

A prediction model for good neurological outcome in successfully resuscitated out-of-hospital cardiac arrest patients

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1 **A prediction model for good neurological outcome in successfully resuscitated out-of-**
2 **hospital cardiac arrest patients**

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56 **Abstract**

57 **Background**

58 In the initial hours after out-of-hospital cardiac arrest (OHCA), it remains difficult to estimate whether the
59 degree of post-ischemic brain damage will be compatible with long-term good neurological outcome. We aimed
60 to construct prognostic models able to predict good neurological outcome of OHCA patients within 48 hours
61 after CCU admission using variables that are bedside available.

62 **Methods**

63 ~~Based on prospectively gathered data, a retrospective data analysis was performed on This prospective,~~
64 ~~observational study enrolled~~ 107 successfully resuscitated OHCA patients ~~with a presumed cardiac cause of~~
65 ~~arrest, in whom~~ Targeted temperature management at 33°C was initiated at CCU admission. Prediction models
66 for good neurological outcome (CPC1-2) at 180 days post-CA were constructed at hour 1, 12, 24 and 48 after
67 CCU admission. Following multiple imputation, variables were selected using the elastic-net method. Each
68 imputed dataset was divided into training and validation sets (80% and 20% of patients, respectively). Logistic
69 regression was fitted on training sets and prediction performance was evaluated on validation sets using
70 misclassification rates.

71 **Results**

72 The prediction model at hour 24 predicted good neurological outcome with the lowest misclassification rate
73 (21.5%), using a cut-off probability of 0.55 (sensitivity=75%; specificity=82%). This model contained sex, age,
74 diabetes status, initial rhythm, percutaneous coronary intervention, presence of a BIS 0 value, mean BIS value
75 and lactate as predictive variables for good neurological outcome.

76 **Conclusion**

77 This study shows that good neurological outcome after OHCA can be reasonably predicted as early as 24 hours
78 following ICU admission using parameters that are bedside available. These prediction models could identify
79 patients who would benefit the most from intensive care.

80 **Keywords**

81 Out-of-hospital cardiac arrest – good neurological outcome – prediction model

82 **Background**

83 Despite improvements in advanced life-support and efforts to improve the quality of post-resuscitation
84 care, in-hospital survival after out-of-hospital cardiac arrest (OHCA) remains poor. Within the current post-
85 cardiac arrest (CA) period, outstanding though expensive treatment strategies exist for all comatose patients
86 successfully resuscitated after OHCA [1-4]. Especially within this time period, the uncertain prognosis of OHCA
87 patients fuels the continuous drive of physicians to identify those patients who will benefit the most from
88 aggressive intensive care. Therefore, any argument in favour of good outcome could support the critical decision
89 to use all ICU resources in those patients. Moreover, healthcare workers continuously encounter the optimistic
90 expectations of relatives, and so providing any early information about the likelihood of a good outcome could
91 facilitate communication with patients' next of kin.

92 Before the era of targeted temperature management (TTM), a careful interpretation of the clinical
93 neurological examination was considered as the gold standard to determine the prognosis in comatose OHCA
94 survivors [5]. With the implementation of TTM and its concomitant use of sedatives, specific clinical signs have
95 become unreliable for outcome prediction within the initial 24 hours [4, 6]. Multiple prognostic markers have
96 been introduced to aid with poor outcome prognostication after OHCA, but do not possess enough
97 discriminatory power on their own to predict outcome (i.e. electroencephalography (EEG), somatosensory-
98 evoked potentials (SSEPs), biochemical markers and brain imaging). Besides, these are not always continuously
99 or sometimes only locally available, are expensive, laborious and above all, require expertise for reliable
100 interpretation [4, 6-8]. Early outcome prognostication should therefore perhaps focus on good rather than poor
101 outcome prediction, especially since guidelines state that the decision to withdraw life-sustaining therapy should
102 be postponed to at least 72 hours after CA. Models for the prediction of neurological outcome have been
103 described previously, but use often variables that are rather ambiguous or unavailable at the bedside [9-14]. A
104 prediction model, capable of estimating the probability on good outcome in the early hours based on parameters
105 that are bedside available, could be of major interest for physicians to identify those patients with a reasonable
106 chance of recovery. Additionally, these prediction models might also provide assistance for patient stratification
107 in future randomized controlled trials or epidemiological studies. Therefore, this retrospective study aimed to
108 construct-develop prognostic models – using a training and (internal) validation set – able to predict good

109 neurological outcome as soon as possible in OHCA patients using variables that are bedside available after ICU
110 admission.

111

112 **Methods**

113 **Study population**

114 All consecutive adult comatose survivors who were successfully resuscitated from OHCA ~~with a~~
115 ~~presumed cardiac cause of arrest~~ and admitted to the Coronary Care Unit (CCU) of our tertiary care hospital
116 (Ziekenhuis Oost-Limburg, Genk, Belgium), were prospectively enrolled between March 2011 and May 2015.

117 ~~Exclusion criteria were an obvious non-cardiac cause of arrest, in-hospital cardiac arrest and inadequately~~
118 ~~performed TTM at 33°C. A head computed tomography (CT) scan was performed if no obvious cause of arrest~~
119 ~~was found.~~ In this patient cohort, we previously investigated the prognostic value of Near-Infrared Spectroscopy
120 (NIRS) and BIS monitoring, which are neuromonitoring tools known for their non-invasiveness, ease of use and
121 bedside availability [15, 16]. Based on these prospectively gathered data, this retrospective study aimed to
122 construct multivariate prediction models for good neurological outcome using these non-invasive cerebral
123 parameters in conjunction with other variables that are readily available following CCU admission. The study
124 protocol was approved by the local Committee for Medical Ethics (11/066). Written informed consent was
125 obtained from the patients' next of kin and was reconfirmed if the patient regained consciousness.

126 **Post-resuscitation protocol**

127 Our institutional post-resuscitation protocol has been described elsewhere [15, 17]. All patients were
128 intubated, mechanically ventilated and sedated by intravenous administration of remifentanyl and propofol or
129 midazolam. ~~When indicated~~ Unless an obvious non-cardiac cause of arrest could be identified, urgent coronary
130 angiography was performed by interventional cardiologists, followed by a percutaneous coronary intervention.
131 Immediately after admission to the emergency department, TTM at 33°C was initiated by administering cold
132 saline intravenously (4°C – 15-30ml/kg). Once admitted at the CCU, TTM was further mechanically induced
133 and maintained at 33°C for 24 hours using endovascular (Icy-Catheter, Coolgard® 3000, Alsius, Irvine, CA,
134 USA) or surface (ArcticGel™ pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling
135 systems. Hereafter, patients were rewarmed over the next 12 hours (0.3°C/hour). All systems were equipped with

136 a feedback loop system to control target temperature using an oesophageal temperature probe. Only in case of
137 muscle shivering, cisatracurium was administered. Within the TTM period, sedation was titrated to obtain values
138 between -3 and -5 on the Richmond Agitation-Sedation scale. Cannulation of the radial artery ensured a
139 continuous registration of blood pressure. Placement of a pulmonary artery catheter was left at the discretion of
140 the treating physician and, while, provided information about mixed venous blood oxygen saturation ~~was~~
141 ~~provided by a pulmonary artery catheter~~. According to the guidelines, mean arterial pressure was strictly
142 maintained above 65mmHg using norepinephrine [18]. Additionally, an hourly blood gas analysis was
143 performed including the determination of lactate. From February 2012 onwards, neuron-specific enolase (NSE)
144 was determined at hour 24 and 48 following CCU admission. Patients were extubated when their neurological,
145 respiratory and hemodynamic status had been recovered sufficiently.

146 **Neuromonitoring**

147 Cerebral tissue oxygen saturation (SctO₂) was continuously measured using FORE-SIGHT™
148 technology (CAS Medical systems, Branford, CT, USA) for 72 hours following CCU admission. Furthermore,
149 Bispectral Index (BIS) monitoring using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA) was
150 started as soon as possible and continued up to 72 hours. Both NIRS and BIS sensors were bilaterally placed on
151 the forehead before the start of TTM and covered to prevent ambient light interference. According to
152 manufacturer's instructions, the BIS sensor was placed above the eyebrows and NIRS sensors were positioned
153 above the BIS sensor. In patients with a limited amount of space on the forehead to place both NIRS and BIS
154 sensors, priority was given to NIRS, ignorant which of both parameters contained the highest prognostic power.
155 Obviously, this clarifies the high degree of missingness of BIS data in our entire study cohort. Together with
156 hemodynamic data, SctO₂ was collected with a 2 second time interval and BIS data was stored every second.
157 Although treating physicians were not blinded to the recorded NIRS and BIS values, therapeutic interventions
158 were performed according to the guidelines and at the discretion of the treating physician. As such, the collected
159 NIRS ~~nor~~ and BIS data were solely being collected for research purposes and were not being used to guide
160 therapeutic interventions or to assist with the process of neuroprognostication.

161 **Outcome assessment**

162 At 180-days post-CA, surviving patients were interviewed at follow-up by attending cardiologists.
163 These medical reports were retrospectively assessed by a single assessor (W.E.) who defined pPatients' outcome
164 was defined using the Cerebral Performance Category (CPC) scale. No outcome data was missing. at 180 days

165 ~~post-CA based on reviews of the medical reports.~~ According to the scale classification, CPC 1 indicates good
166 cerebral performance; CPC 2 signifies a moderate disability but sufficient cerebral functioning for independent
167 daily-life activity; CPC 3 implies severe disability with dependency on others; CPC 4 indicates coma or
168 vegetative state and CPC 5 stands for death [19]. A CPC1-2 and CPC3-5 was considered as a good and a poor
169 neurological outcome, respectively.

170 **Statistical analysis**

171 Prediction models for good neurological outcome at 180 days post-CA (CPC1-2) were constructed at
172 hour 1, 12, 24 and 48 after CCU admission (Fig. 1). Variables considered to be included at all time points were:
173 sex, age, diabetes status, witnessed arrest, initial rhythm (with asystole as reference category), percutaneous
174 coronary intervention, initial lactate, initial haemoglobin, initial creatinine, mean arterial pressure, BIS value of
175 0, mean BIS, mean cerebral oxygen saturation. Along with these variables, the following parameters were
176 considered to be included: lactate, haemoglobin, creatinine and mixed venous oxygen saturation levels at the
177 respective time points. Furthermore, ~~neuron-specific enolase~~ (NSE) was considered at hour 24 and 48.

178 To account for missing variables, multiple data imputation was performed. Predictive mean matching
179 imputation was used for continuous variables and logistic regression with bootstrap was performed to impute
180 binary variables. For categorical variables with more than two levels, polytomous logistic regression was used to
181 impute [20]. The number of imputations was equal to the percentage of missingness at each data set for four
182 different time points [21]. The elastic-net method was then used to perform variable selection for all imputed
183 datasets [22]. Variables repeatedly retained in more than 50% of the imputed datasets were chosen for model
184 fitting. To select the optimal values of the elastic-net penalty α and the tuning parameter λ , ten-fold cross-
185 validation was used. The logistic regression model could be specified as:

$$186 \quad \log \left[\frac{P(Y_i = 1)}{1 - P(Y_i = 1)} \right] = \beta_0 + \sum_{j=1}^p \beta_j X_{ij}$$

187 Where j (1, p) is the j predictor included in the model and $i = 1, n$ is the number of observations in each imputed
188 data set and $P(Y_i = 1)$ is the probability of survival for patient i .

189 Once the variables were selected, the performance of the final multivariate logistic regression was
190 assessed for each imputed dataset and results were pooled to make final inference for data at each time point.
191 Each imputed dataset was randomly divided into a training set (80% of patients) and a validation set (20% of

192 patients). Logistic regression was fitted on the training sets and the prediction performance of the resulting
193 model was evaluated on the validation sets by means of misclassification rates (i.e. percentage of cases
194 misclassified; Fig. 1). For this purpose, diverse cut-off points were prespecified. Logistic regression was fitted on
195 all imputed datasets per time point with cut-off points ranging from 0.10 to 0.90 by an increment of 0.05. When
196 the calculated probability from logistic regression was larger than the chosen cut-off point, the patient was
197 categorized as survival (CPC1-2). The corresponding sensitivities and specificities were calculated. Cut-off
198 points that produced both a sensitivity and specificity larger than 70% were chosen. ~~In our approach, the~~
199 ~~probability of survival was modelled, hence the sensitivity was considered to be very important. Based on this~~
200 ~~argument, cut-off points yielding a sensitivity above 90%, irrespective of specificity, were additionally chosen.~~
201 After the cut-off points were determined, the performance of the final (multivariate) logistic regression models
202 constructed at the four time points was assessed by means of the misclassification rate. The optimal cut-off point
203 for each time point was the one with the smallest misclassification rates. We used R 3.2.1 statistical software (R
204 Foundation for Statistical Computing, Vienna, Austria) for multiple imputation, model selection and SAS
205 Software version 13.2 (SAS, Cary, NC, USA) for pooling the results over the different imputed data sets using
206 logistic regression.

207 Results

208 Between March 2011 and May 2015, 147 successfully resuscitated comatose OHCA patients, admitted
209 to the emergency department and transferred to the Coronary Care Unit, were ~~enrolled~~screened for eligibility.
210 Data of ~~40-25~~ patients were excluded ~~from further analysis~~ due to the following ineligibility reasons: cooling
211 with mattress (n=8), in-hospital cardiac arrest (n=10), drowning/hanging (n=3), no TTM at 33°C (n=4).
212 ~~Furthermore, 15 out of 122 eligible patients were not retained for final data analysis due to the following~~
213 ~~reasons: coronary-artery bypass graft surgery at day 2 (n=1) and not included due to no storage of issues with~~
214 ~~data collection (continuous) hemodynamic, SctO₂ and BIS data~~ (n=14). In total, 107 successfully resuscitated
215 comatose OHCA patients with a cardiac cause of arrest were included for data analysis of whom 50 (47%) had a
216 good (CPC1-2) and 57 (53%) a poor neurological outcome (CPC3-5) at 180 days post-CA. Demographic data of
217 all included patients are provided in table 1. Prediction models for good neurological outcome at 180 days post-
218 CA were constructed at hour 1, 12, 24 and 48 after CCU admission. As two patients died before hour 12, 105
219 patients were retained for the models at hour 12 and hour 24. Ten patients died between hour 24 and hour 48,
220 resulting in 95 patients who were retained for the model at hour 48.

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221 In total, 13, 17, 18 and 18 variables were considered in the prediction models at hour 1, 12, 24 and 48,
 222 respectively (Table 2). Based on the elastic-net method, 5, 9, 8 and 7 variables were retained in the models at
 223 hour 1, 12, 24 and 48, respectively. Variables retained in all prediction models were diabetes, initial rhythm,
 224 percutaneous coronary intervention, mean BIS value at the respective time point and the presence of a BIS 0
 225 value within the respective time frames. Lactate and sex were present at hour 12, 24 and 48, while age was only
 226 retained at hour 12 and 24 following CCU admission. In addition, creatinine was predictive for good
 227 neurological outcome at hour 12 after CCU admission. NSE was determined at hour 24 and 48, but was only
 228 retained in the model at hour 48. Mean SctO₂ values were not present at a single time point (Table 2).

229 Multivariate logistic regression was performed and results were pooled for each time point (Table 2).
 230 The pooled χ^2 of the Hosmer and Lemeshow test for the prediction model at hour 1, 12, 24 and 48 was 0.95,
 231 0.90, 0.96 and 0.99, respectively, indicating a good fit for all models. Then, the performance of all prediction
 232 models was assessed by means of the misclassification rate, where the most optimal model is considered as the
 233 one generating the lowest misclassification rates. All models predicted good neurological outcome with a
 234 sensitivity and specificity above 70% (Table 3). However, the prediction model at hour 24 predicted good
 235 neurological outcome with the lowest misclassification rate (21.5%) using a cut-off probability of 0.55 (Fig. 1).

236 The probability (P) of survival at hour 24 following CCU admission can be calculated using the following
 237 equation where β ratios are given with 95% confidence intervals:

$$238 \text{Log} \frac{P(\text{Survival})}{(1-P(\text{Survival}))} = - 3.504 (\text{xxx} - \text{xxx}); \text{intercept}$$

- 239 - 1.244 (xxx - xxx); if patient is female
- 240 - 0.025 (xxx - xxx); multiplied with age of patient
- 241 + 2.014 (xxx - xxx); (if diabetes is absent)
- 242 + 1.204 (xxx - xxx); if initial rhythm is ventricular fibrillation*
- 243 - 0.139 (xxx - xxx); if initial rhythm is pulseless electrical activity*
- 244 *asystole as initial rhythm was set as reference category
- 245 - 0.210 (xxx - xxx); (if no percutaneous coronary intervention was
- 246 performed)
- 247 + 3.139 (xxx - xxx) (if a BIS value of 0 was absent within the first 24 hours)
- 248 + 0.033 (xxx - xxx) x mean BIS value at hour 24
- 249 - 0.216 (xxx - xxx) x lactate value at hour 24

250 Using this cut-off point of 0.55, the prediction model at hour 24 predicted good neurological outcome with a
251 sensitivity of 75% and specificity of 82% (Fig. 1).

252 At hour 24, missingness was present in 12 variables, namely initial haemoglobin (0.9%), diabetes
253 (1.9%), witnessed arrest (2.8%), initial Rhythm (3.7%), initial lactate (8.4%), initial creatinine (8.4%), mean
254 MAP at hour 24 (9.5%), mean SvO₂ at hour 24 (21%), NSE (26.7%), BIS 0 value (27.6%) and mean BIS value
255 at hour 24 (38.1%). Missingness at the other time points is shown in figure 2.

256

257 **Discussion**

258 Our data show that good neurological outcome at 180 days post-CA can be predicted in successfully
259 resuscitated comatose OHCA patients treated with TTM at 33°C using prediction models containing variables
260 that are early and bedside available after CCU admission. In order to predict good neurological outcome as early
261 as possible, multilevel ~~prognostic-prediction~~ models were constructed at hour 1, 12, 24 and 48 after CCU
262 admission which all reached a sensitivity and specificity above 70%. Using a cut-off point of 0.55, the prediction
263 model at hour 24 predicted good neurological outcome with the smallest misclassification rate, corresponding to
264 a sensitivity of 75% and specificity of 82%.

265 Identifying post-CA patients who would maximally benefit from full supportive therapy without
266 unnecessary suffering remains hard to achieve once admitted to the ICU. Nowadays, specific clinical signs in the
267 initial 24 hours have become inaccurate due to the implementation of TTM [4, 6]. Electro-encephalography,
268 SSEPs, biomarkers and brain imaging are prognostic tools recommended by current guidelines to assist with
269 outcome prognostication, but are often not constantly available in daily clinical practice, are time-consuming,
270 expensive and require clinical expertise [4, 23-26]. In an attempt to account for these hurdles and facilitate
271 bedside prognostication, we previously investigated the role of NIRS and BIS monitoring in terms of outcome
272 prediction [15, 16, 27]. This retrospective analysis now aimed to construct multivariate regression models
273 including these cerebral parameters combined with variables, readily available at ICU admission, in order to
274 predict good neurological outcome after OHCA. Unlike scoring systems developed by others, we decided to
275 ignore ambiguous variables such as 'low-flow' and 'no-flow' times as these are often unknown or incorrectly
276 reported [9-14]. In this study, the constructed prediction models at hour 1, 12, 24 and 48 after admission
277 succeeded to predict good neurological outcome at 180 days post-CA, all with a sensitivity and specificity above

278 70%. The model which classified OHCA patients with the lowest misclassification errors was the one at hour 24
279 and contained sex, age, diabetes status, initial rhythm, percutaneous coronary intervention, the ~~presence-absence~~
280 of a BIS 0 value within the first 24 hours, mean BIS value at hour 24 and lactate as predictive variables for good
281 neurological outcome. This model was able to predict good neurological outcome with a sensitivity of 75% and
282 specificity of 82% when 0.55 was used as cut-off point. ~~It has to be stated that the obtained predictive~~
283 ~~performance of our model should be considered as rather modest. Hence, we certainly do not advise the use of~~
284 ~~our prediction models to assist with the clinical prognostication process at the moment. On the contrary, external~~
285 ~~validation in a large patient cohort without missing data will be a prerequisite before clinical implementation will~~
286 ~~be possible. Additionally, further research attempts should now investigate whether the performance of our~~
287 ~~constructed prediction models could be improved by adding other prognostic parameters. Therefore, our research~~
288 ~~findings might be considered as one of the first steps in~~ For now, we believe that these models should be
289 ~~considered as the development of an easy tool, for the identification that is able to identify of~~ OHCA patients who
290 might benefit the most from aggressive treatment, and for whom finite healthcare sources should be optimized.
291 ~~Additionally~~ For now, our models might be of potential interest as guidance for designing risk stratification
292 models in clinical research with variable resource allocation or could be used to enhance future research
293 initiatives focusing on new therapies. ~~Aside from these clinical benefits~~ Additionally, the results of this study
294 could be helpful for the design of future epidemiological studies as it is often difficult to select which data should
295 be assembled and when these should optimally be collected after CCU admission [28].

296 As shown by others, initial rhythm, percutaneous coronary intervention and diabetes status prior to CA
297 were variables retained at all selected time points in this study [29-31]. Likewise, both mean BIS values and the
298 ~~presence-absence~~ of a BIS 0 value appear to be predictors for good neurological outcome across all time points,
299 thereby confirming the prognostic validity of BIS monitoring in the post-CA setting once again [16, 27, 32-34].
300 In line with previous studies, gender, age as well as lactate and creatinine levels were predictive for good
301 neurological outcome, albeit not immediately following ICU admission [35-38]. Finally, NSE was only retained
302 in the model at hour 48 which is in accordance with previous studies [25, 39].

303 In recent years, the prognostic value of SctO₂ has been examined thoroughly in the post-CA setting.
304 Several studies demonstrated that high SctO₂ values during TTM at 33°C were associated with a higher
305 likelihood of favourable neurological outcome [17, 40]. Storm and co-authors even suggested a SctO₂ value of
306 50% as therapeutic target [41]. In the largest post-resuscitation cohort so far, we previously showed that the
307 overall course of SctO₂ was different between OHCA patients with a good and poor neurological outcome.

308 Nonetheless, the observed SctO₂ margin seemed to be too narrow to likely represent outcome differentiation. As
309 such, it was concluded that SctO₂ lacked prognostic power on its own to serve in outcome prognostication [15].
310 The role of SctO₂ as prognostic marker included in a multivariate prediction model, on the other hand, has not
311 been investigated until now. Based on our analysis, we are the first to show that SctO₂ was not retained in any
312 multivariate regression model at a single time point upon CCU admission. Therefore, this study illustrates once
313 more the limited prognostic value of SctO₂ by itself in the early hours following ICU admission.

314 This study has several limitations. First, this was a single-centre study with a limited number of patients
315 included. Secondly, multiple imputation was used to account for missingness in certain variables. Nevertheless,
316 imputed values were deemed as persuasive based on the generated density plots of the observed and imputed
317 data (*not shown*). On the other hand, a possible selection bias could not have been excluded if only the cases
318 were included with all available parameters. Third, BIS monitoring ~~has become standard practice in our hospital,~~
319 ~~which might be different in other centres~~ might not be routinely applied in other centres which might complicate
320 ~~the usefulness of our prediction models~~. Nonetheless, BIS monitoring is cost-effective, non-invasive and can be
321 made available at the bedside rather easily. ~~On the other hand, BIS data were not kept blinded for treating~~
322 ~~physicians through which we cannot fully exclude the possibility that the prognostic value of BIS was being~~
323 ~~artificially inflated during the study period. Nonetheless, treating physicians were cardiologists who are not~~
324 ~~familiar with the use and interpretation of BIS values~~. Finally, our prediction models were only validated
325 internally. Even though it has been shown that n-fold cross validation generates stable estimates with low bias,
326 external validation on an independent data set will be mandatory before these models can be used in routine
327 clinical practice [42].

328 **Conclusion**

329 Prognostic models for the prediction of survival in OHCA patients were constructed at hour 1, 12, 24
330 and 48 following CCU admission. The prediction model which classified OHCA patients with the lowest
331 misclassification errors was the one at hour 24, yielding a sensitivity of 75% and specificity of 82%. In this
332 model, sex, age, diabetes status, initial rhythm, percutaneous coronary intervention, the presence of a BIS 0
333 value, mean BIS value and lactate were the variables identified as predictive for good neurological outcome.
334 ~~Before this model can be translated into clinical practice~~At the moment, external validation in a larger patient
335 cohort will be mandatory ~~before this model can be translated into clinical practice~~. ~~For now, these models might~~
336 ~~identify those patients who would maximally benefit from full supportive intensive care~~.

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345 **List of abbreviations**

346 BIS: bispectral index

347 CA: cardiac arrest

348 CCU: Coronary Care Unit

349 CPC: Cerebral Performance Category

350 EEG: electro-encephalography

351 ICU: Intensive Care Unit

352 NIRS: Near-Infrared Spectroscopy

353 NSE: neuron-specific enolase

354 OHCA: out-of-hospital cardiac arrest

355 P: Probability

356 SctO₂: cerebral tissue oxygen saturation

357 SSEP: somatosensory evoked potential

358 TTM: targeted temperature management

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365 **Declarations**

366 **Ethics approval and consent to participate**

367 The study complies with the Declaration of Helsinki. Ethical approval was obtained before study onset from the
368 local medical ethics committee (Comité Medische Ethiek Ziekenhuis Oost-Limburg 11/066). Written informed
369 consent was obtained from the patients' next of kin.

370 **Consent for publication**

371 Not applicable

372 **Availability of data and material**

373 The datasets used and/or analyzed during the current study are available from the corresponding author on
374 reasonable request.

375 **Competing interests**

376 The authors declare that they have no competing interests.

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380 **Authors' contribution**

381 WE was responsible for the study execution, data management, data analysis, data interpretation, and manuscript
382 writing. TT was responsible for statistical data analysis. CG was responsible for the study design, study
383 execution, oversight of data management, data interpretation and critically revising the manuscript. LP was
384 responsible for study execution and data management. DM and FJ were responsible for study design,
385 interpretation of results and manuscript editing. JD and CDD were responsible for the conception, study design,
386 study execution, data interpretation and manuscript editing. All authors read and approved the final manuscript.

387

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574 **Legends to figures**

575 **Fig. 1** Development of prediction models and calculation used to predict good neurological outcome at hour 24.
576 This flowchart demonstrates the developmental process of the constructed prediction models at selected time
577 points following CCU admission. Twenty-four hours after CCU admission, good neurological outcome was
578 predicted with the lowest misclassification rate (i.e. the optimal model; *top of figure*). The probability for good
579 neurological outcome can be calculated using the correlation coefficients from all variables (*bottom of figure*).
580 For example, an 84-year old female patient without diabetes, successfully resuscitated from an OHCA with
581 ventricular fibrillation as initial rhythm, was admitted to the emergency department and was transferred to the
582 catheterization lab where she received a percutaneous coronary intervention. Twenty-four hours after CCU
583 admission, she did not experienced a BIS value of 0, mean BIS over 24 hours was 46 and lactate was 1.2mmol/l.
584 Based on the formula, the calculated probability of good neurological outcome in this patient would be 0.68
585 which is higher than the proposed cut-off probability of 0.55. In this specific patient, good neurological outcome
586 can be predicted with a sensitivity of 75% and specificity of 82%.

587 Fig. 2. Missingness across all selected time points. This figure shows the variables considered to be included at
588 all selected time points that have more than 5% missingness across the study cohort.

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599 **Table 1.** Demographics

Parameter	Survivors (CPC1-2)	Non-survivors (CPC3-5)	P-value
Patients, n (%)	50 (53)	57 (47)	/
Age, mean (\pm SD)	61 \pm 13	65 \pm 13	0.058
Male, n (%)	39 (78)	36 (63)	0.094
Surface cooling, n (%)	25 (50)	36 (63)	0.178
Endovascular cooling, n (%)	25 (50)	21 (37)	0.178
Initial rhythm			
<i>Ventricular fibrillation, n (%)</i>	42 (84)	26 (46)	<0.001
<i>Pulseless electrical activity, n (%)</i>	4 (8)	7 (12)	0.527
<i>Asystole, n (%)</i>	4 (8)	20 (35)	<0.001
Witnessed arrest, n (%)	45 (90)	46 (81)	0.246
Coronary angiography, n (%)	46 (92)	41 (72)	0.012
Percutaneous coronary intervention, n (%)	36 (72)	22 (39)	0.001

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609 **Table 2.** Prediction models with retained variables at the four time points following ICU admission

Variables	Hour 1 ($\chi^2 = 0.95$)		Hour 12 ($\chi^2 = 0.90$)		Hour 24 ($\chi^2 = 0.96$)		Hour 48 ($\chi^2 = 0.99$)	
	<i>Estimate (SE)</i>	<i>P-value</i>	<i>Estimate (SE)</i>	<i>P-value</i>	<i>Estimate (SE)</i>	<i>P-value</i>	<i>Estimate (SE)</i>	<i>P-value</i>
Intercept	-4.462 (1.258)	<0.001	-1.213 (2.297)	0.598	-3504 (2.242)	0.118	-1.124 (1.544)	0.467
Female	-	-	-1.819 (0.843)	0.031	-1.244 (0.763)	0.103	-1.622 (0.939)	0.085
Age	-	-	-0.032 (0.028)	0.245	-0.025 (0.025)	0.332	-	-
Absence of diabetes	1.196 (0.725)	0.099	1.673 (0.982)	0.089	2.014 (0.977)	0.039	1.880 (1.176)	0.110
Initial rhythm								
<i>Ventricular fibrillation</i>	2.213 (0.734)	0.003	0.653 (0.915)	0.475	1.204 (0.872)	0.168	0.717 (0.960)	0.455
<i>Pulseless electrical activity</i>	0.861 (0.972)	0.376	-1.456 (1.234)	0.238	-0.139 (1.228)	0.910	-0.504 (1.387)	0.716
No PCI	-0.776 (0.553)	0.160	-0.630 (0.752)	0.402	-0.210 (0.662)	0.751	-0.315 (0.734)	0.668
Absence of BIS value of 0	1.966 (0.751)	0.009	3.717 (0.942)	<0.001	3.139 (0.898)	0.001	2.878 (0.942)	0.002
Mean BIS at respective hour	0.017 (0.014)	0.231	0.027 (0.016)	0.085	0.033 (0.019)	0.092	-	-
Lactate at respective hour	-	-	-0.219 (0.187)	0.242	-0.216 (0.235)	0.358	-0.136 (0.533)	0.799
Creatinine at respective hour	-	-	-0.331 (0.310)	0.287	-	-	-	-
NSE					-	-	-0.023 (0.016)	0.153

610 BIS = Bispectral Index; NSE = Neuron-specific enolase; PCI = Percutaneous coronary intervention; SE = Standard error; χ^2 = chi-square statistic indicating the goodness-of-

611 fit

612 These are the final multivariate logistic regression models with retained variables based on the elastic-net method.

613 • Variables considered to be included at all time points: sex, age, diabetes status, witnessed arrest, initial rhythm (with asystole as reference category), PCI, initial
614 lactate, initial haemoglobin, initial creatinine, mean arterial pressure, BIS value of 0, mean BIS, mean cerebral oxygen saturation

615 • Variables considered to be included at hour 12, 24 and 48: lactate, haemoglobin and creatinine and mixed venous oxygen saturation at respective time points

616 • Variable considered to be included at hour 24 and 48: NSE at respective time points

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627 **Table 3.** Prediction performance of the four prediction models.

<i>Cut-off probability</i>	Misclassification rate				Sensitivity				Specificity			
	<i>H1</i>	<i>H12</i>	<i>H24</i>	<i>H48</i>	<i>H1</i>	<i>H12</i>	<i>H24</i>	<i>H48</i>	<i>H1</i>	<i>H12</i>	<i>H24</i>	<i>H48</i>
<i>0.45</i>	26.2 (9.1)	22.9 (8.0)	21.8 (8.2)	-	75.2 (12.5)	78.4 (12.2)	79.8 (12.4)	-	70.8 (14.9)	76.2 (11.8)	77.4 (13.2)	-
<i>0.50</i>	25.3 (9.2)	22.5 (8.2)	21.5 (8.2)	-	72.9 (12.8)	76.5 (12.8)	77.6 (12.9)	-	77.4 (13.7)	78.9 (11.6)	79.9 (12.6)	-
<i>0.55</i>	24.8 (9.2)	22.3 (8.3)	21.5 (8.4)	23.7 (9.6)	70.5 (13.1)	74.1 (13.5)	75.3 (13.6)	78.6 (14.2)	74.3 (14.4)	81.5 (11.3)	82.2 (12.3)	74.6 (15.6)
<i>0.60</i>	-	-	-	23.4 (9.5)	-	-	-	76.8 (14.4)	-	-	-	77.2 (15.0)
<i>0.65</i>	-	-	-	23.3 (9.4)	-	-	-	74.6 (14.6)	-	-	-	77.4 (13.2)

628 Misclassification rate is the percentage of cases misclassified. The optimal cut-off probability yielding the smallest misclassification rate is indicated in bold for each time

629 point. Misclassification rate, sensitivity and specificity are presented in percentage (standard errors).