Figure 1 and Supplemental Table S3.

191 Biomarker ROC curves according to the day of sampling are depicted in Figure 2 and
192 Supplemental Table S4. At admission, best AUC for prediction of outcome was observed for
193 PS100B-Adm compared with all other biomarkers ($P<0.0001$), AUC for lactate-Adm being
194 also higher than for NSE-Adm (Supplemental Figure S2a). At H24, AUC for PS100B-H24
195 was significantly higher than for all other biomarkers except NSE-H24 ($P\leq 0.0001$,
196 Supplemental Figure S2b), while AUC for NSE-H24 was higher than AUCs for lactate-H24
197 and pH-H24. At H48, best AUCs were observed for both PS100B-H48 and NSE-H48 versus
198 all other biomarkers for outcome prediction ($P<0.001$, Supplemental Figure S2c). No
199 differences were observed between all PS100B AUCs from admission to H48, whereas AUC
200 for NSE-Adm was significantly lower than AUCs for NSE-H24 and NSE-H48 ($P<0.0001$,
201 Supplemental Figure S3).

202 PS100B serial measurements are described in Table 3. PS100B values significantly decreased
203 over time ($P<0.0001$). An increasing value between admission and H24 was significantly
204 associated with poor outcome compared to patients with decreased PS100B values over time
205 ($P=0.001$, only 1 patient with good outcome experiencing an increasing PS100B value).
206 Comparable results were observed for PS100B differences between admission and H48
207 measurements but not between H24 and H48.

208 Biomarkers sensitivity and specificity according to the maximum accuracy at all time-points
209 are detailed in Table 4. A PS100B-Adm threshold of $3.78\mu\text{g/L}$ correctly classified all patients
210 except one as experiencing poor outcome with a 99%-specificity (95%-CI [94-99]) and a
211 positive predictive value of 98% (1 false positive; Supplemental Figure S4, Tables S5 and
212 S6).

213 In multivariate analysis, early predictors independently associated with poor outcome at
214 hospital discharge were: no-flow duration, PS100B-Adm, pH-Adm, and lactate-Adm values,

215 initial non-shockable rhythm, clinical seizures, and absence of therapeutic hypothermia
216 (Supplemental Table S7, AUC of the model: 0.91 [95%-CI: 0.86-0.95]). NRI was 70%, 64%,
217 and 81% when PS100B-Adm was added to the clinical model alone, to the clinical model
218 with NSE-Adm, and to the model including clinical with standard biological parameters,
219 respectively (Table 4 and Supplemental Table S8).

220

221 **Discussion**

222 Results can be summarized as follows: 1/ Initial PS100B after admission was significantly
223 associated with good outcome at hospital discharge and 3-month after CA; 2/ PS100B-Adm.
224 was the most accurate biomarker to correctly predict good outcome as evaluated by ROCs
225 analyses, compared with lactate, creatinine, pH, and NSE; 3/ An increasing PS100B value
226 from admission to H24 was significantly associated with poor outcome (1 false negative); 4/
227 A PS100B-Adm. threshold of 3.78 μ g/L correctly classified all patients except one as
228 belonging to poor outcome group; 5/ In multivariate analysis, PS100B-Adm. was associated
229 with poor outcome at 3-month, besides no-flow duration, initial non-shockable rhythm,
230 lactate-Adm. and pH-Adm. values, presence of clinical seizures, and absence of therapeutic
231 hypothermia; 6/ NRI was 70%, 64%, and 81% when PS100B-Adm was added to the clinical
232 model alone, to the clinical model with NSE-Adm, and to the model including clinical with
233 standard biological parameters, respectively; 7/ PS100B and NSE were highly discriminative
234 at H24 and H48 to correctly predict good outcome.

235

236 Prognostication after CA using PS100B/NSE

237 In the meta-analysis describing biomarkers and outcome before TTM era, biomarkers values
238 associated with a 0% false positive rate (FPR) varied considerably within studies with a very
239 low level of evidence according to the timing of sampling.²⁶ After TTM implementation,
240 other studies were reported.⁴ Two studies observed PS100B values of 0.18µg/L and 0.21µg/L
241 at H24 as predicting poor outcome in 100% of cases.^{7,27} One of these studies showed a
242 sensitivity of 65%, FPR being 4%, and the other that PS100B measured 24h after ROSC was
243 the best predictor of poor outcome (sensitivity: 87%, specificity: 100%). Another study
244 described a threshold of 0.3µg/L at H48 associated with outcome with a 21%-sensitivity and
245 0% FPR.²⁸ None of these 3 studies evaluated PS100B in large enough populations.

246 The largest study sampling PS100B after 24h post-CA showed that PS100B could be better
247 than NSE at H24 to predict outcome, but the added information was limited in all
248 prognosticating models with or without NSE.²² Interestingly, AUC for PS100B-H24 observed
249 in our paper and this study were globally similar. However, early prognostication was herein
250 not evaluated, biomarkers not being sampled immediately after admission. Our study affirms
251 in another large cohort that PS100B adds a significant value regarding prognostication, while
252 NSE is robust to accurately predict outcome at a delayed phase after CA, as previously
253 suggested.^{4,6,8,19,22}

254 By contrast to PS100B keeping interesting NRI values from admission to H48, NSE's NRI
255 increases progressively after H24 where its value contributes to neuroprognostication, these
256 biomarkers describing two aspects of brain injury (i.e. glial versus neuronal cells). According
257 to PS100B high specificity/low sensitivity on admission and the validated NSE value at H24-
258 H48, we could use PS100B from admission to H48 and NSE samples from H24 to H72 to
259 better refine the neuroprognostication process. However, this suggestion needs to be adapted
260 in each centre and to strictly follow prognostication guidelines using a multimodal approach
261 performed after the first 2 days post-CA.

262 Some studies also suggested that PS100B could potentially help the early prognostication
263 strategy,²⁹ confirming our findings that PS100B on admission was significantly associated
264 with outcome. Combining NSE >41.1µg/L with PS100B >0.461µg/L at H24 was the most
265 specific criteria of poor long-term outcome.³⁰ An initial PS100B threshold of 0.92µg/L
266 predicted poor outcome with a 90%-specificity, besides initial shockable rhythm, PS100B and
267 NSE being highly predictive of hospital survival.¹⁶ Mörtberg et al. observed that PS100B
268 levels significantly differed between good and poor outcome groups as early as 1h after
269 ROSC, this difference persisting thereafter.⁷ Only one study did not reach significance
270 regarding the discriminative value for PS100B on admission, AUC of ROC curves on
271 admission being lower than at H24 and H48.³¹ However, its limited sample size could explain
272 this observation. PS100B half-life is (0.5 to) 2h with a molecular weight of 21kDa, compared
273 with 24h and 78kDa for NSE.^{18,28} This possibly explains discrepancies in case of interrupted
274 integrity of the blood-brain barrier after brain damages with an earlier release of PS100B into
275 cerebral spinal fluid and blood.³² More understanding of the “early” PS100B kinetic is
276 warranted.

277

278 Serial PS100B measurements

279 In the first study published in 2001 before the TTM era and the modern post-CA syndrome
280 management,³³ serial PS100B measurements showed significant differences over time
281 according to outcome as soon as 30min after resuscitation.. In the recent study by Duez et al,³¹
282 the daily change remained non-significant for PS100B, but the decrease was significant in the
283 group showing good outcome. Other studies have previously described these PS100B
284 variations in smaller cohorts.^{7,19,34} Mörtberg suggested that levels of PS100B decreased in the
285 good outcome group from the acute phase after ROSC to 24h post-CA, and increased between
286 these time points in the poor outcome group.⁷ Einav et al. observed comparable results as ours

287 with a “steep decrease” between admission compared to day 3, while the decrease between
288 day 1 to day 3 was less pronounced.¹⁹ Our study highlights the time course of PS100B within
289 the first hours after CA and is to date the largest study confirming that serial PS100B
290 measurements, especially in the early phase after CA, can correctly predict outcome.

291

292 Biomarkers and scores for early prognostication

293 Our study is the first to evaluate simultaneously all “usual” biomarkers using ROCs,
294 biomarkers that were correlated with outcome but with lower AUCs than PS100B-Adm.
295 Interestingly, PS100B, pH and lactate were correlated in multivariate analyses, suggesting
296 that these biomarkers could finally find a place in scores used in the early phase post-CA.¹³
297 Creatinine remained significantly but moderately different between good and poor outcome
298 groups, whereas pH was no longer significant at H24 and H48, neither lactate at H48. Our
299 results are concordant with literature for lactate variations over time¹² and suggest that lactate
300 or pH could be useful predictors early after CA but less thereafter. Except PS100B-Adm,
301 overlaps for these biomarkers between good and poor outcome were important as early as
302 admission. In our study, only PS100B was blinded to physicians preventing the risk of “self-
303 fulfilling prophecy”. Therefore, according to literature and our data, early PS100B could
304 interestingly be incorporated in such prognosticating scores.

305

306 Limitations

307 Our study is a single-center study. However, regarding our main endpoint, this fact guarantees
308 a correct homogeneity of samplings and biochemical tests, considering that the ECLIA
309 method with immunoluminescent sandwich used in our unit is the most used method in

310 literature.^{8,19,22,28,31} First sampling was performed after a 4-hour delay post-CA, consequence
311 of the important deployment of resources performed to find the aetiology of CA.^{2,3} Choice of
312 the days of sampling could be criticized as we did not pursue the biomarker evaluation after
313 H48. However, our main goal was to specifically evaluate biomarkers in the early phase after
314 CA.

315 Several exclusion criteria were prospectively applied in our study. However, this selection of
316 patients added precision, as biomarkers could be modified by ECLS and haemolysis.⁴ Both
317 OHCA and IHCA were enrolled in our pragmatic trial. However, similar results were
318 observed in the OHCA subgroup (data not shown). It could be argued that extra-cerebral
319 sources of PS100B are potentially confounders, decreasing its specificity to predict
320 outcome.³² However, in our study, neither body mass index nor CPK were associated with
321 PS100B values at admission (data not shown).

322 Finally, the cost of PS100B dosages, the duration of its measurement, or its unavailability in
323 some laboratories could limit its spreading.¹⁵ Meanwhile, more studies are warranted before
324 any generalization of PS100B measurement: multicentre prospective trials to definitively
325 confirm our results, refining early PS100B added value and its cut-off levels, and meta-
326 analyses to pool all PS100B data in its ability to early predict outcome.

327

328 **Conclusions**

329 In our cohort of comatose patients resuscitated from CA without ECLS implementation,
330 PS100B after hospital admission was the biomarker with the best accuracy for outcome's
331 prognostication, and the sole biomarker with a high accuracy persisting during the first 3 days
332 after CA.

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- 441

442 **Figure legends.**

443

444 **Figure 1. Protein S100 time course according to CPC assessment at 3 months after**
445 **cardiac arrest (N=330).**

446 Box plots represent PS100B sampling over the first 3 days after CA. Data are presented as
447 median, quartiles 1 and 3, lower and upper fence.

448 Legend (x axis) = Adm: day of sampling after admission in ICU, H24 and H48 correspond to
449 the day of sampling during the following 24h and 48h. « C » denotes CPC assessment,
450 ranging from CPC-1 (no sequellae) to CPC-5 (death or brain death). No CPC-4 was observed
451 in our study at hospital discharge.

452 At admission, significant differences were observed between CPC5 vs. CPC1, 2, and 3, and
453 between CPC1 vs. CPC2 ($P<0.01$). At H24 and H48, significant differences were observed
454 between CPC5 vs. CPC1, 2, and 3.

455

456 **Figure 2. Forest plot for biomarker Receiver Operating Characteristic (ROC) curves**
457 **from admission to H48 to predict outcome.**

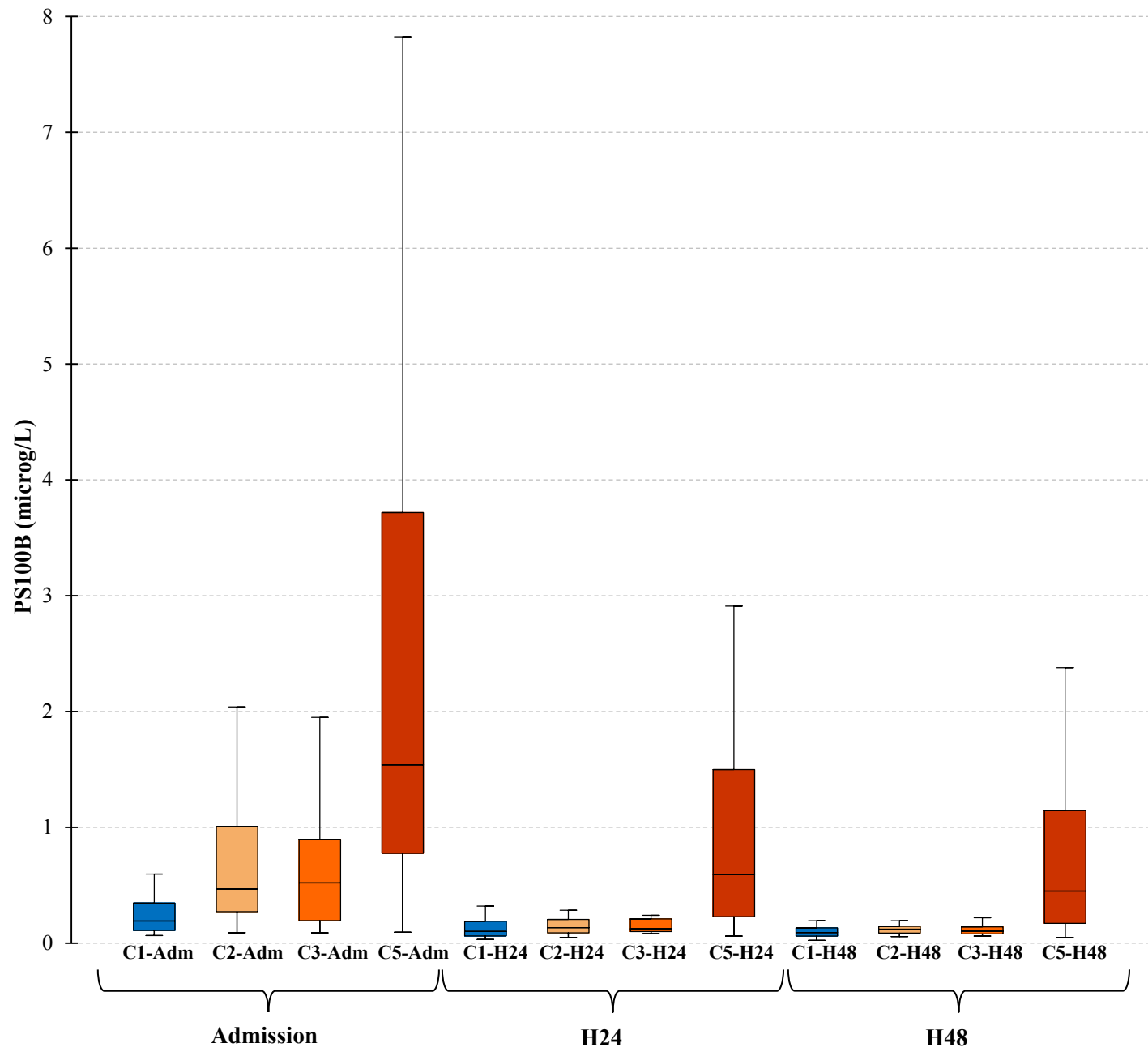
458 Biomarkers' Receiver Operating Characteristic (ROC) curves are represented with their area
459 under the curve (AUC) and CI-95% at admission (upper part), H24 (middle part), and H48
460 (lower part) for their ability to discriminate good versus poor outcome at hospital discharge
461 (black square) and at 3-month follow-up (white circle).

462 PS100B: protein S100B; NSE: Neuron specific Enolase.

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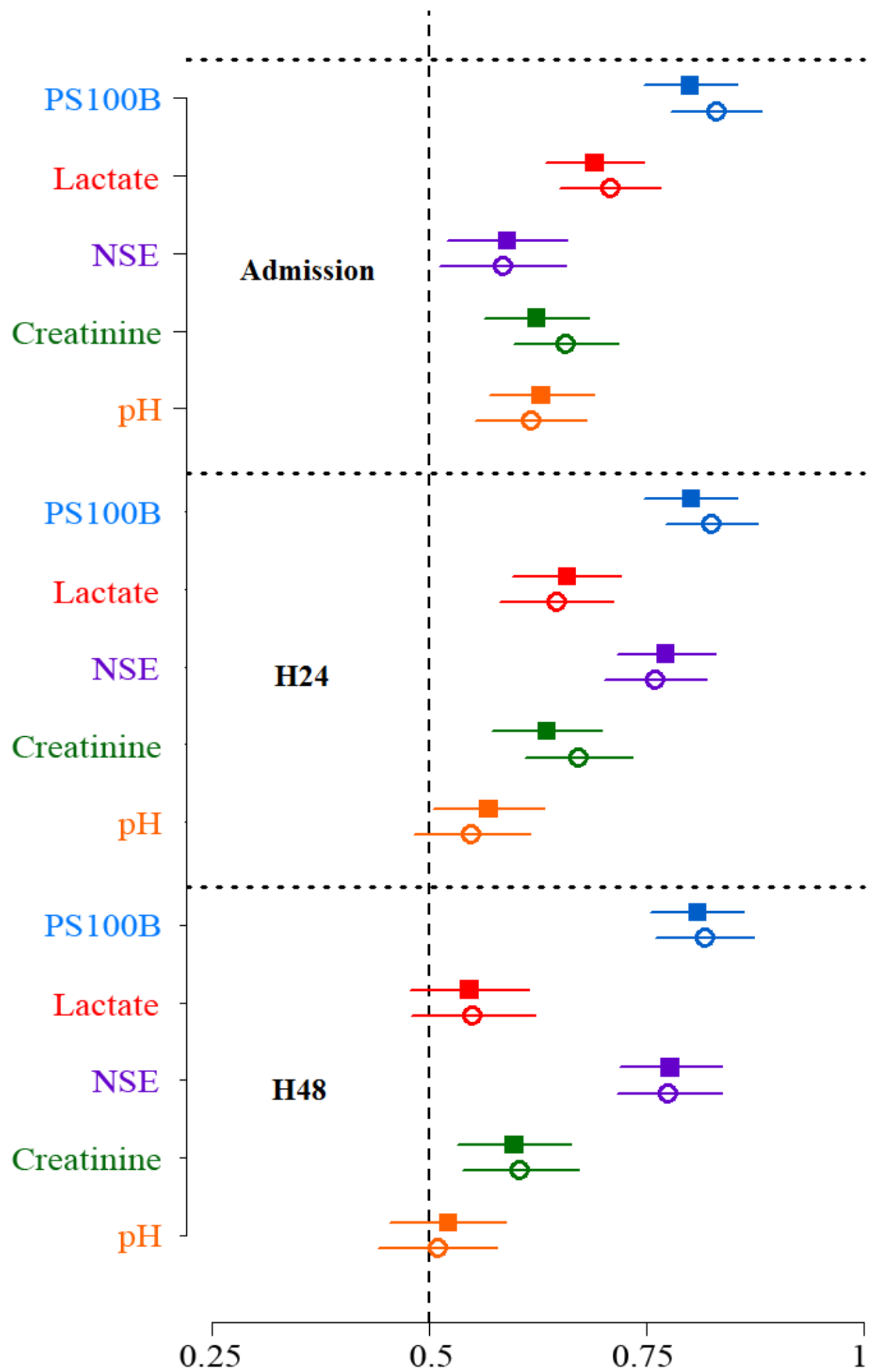


Table 1. Patient general characteristics according to outcome at 3 months

Characteristic	Overall (N=330)	Good outcome (N=109)	Poor outcome (N=221)	P
Age, yr	61 [49-72]	55 [45-67]	63 [52-76]	0.0002
Male sex, no. (%)	230 (70)	84 (77.1)	146 (66.1)	0.043
Body Mass Index, kg/m²	26 [23-29]	25 [24-29]	26 [23-30]	0.54
Previous hypertension, no. (%)	126 (38.1)	36 (33.0)	90 (40.7)	0.23
Previous coronary disease	60 (18.1)	13 (11.9)	47 (21.3)	0.034
Previous chronic heart failure	29 (8.8)	6 (5.5)	23 (10.4)	0.15
Diabetes, no. (%)	72 (21.8)	15 (13.8)	57 (25.8)	0.01
Chronic renal failure, no. (%)	25 (7.6)	1 (0.9)	24 (10.9)	0.001
Location of arrest: in-hospital, no. (%)	79 (23.9)	24 (22.0)	55 (24.9)	0.59
Location of arrest: out-of-hospital, no. (%):	251 (76.1)	85 (78.0)	166 (75.1)	
{ Home, no. (%)	127 (50.6)	36 (48.0)	91 (54.8)	
{ Public place, no. (%)	124 (49.4)	49 (52.0)	75 (45.2)	
Bystander, no (%)	312 (94.3)	103 (94.5)	209 (94.6)	0.99
Bystander CPR, no. (%)	226 (68.3)	87 (79.8)	139 (62.9)	0.002
Initial documented rhythm, no. (%)				<0.0001
Shockable rhythm: VF / pulseless VT, no. (%)	125 (37.8)	80 (73.4)	45 (20.4)	
Non-shockable rhythm: asystole / PEA, no. (%)	206 (62.2)	29 (26.6)	176 (79.6)	
No-flow, min^a	2 [0-8]	1 [0-4]	4 [0-10]	0.0001
Low-flow, min^a	17 [10-27]	13 [7-23]	19 [12-28]	0.0005
Adrenaline bolus, mg (total IV, N=243)	2 [0-4]	0 [0-2]	2 [1-4]	<0.0001
Initial catecholamine perfusion, mg/h (N=162)	0.5 [0-1.5]	0 [0-1]	1 [0-2]	<0.0001

(Table 1, continued)	Overall (N=330)	Good outcome (N=109)	Poor outcome (N=221)	P
SAPS II	69 [56-83]	63 [53-73]	73 [59-86]	<0.0001
Cardiac cause responsible for or participating to CA, including APE and PE, no (%)^b	190 (57.4)	91 (83.5)	99 (44.8)	<0.0001
CA related to acute coronary occlusion, no (%)^b	115/220 (52.3)	65/90 (72.2)	50/130 (38.5)	<0.0001
PCI with stenting, no (%)^b	82/220 (37.3)	49/90 (54.4)	33/130 (25.4)	<0.0001
Post-CA shock, no. (%)	234 (70.7)	70 (64.2)	164 (74.2)	0.092
Clinical seizures, no. (%)	62 (18.7)	10 (9.2)	52 (23.5)	0.002
Acute hepatic injury and failure, no. (%)	103 (31.1)	27 (24.8)	76 (34.4)	0.078
DIC, no. (%)	64 (19.3)	16 (14.7)	48 (21.7)	0.14
Renal replacement, no. (%)	50 (15.1)	9 (8.3)	41 (18.6)	0.014
32-34°C TTM, no (%)^c	266 (80.4)	102 (93.6)	164 (74.2)	<0.0001
Mechanical ventilation duration^d, days	6 [3-10]	5 [3-10]	6 [3-10]	0.75
Decision to limit treatment(s), no. (%)	149 (45.0)	0	149 (67.4)	<0.0001
Delay to first treatment limitation decision, days	4 [2-7]	0	4 [2-7]	0.10
Duration of hospitalization in ICU, days	7 [4-13]	9 [6-16]	7 [4-12]	0.001
In-hospital length of stay, days	10 [5-22]	21 [14-31]	7 [4-13]	<0.0001

Abbreviation.

CPR: cardio-pulmonary resuscitation; IV: intra-venous; Low-flow time: delay between the first CPR and the return of spontaneous circulation (ROSC); No-flow time: delay between collapse (or time for emergency call in non-witnessed cardiac arrests) and the first CPR; PEA: pulseless electrical activity; VF: ventricular fibrillation; VT: ventricular tachycardia; SAPS II: simplified acute physiologic score II; CA: cardiac arrest, DIC: disseminated intravascular

coagulation; PCI: percutaneous coronary intervention; TTM: targeted temperature management.

Footnote.

^a: Time between collapse to ROSC was 22 min [14-33]; ^b: coronary angiogram was performed in 220/330 patients (67%), brain and chest CT-scans in 194/330 (59%) and 132/330 (40%), respectively; ^c: all patients were TTM-treated between 32°C and 36°C; ^d: all patients were initially intubated and mechanically ventilated after cardiac arrest. Good outcome depicts CPC 1 and 2 at hospital discharge, and poor outcome CPC 3 to 5. Survival and good outcome were observed in 45% and 32% at ICU discharge, in 44% and 36% at hospital discharge, and in 39% and 33% at 3 months after CA, respectively.

Table 2. Biomarker values within the first 3 days after cardiac arrest according to outcome at 3-month follow-up.

Biomarker	Overall (N=330)	Good outcome (N=109)	Poor outcome (N=221)	P
Lactate Adm, mMol/L	6.5 [3.0-10.1]	3.8 [2.3-6.7]	8.0 [4.7-11.6]	<0.0001
pH Adm	7.21 [7.11-7.31]	7.26 [7.17-7.33]	7.20 [7.08-7.29]	0.001
Creatinine Adm, μMol/L	105 [84-148]	93 [77-113]	111 [89-165]	<0.0001
PS100B Adm, μg/L	0.90 [0.30-2.16]	0.28 [0.15-0.52]	1.38 [0.64-3.41]	<0.0001
NSE Adm, μg/L	27 [20-39]	24 [19-35]	29 [21-40]	0.03
Lactate H24, mMol/L	2.5 [1.5-4.8]	1.9 [1.3-3.1]	2.9 [1.8-5.8]	<0.0001
pH H24	7.30 [7.23-7.39]	7.32 [7.26-7.38]	7.30 [7.22-7.39]	0.16
Creatinine H24, μMol/L	83 [62-143]	69 [56-92]	107 [66-182]	<0.0001
PS100B H24, μg/L	0.26 [0.12-0.84]	0.12 [0.08-0.20]	0.55 [0.19-1.44]	<0.0001
NSE H24, μg/L	33 [22-63]	24 [18-34]	42 [26-91]	<0.0001
Lactate H48, mMol/L	1.8 [1.3-2.8]	1.8 [1.2-2.7]	1.8 [1.3-2.9]	0.16
pH H48	7.36 [7.30-7.44]	7.36 [7.33-7.41]	7.36 [7.28-7.45]	0.79
Creatinine H48, μMol/L	81 [61-153]	75 [60-96]	96 [63-195]	0.004
PS100B H48, μg/L	0.17 [0.10-0.57]	0.10 [0.08-0.14]	0.36 [0.14-0.96]	<0.0001
NSE H48, μg/L	30 [19-84]	21 [17-28]	58 [25-144]	<0.0001

Abbreviation. Adm: day of initial sampling after return of spontaneous circulation, i.e. after admission; H24 corresponds to the following 24 hours after the day of initial sampling, and H48 to the following 24 hours after H24; NSE: Neuron Specific Enolase; PS100B: protein S100B.

Footnote. The total number of samples for PS100B and NSE were on admission: 262 and 256, at H24: 243 and 237, at H48: 224 and 214, respectively. The number of PS100B and NSE samples per patient during the first 72h after cardiac arrest were 2 [2-3] and 3 [1-3], respectively. Good outcome depicts CPC 1 and 2 at M3 after cardiac arrest, and poor outcome CPC 3 to 5 at M3-follow-up.

Table 3. Time course of PS100B values between the first 3 days after CA according to outcome.

Δ PS100B	Good outcome at discharge	Poor outcome at discharge	Good outcome at M3	Poor outcome at M3	P value ^b Discharge / M3
Δ Adm-H24 neg.	1 ^a	23	1 ^a	23	0.0001 / 0.001
Δ Adm-H24 pos.	62	84	51	84	
Δ Adm-H48 neg.	4	27	4	26	0.002 / 0.006
Δ Adm-H48 pos.	65	89	56	87	
Δ H24-H48 neg.	27	42	23	41	0.75 / 0.74
Δ H24-H48 pos.	43	77	37	77	

Abbreviation. Adm: day of initial sampling after ROSC, i.e. after admission; H24 corresponds to the following 24 hours after the day of initial sampling, and H48 the following 24 hours after H24; M3 denotes the 3rd month of follow-up after CA; Discharge denotes hospital discharge.

Footnote. Δ PS100B Adm-H24 is defined as the difference between the first blood sample on admission (n=278) and the sample at H24 (n=257), the Δ PS100B Adm-H48 is the difference between the first blood sample on admission (n=278) and the sample at H48 (n=239), and Δ PS100B H24-H48 is the difference between the blood sample at H24 and the sample at H48. Pos. means a positive difference between the first and second samples (i.e. decreasing PS100B value measured on the second sampling). Neg. means a negative difference between the first and second samples (i.e. increasing PS100B value measured on the second sampling).

^a: PS100B values for this patient were 0.102 at D0 and 0.123 at D1. ^b: Fisher exact tests are expressed.

Table 4. Biomarkers to predict outcome at 3 months after CA: sensitivity, specificity, AUC, NRI versus clinical model, and NRI versus clinical model + NSE-Adm.

Biomarker	Se^a	Sp^a	Criterion	AUC^b	NRI (%) vs. clinical model^c	NRI (%) vs. clinic + NSE^d
PS100B Admission	76.7	79.0	0.539	0.831 [0.779 - 0.883]	69.8 [48.1 - 91.6]	63.8 [41.6 - 86.1]
PS100B H24	88.8	63.6	0.321	0.825 [0.772 - 0.879]	101.2 [79.5 - 122.9]	66.1 [36.2 - 96.0]
PS100B H48	79.5	75.9	0.139	0.818 [0.761 - 0.874]	53.4 [31.8 - 75.0]	97.8 [71.6 - 124.0]
NSE Admission	71.4	45.9	31.92	0.585 [0.512 - 0.658]	-21.7 [-46.3 - 2.9] ^e	Reference
NSE H24	98.7	44.3	49.28	0.761 [0.702 - 0.820]	77.1 [52.9 - 101.3]	67.4 [37.5 - 97.2]
NSE H48	92.3	59.6	38.30	0.776 [0.716 - 0.837]	99.8 [77.7 - 121.8]	89.7 [64.4 - 115.1]
Lactate Admission	77.8	57.7	7.00	0.709 [0.650 - 0.767]	64.4 [42.5 - 86.2]	52.2 [27.0 - 77.5]
Lactate H24	71.3	55.0	2.77	0.647 [0.582 - 0.712]	42.2 [19.9 - 64.4]	19.1 [-5.8 - 44.1] ^e
Lactate H48	31.6	82.8	1.24	0.551 [0.480 - 0.622]	34.2 [10.5 - 57.8]	-2.9 [-28.1 - 22.2] ^e
pH Admission	57.0	63.9	7.23	0.618 [0.554 - 0.682]	57.6 [35.5 - 79.8]	57.6 [35.5 - 79.8]
pH H24	82.7	29.7	7.23	0.549 [0.483 - 0.616]	22.8 [-0.8 - 46.4] ^e	-7.5 [-31.1 - 16.1] ^e
pH H48	77.2	36.4	7.32	0.510 [0.442 - 0.578]	32.8 [9.4 - 56.2]	-6.0 [-30.9 - 18.9] ^e
Creat. Admission	85.2	44.7	126	0.658 [0.598 - 0.718]	67.6 [48.0 - 87.2]	32.9 [8.4 - 57.4]
Creat. H24	70.2	62.8	81	0.672 [0.610 - 0.735]	51.7 [29.5 - 73.8]	32.3 [7.5 - 57.1]
Creat. H48	84.5	42.9	116	0.605 [0.539 - 0.672]	42.3 [21.6 - 63.0]	30.2 [8.0 - 52.4]

Abbreviation. Se: sensitivity. Sp: specificity. AUC: area under the curve. NRI: Net Reclassification Index.

Footnote. ^a : Best sensitivity / specificity (with their criterion) according to the maximum accuracy.

^b : Biomarkers Receiver Operating Characteristic (ROC) curves are represented with their area under the curve (AUC) and CI-95% for their ability to discriminate good versus poor outcome at 3-month follow-up.

^c : Net Reclassification Index (NRI) of each biomarker at all time-points against clinical model (including clinical parameters with statistical significance in the multivariate analysis: initial shockable rhythm, no-flow duration, clinical seizures, and therapeutic hypothermia).

^d : NRI against clinical model (with parameters with statistical significance in the multivariate analysis) + NSE-Adm as the reference biomarker.

^e : no added value according to NRI. Biomarkers with NRI >50% with and without NSE are PS100B at all time-points, NSE after H24, and pH and lactate on admission.