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Risk prediction of cognitive decline after stroke

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Abstract

Background and Purpose

Cognitive decline is one of the major outcomes after stroke. We have developed and evaluated a risk predictive tool of post-stroke cognitive decline and assessed its clinical utility.

Methods

In this population-based cohort, 4,783 patients with first-ever stroke from the South London Stroke Register (1995-2010) were included in developing the model. Cognitive impairment was measured using the Mini Mental State Examination (cut off 24/30) and the Abbreviated Mental Test (cut off 8/10) at 3-months and yearly thereafter. A penalised mixed-effects linear model was developed and temporal-validated in a new cohort consisted of 1,718 stroke register participants recruited from (2011-2018). Prediction errors on discrimination and calibration were assessed. The clinical utility of the model was evaluated using prognostic accuracy measurements and decision curve analysis.

Results

The overall predictive model showed good accuracy, with root mean squared error of 0.12 and R² of 73%. Good prognostic accuracy for predicting severe cognitive decline was observed AUC: (88%, 95% CI [85-90]), (89.6%, 95% CI [86-92]), (87%, 95% CI [85-91]) at 3 months, one and 5 years respectively. Average predicted recovery patterns were analysed by age, stroke subtype, Glasgow-coma scale, and left-stroke and showed variability.

41 Decision curve analysis showed an increased clinical benefit, particularly at threshold
42 probabilities of above 15% for predictive risk of cognitive impairment.

43

44 **Conclusions**

45

46 The derived prognostic model seems to accurately screen the risk of post-stroke cognitive
47 decline. Such prediction could support the development of more tailored management
48 evaluations and identify groups for further study and future trials.

49

50 **Keywords:** Post-stroke, rehabilitation, Cognitive decline, monitoring, recovery, clinical
51 prediction, case mix, mixed-effects model.

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1. Introduction

Stroke is a common long-term condition with an increasing incidence as the population ages. Patients who have had a stroke have an increased likelihood of cognitive deficit compared to those who have not had a stroke [1]. It remains persistently high up to fifteen years post-stroke and is associated with higher disability, lower quality of life and depression. An increasingly ageing population coupled with the decline in mortality after stroke [2] means that post-stroke cognitive impairment will become more prevalent particularly since the risk of stroke [3] and cognitive impairment [4] rise exponentially with age. Studies have suggested that cognitive decline could be predictable after stroke [5-6].

A longitudinal follow-up and a patient-specific predictive models may be more appropriate to accurately capture health outcomes with the aim of planning immediate, mid and long-term care simultaneously for individual patients with poor physical and psychological outcomes. Preventive medication and rehabilitation programs are available for controlling risks but a patient-centred instrument to determine in advance when a poor health outcome might occur would assist management of care of these patients, and therefore, allow them to live a more normal life.

The Mini-Mental State Examination (MMSE) is the most widely used instrument for screening dementia [7] and it is significantly correlated with cognitive decline following stroke. Suzuki et al [8] used MMSE scores at baseline (stroke onset) to predict MMSE scores over time (model 1 $R^2 = 67.6\%$, model 2 $R^2 = 59.8\%$). However, this may not capture recovery accurately as MMSE scores at stroke onset are often much lower than at subsequent time points because many patients experience some improvement following the acute phase. Ross et al [9] used imaging metrics from proton magnetic resonance spectroscopy to predict cognitive decline in patients up to three years following stroke ($R^2=54.6\%$). Measures in the frontal white matter of the brain were associated with change in composite z-score of tests assigned to each cognitive domain three years post-stroke ($R^2=54.6\%$). Similarly, Saini et al [10] used metrics from computed tomography scans to predict cognitive decline three to six months following ischemic stroke. The presence of significant atrophy and white matter lesions were associated with cognitive decline with an odds ratio of 3.07 and 3.13 respectively. Whilst these models could be a useful assistive tool to predict cognitive decline, atrophy are not systematically measured in the practice.

Tang et al [11] reported that several models have been developed for people with stroke to predict dementia [12] [13] or cognitive impairment [14][15] and their predictive accuracy was found to be acceptable. Different variables including demographic, cognitive test scores and neuroimaging markers have been incorporated into different models, with predictive accuracy found to be moderate to high. However, their utility is challenging as they include neuroimaging variables that are not easily accessible.

A recent systematic review [16] shows that cognitive decline seems to become more apparent over a longer follow-up period, and thus new models could be developed to predict post stroke cognitive impairment and dementia over longer time periods.

96 In this study, we develop and validate a patient-specific predictive model to estimate risk for
97 cognitive decline up to 5 years after ischemic stroke and assess deviations from observed and
98 predicted recovery and differences in recovery trends.

99 The output from this research will be used to aid long-term monitoring and provide prognostic
100 information to stroke survivors and their families, and to assist the development of more
101 tailored long-term management and care plans.

102 103 **2. Methods**

104 105 **2.1 Source of data**

106
107 Data for this analysis were derived from the South London Stroke Register (SLSR), an
108 ongoing population-based register that has prospectively recorded first ever strokes in patients
109 of all age groups living within a geographically defined area of south London since 1995. In
110 this analysis we used data collected between 1995 and 2018.

111 The methods of the SLSR have been described in detail by Wolfe et al [6-17] and are
112 summarised here. All patients with a first ever stroke after 1st January 1995 and residing in a
113 defined inner-city area of South London were eligible for inclusion. According to the 2011
114 Census, with annual predicted changes, the north Southwark and Lambeth (n=357,308)
115 comprises a multi-ethnic population with a large proportion of black Caribbean and African
116 residents (25.3%). Stroke is defined according to WHO definition of stroke [17]. Case
117 ascertainment is estimated as 88% complete by a multinomial-logit capture-recapture model
118 [17].

119 120 **2.2 Participants**

121
122 Patients admitted to hospitals serving the study area (2 teaching hospitals within and 3
123 hospitals outside the study area) were identified by regular reviews of acute wards admitting
124 stroke patients, national data on patients admitted to any hospital in England and Wales with a
125 diagnosis of stroke are screened for additional patients.

126 All general practitioners (N=699 (2011)) within and on the borders of the study area are
127 contacted regularly and asked to notify the SLSR of stroke patients. Referral of non-
128 hospitalized stroke patients to a neurovascular outpatient clinic (from 2003) or domiciliary
129 visit to patients by the study team is also available to general practitioners. Community
130 therapists are contacted every 3 months. Death certificates are checked regularly. Patients are
131 assessed at the stroke onset, 3 months and annually after stroke.

132 133 **2.3 Outcome and Predictors**

134
135 The outcome of interest is cognitive impairment up to five years following stroke, measured
136 by the Mini Mental State Examination (MMSE) or Abbreviated Mental Test (AMT) score
137 [18]. Patients were assessed at seven days, 3 months, and annually after stroke. Before
138 January 1, 2000, cognitive state was assessed with the Mini-Mental State Examination; after
139 that date, the Abbreviated Mental Test was adopted. Subjects were defined as cognitively

140 impaired according to predefined cut-off points (Mini-Mental State Examination <24 or
141 Abbreviated Mental Test <8). It has been shown that the Mini-Mental State Examination and
142 Abbreviated Mental Test are insensitive to mild cognitive impairment and executive function
143 [19][20]. The AMT shows good concordance with the MMSE (c-statistic from 0.83 to 0.87)
144 [21].

145 The meta-analysis (73 studies) conducted by Pendlebury and Rothwell [22] was used to
146 identify an initial list of candidate predictors for post-stroke cognitive decline.

147 These candidate predictors were subsequently screened for practicality based on clinical
148 availability, ease of measurement, prevalence in academic literature, and on biological
149 reasoning with experts (stroke physician, statistician and epidemiologist). This yielded an
150 initial list of 93 candidate predictors available in the SLSR. Data are collected by SLSR field
151 workers uninvolved in this study at baseline, 3months, one year and annually thereafter.

152

153 **2.4 Missing data**

154

155 Multiple imputation using Markov chain Monte Carlo methods was used to impute missing
156 values, under a missing at random assumption, so as to reduce bias and avoid excluding
157 participants from the analysis [23].

158

159 **2.5 Statistical prediction methodology and analyses**

160

161 **2.5.1 Variables selection**

162

163 Random forest method [24] was used to rank the candidate predictors in order of
164 importance. Predictors considered to have great clinical relevance were forced back into the
165 model. Penalized mixed models [25] were then adapted to develop trajectories of cognitive
166 decline for a patient with the selected prognostic factors. Clinically meaningful interactions
167 were included in the model. Their significance was tested as a group to avoid inflating type I
168 error. All interaction terms were removed as a group, and the model was refitted if results
169 were nonsignificant. Interactions with time were also examined.

170

171 **2.5.2 Performance measures**

172

173 We assessed internal validity with cross validation method for a realistic estimate of the
174 performance of prediction model in similar future patients. Performance measures included
175 the area under the Receiver Operating Curve (AUROC) curve, sensitivity and specificity,
176 calibration slope, Brier score and Decision Curve Analysis (DCA) [26-27]. Discrimination
177 refers to the ability of the risk score to differentiate between cognitively intact and cognitively
178 impaired patients. DCA was performed in order to evaluate further the clinical usefulness of
179 survival curves in prognostication of cognitive impairment at three months, one year and five
180 years. DCA is a method to assess the added value of information provided by a prognostic test
181 across a range of a patient's risks and benefits to facilitate clinical decisions, without the need
182 for actually measuring these for individual patients. The DCA is expressed graphically as a

183 curve, with the clinical net benefit on the vertical axis and probability thresholds on the
184 horizontal axis. The net benefit of prediction models was then evaluated by adding the
185 benefits (true positives) and subtracting the harms (false positives). The weight assigned to
186 true positives and false positives was derived from the threshold probability of the outcome.
187 When the curve is at its highest over the range of probability thresholds, the associated
188 intervention would be the best decision. Statistical analysis was performed using R-software.

189

190 **2.5.3 Recovery curve trajectories**

191

192 We plotted recovery curve trajectories to visually examine different well-defined at-risk
193 subgroups. Average predicted patterns were analysed by age, stroke subtype, Glasgow coma
194 scale and left- stroke occurrence. To assess the prognostic effectiveness and clinical utility of
195 predicted recovery curves to estimate different cognitive outcomes at different time points,
196 cognitive impairment was dichotomized using mild cognitive impairment (cut-off: 24/30
197 MMSE and 8/10 AMT) and severe cognitive impairment (cut-off: MMSE and 4/10 AMT)
198 [28-29-30]. Clinical utility was also assessed at these thresholds of the predicted recovery
199 curves at three months, one year and five years.

200

201 **2.5.4 Model development and validation**

202

203 A penalised mixed-effects linear model was developed and temporal-validated. Repeated
204 random sub-sampling cross-validation methods were used to select best competing models
205 and model parameter. Internal cross-validation was used to assess the performance of the
206 developed prognostic recovery curve model. R2 and root-mean-square error (RMSE) were
207 considered together to estimate the predictive error. Patient age, sex, ethnic group, cognition
208 score at the onset of stroke, Barthel-index score at baseline, Glasgow coma scale (GCS),
209 stroke subtype (LACI, PACI, POCI, TACI) [31], diabetes, left hemisphere stroke, dysphasia
210 and interactions between predictor variables and the time in years were identified as good
211 independent predictors.

212

213 **Ethics**

214

215 Patients, or for patients with communication problems their relatives, gave written informed
216 consent to participate in stroke-related studies within the SLSR. The design was approved by
217 the ethics committees of Guy's and St Thomas' NHS Foundation Trust, Kings College
218 Hospital, Queens Square, and Westminster Hospitals (London).

219

220 **3. Results**

221

222 **3.1 Participants' Characteristics**

223

224 A total of 6,504 patients with their first-ever stroke between 1995 and 2018 were registered in
225 the SLSR. Of whom n=3411 patients had cognitive function measured at seven days, of them
226 n=1204 had cognitive impairment. A total of n = 1608 completed a follow-up interview at one

227 year, and n = 846 completed a follow-up interview at five years. A total of n = 2171
228 individuals died within three months. A total of n=2000 individuals did not have cognitive
229 function measured at 7 days after stroke, due to medical reasons. At stroke onset, the medical
230 reasons were communication impairment n = 992 and coma n = 737. The remaining number
231 was due to late registration or because their date of follow-up was not reached n = 271.
232 The development cohort consisted of 2,468 participants from (1995-2010) and the validation
233 cohort consisted of 940 stroke register participants recruited from (2011-2018).
234 Table 1 summaries the patients' characteristics in both development and validation cohorts.
235 Missing data accounted for less than 15% of the data. Key characteristics were typically
236 evenly distributed between both cohorts.

237

238

239 **3.2 Model performance**

240

241 Patient age, sex, ethnic group, cognition score at the onset of stroke, Barthel-index score at
242 baseline, Glasgow coma scale (GCS), stroke subtype (LACI, PACI, POCI, TACI) [29],
243 diabetes, left hemisphere stroke, dysphasia and interactions between predictor variables and
244 the time in years were identified as good independent predictors.

245 The predictive recovery curves showed a good fit and prediction. In the internal-cross
246 validation, predictive error RMSE over all time points was 0.12 and R2 was 73%. Average
247 cognition score was characterized by an initial improvements over the first 3 months and then
248 a gradual decline thereafter. Figure 1 presents the average predicted trajectories compared to
249 the average observed cognition score after stroke up to 5 years.

250 The predictive curves show similarities between LACI and POCI stroke at baseline but large
251 difference 1 year later, with LACI having the largest decline compared to POCI.

252 Dissimilarities were observed between TACI and PACI stroke at the baseline but was
253 comparable after 3 years. For instance, we have shown that changes in cognition score vary
254 between different age groups. We observed an improvement phase the first year in younger
255 patients but a significant decrease in older stroke survivors up to 5 years. But despite the
256 improvement phase in the younger patients, we would expect a small decline in the cognition
257 score after 1 year. Severe stroke (moderate to severe Glasgow coma scale (GCS) or left-stroke
258 occurrence at onset) showed significant association with cognitive decline.

259 Figure 2 presents average cognition score after stroke stratified by age group, stroke subtype
260 and GCS.

261 The model was further evaluated to identify the prognostic accuracy, the sensitivity and
262 specificity and the utility of the model at different cognitive decline cut-off scores that enable
263 the discrimination between severe and mild cognitive impairment at 3 months, 1 year and 5
264 years following stroke. The validity of the model is good, at 3 months (sensitivity ranging
265 from 52-71% and specificity 91- 94%) for severe cognition and (sensitivity ranging from 73-
266 82% and specificity 68-75%) for mild cognition score.

267 The model has also shown potential utility, the negative predictive values were
268 (96%, 95% CI [94- 97]), (96%, 95% CI [94- 97]), (97%, 95% CI [96- 98]) for severe
269 cognitive impairment at 3 months, 1 year and 5 years respectively.

270 Table 2 summaries all the predictive values and likelihood ratios for classifying each
271 cognitive impairment score of interest.

272 The net benefit as a function of a threshold probability of cognitive impairment at 3 months
273 1 year and 5 years was illustrated in Figure 3. The grey line was drawn to reflect the strategy
274 of assuming that all patients are cognitively impaired (i.e. recommend intervention for all),
275 and the black line was drawn to reflect the strategy of assuming that all patients are not
276 cognitively impaired (i.e. do not recommend any intervention).

277 The net benefit was maximized by the cognitive decline curve of the predictive model (red
278 line) with threshold probabilities of 15–80% at 3 months, 15–79% at 1 year and 15-82% at 5
279 years. For higher thresholds (>80% for 3 months, >79% for 1 year and > 82% for 5 years)
280 where the concerns are more about unnecessary interventions than missed prognosis, the
281 option to not intervene was preferred.

282

283

284 **4. Discussion**

285

286 In this study, we have developed and validated a patient-specific prognostic tool for cognitive
287 decline post-stroke in a population-based cohort. The proposed model is patient-specific and
288 enables cognitive impairment to be predicted using a continuous score. It has additionally
289 provided the ability to accurately predict trajectories up to 5 years post-stroke.

290 A recent systematic review reported that several models have been used to predict dementia
291 and cognitive impairment [16]. Regarding global cognitive function, the majority of studies
292 reported decline [32-33-34-35-36-37] whereas [38-39-40-41] reported no change. Most
293 models have a relatively short predictive period and don't assess the risk of cognitive decline
294 over longer periods particularly in those who have a stroke at a younger age. Furthermore,
295 they predict risk of cognitive impairment at predefined time points only. At predefined time
296 points, the accuracy of the proposed model has been shown to be superior compared to other
297 existing prediction models cited earlier. The general pattern of cognitive decline from stroke
298 has already been discussed and illustrated at population level in previous studies [6][42]. This
299 could be useful for early rehabilitation and discharge planning, by predicting whether a
300 patient is likely to be dependent, require some assistance, or be independent, at a certain time
301 post-stroke. Factors influencing recovery were the laterality of the stroke and lowered
302 consciousness on admission. Patients with right-side brain damage performed better than
303 those with left-side brain damage and showed more improvement in cognition score over
304 time. Cognitive impairment progression in patients with lowered consciousness on admission
305 was worse than patients without lowered consciousness overtime. Specialized stroke
306 rehabilitation may be beneficial for all ages but important for over 65. It also confirms that
307 older patients may need longer rehabilitation and are less likely to be discharged earlier. Apart
308 from old age, factors such as onset stroke severity should also be taken into consideration
309 when planning interventions and rehabilitation after stroke. We have shown that using a
310 multivariate patient-specific predictive model, we can make individual recovery profiles and
311 accurately classify future risks of cognitive decline. This model makes predictions of
312 continuous outcome rather than restricting to binary abstractions. Furthermore, the predictions
313 are not restricted by specific time points, as demonstrated by the average recovery patterns

314 and subgroup analyses up to 23 years post-stroke. The final model parameters were selected
315 using k-fold cross validation.

316 This signifies that the final coefficients reflect averages of many models built on random
317 subpopulation permutations to ensure that the final model parameters reflect real associations
318 rather than being subject to overfitting. In addition, the sample size is large in relation to the
319 number of prognostic variables, increasing the power of the study. The variables incorporated
320 into the model were selected for their association with cognitive decline following stroke, and
321 tested using several, robust methods, thus ensuring complete confidence in the predictive
322 abilities of the variables. In addition, these variables are routinely collected during acute
323 stroke care and follow-up assessments, thus increasing the ease of use of the model. Patient-
324 specific recovery curves predictions could allow more insight into both spontaneous and
325 directed neurological recovery after stroke. This prognostic information is important for
326 clinicians, stroke survivors and their careers. In clinical research, this could also be applied as
327 an aid in assessing the beneficial effects of evidence-based interventions and care settings. As
328 a research tool, this could be used to test novel interventions or to identify enriched samples,
329 reducing the reliance on the need for expensive and often impractical randomized controlled
330 trials. This predictive enrichment strategy is of importance for designing future trials as it
331 enables the enrolment of the most suitable patients thereby permitting the use of a smaller
332 study population. Another potential application could be to derive a set of preliminary cost
333 weights on resource uses which could help commissioners build personalised patient care
334 funding models.

335 A key strength of the current study is that the model was built using a prospective, non-
336 selected population-based cohort of first ever stroke. This is preferable to hospital based
337 populations, which may result in case-mix specific models, or aggregate data from clinical
338 trials, which usually represent heavily selected and thus non-representative populations. Our
339 data sample is truly reflective of the geographic population of interest and therefore optimal
340 for deriving a representative model.

341 Appropriate vascular risk management was associated with a long-term reduced risk of
342 cognitive impairment. Focus on optimal preventive drug therapy of vascular risk factors and
343 management should be supported [43]. This model can potentially assist clinicians in
344 organizing a program of care for patients following stroke, which is tailored to their predicted
345 pattern of cognitive development. It can also aid in communicating risk to patients and their
346 families and careers, in a straightforward and clear manner, especially through the use of the
347 graphical representations of cognition score as a function of time.

348

349 **Limitations:**

350

351 Notwithstanding the strengths, the following limitations of this study must be acknowledged.

352 Firstly, the study could be improved further if the model were to be validated in a completely
353 independent population, preferably from another country and by independent researchers.

354 Secondly, we used a penalized mixed effect model that automatically selects and
355 subsequently shrinks effect sizes of important predictors. This regularization strategy may
356 have led to some underestimation of predictor effects in the development sample, but it
357 increases the likelihood of replication in validation studies.

358 Thirdly, an impact study needs to be conducted in a randomized control trial (RCT) setting to
359 confirm whether being able to predict recovery and the resulting intervention, could make a
360 difference to the patient. Fourthly, mild cognitive decline is measured by executive function,
361 the MMSE and AMT scores do not measure this. Perhaps the accuracy of the model would be
362 increased by using measures that take into account executive function such as the Montreal
363 Cognitive Assessment tool (MoCA)[44]. MoCA was feasible and reliable, however,
364 examination of Visio executive and complex language tasks was limited compared with face-
365 to-face assessment. MMSE scores were predictive of cognitive impairment and dementia on
366 follow-up, and most widely used by clinicians in routine care.

367 It can be noted that a key limitation of the current study was including only routinely
368 collected data and no other important variables that could potentially refine the model further,
369 for instance genomic data. However, the objective of this work was to produce simple
370 models that can be used in a wider clinical setting. Finally, cognitive impairment prediction
371 without an effective therapy at hand raises ethical concerns. Such models are unlikely to be
372 rolled out into clinical practice before further validation and assessment are undertaken.

373

374 **Future directions:**

375

376 Future work may wish to consider further evaluation of the proposed model, impact study to
377 bring such models into clinical practice and application of the recovery curves methods to
378 other outcomes.

379

380

381 **5. Implications**

382

383 The research implications for this study lie in the increased understanding of patient-specific
384 post-stroke cognitive decline patterns. The model can predict long-term risk up to 5 years
385 post-stroke, which to the knowledge of the authors, has not been performed for cognitive
386 decline in stroke patients. The model may be used as a research tool to test the influence of
387 novel interventions and drugs on cognitive decline.

388 The proposed model yields personalized patterns of cognitive decline scores, up to 5 years
389 post-stroke by taking into account clinically available predictors for post-stroke cognition.

390 The predictions can be altered in light of observed recovery, thus refining the model and
391 allowing for more precise predictions. The cut-off used by the model can be adjusted to
392 emphasize detection of mild or severe cognitive impairment, thus enabling flexibility
393 depending on the patient's characteristics. The model can detect those at higher risk of
394 cognitive decline, as demonstrated by our subgroup analyses, thus identifying patients who
395 will most benefit from treatment and improving cost-effectiveness in stroke care.

396 The implications of this study are wide ranging, providing a way to effectively organize post-
397 stroke care by determining groups at higher risk, communicating risk to patient and families
398 and predicting drug treatment outcomes on cognition for research purposes.

399

400 **6. Conclusion**

401

402 The derived prognostic model seems to accurately predict the risk of post-stroke cognitive
403 decline. This confirm that the recovery curves models applied to patient specific stroke data
404 can predict trajectories accurately. Longitudinal measurement adds greater dimension to
405 predictions and more accurate than measurement at an isolated time-point . The predictors of
406 post stroke cognition used in the proposed model, were typically common routinely collected
407 information. Therefore, could be used in post-stroke care, particularly in early detection and
408 prevention to support clinical decisions.

409

410 **DATA SHARING STATEMENT**

411

412 The study and its consent procedure were approved by the ethics committees of Guy's and St
413 Thomas' Hospital Trust, King's College Hospital, Queen's Square, and Westminster Hospital.
414 Consent for data sharing was not obtained from study participants. The research team will
415 consider reasonable requests for sharing of anonymised patient level data.

416

417 **Conflict of Interest**

418

419 We declare that we have no conflicts of interest.

420

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422

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431 Department of Health.

432

433 **Authors' contribution**

434 CDAW, AD conceived the study and provided study design guidance. YH performed
435 statistical work for the study and drafted the manuscript. MF Marion Fahey worked in post
436 stroke cognitive decline during her PhD and have thoroughly revised the manuscript and
437 checked all analyses. MO reviewed the manuscript.

438 All authors contributed substantially to its revision.

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References

1. Allan LM, Rowan EN, Firbank MJ, et al. (2011). Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain*.134(pt 12):3716–3727.
2. Rothwell PM, Coull AJ, Giles MF, et al. (2004). Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. ;363(9425):1925-1933. doi:10.1016/S0140-6736(04)16405-2
3. Rothwell PM, Coull AJ, Silver LE, et al. (2005) Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet*.;366(9499):1773-1783. doi:10.1016/S0140-6736(05)67702-1
4. Fratiglioni L, Launer LJ, Andersen K, et al. (2000) Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurologic Diseases in the Elderly Research Group*. *Neurology*.; 54(11 Suppl 5):S10-S15.
5. Tilling K, Sterne JA, Wolfe CD. (2001). Estimation of the incidence of stroke using a capture-recapture model including covariates. *Int J Epidemiol*.;30:1351–1359; discussion 1359.
6. Wolfe C, Crichton S, Heuschmann P, et al. (2011). Estimates of outcomes up to ten years after stroke: analysis from the prospective south london stroke register. *PLoS Med*; 8(5): e1001033.
7. Folstein MF, Folstein SE, McHugh PR. (1975). “Mini-mental state.” A p cal method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*.;12:189–198.
8. Suzuki M, Sugimura Y, Yamada S, et al. (2013). Predicting recovery of cognitive function soon after stroke: differential modeling of logarithmic and linear regression. *PLoS One*.;8(1):e53488. doi:10.1371/journal.pone.0053488
9. Ross, Amy J. et al. (2006). Prediction of cognitive decline after stroke using proton magnetic resonance spectroscopy. *Journal of the Neurological Sciences*, Volume 251, Issue 1, 62 - 69

- 490 10. Saini et al. (2014). Computer tomography for prediction of cognitive outcomes after
491 ischemic cerebrovascular events. *Journal of stroke and cerebrovascular diseases : the*
492 *official journal of National Stroke Association*, 23 7, 1921-7
493
- 494 11. Tang EYH et al. Risk Prediction Models for Post-Stroke Dementia. *Geriatrics (Basel)*.
495 2017 Jun 22;2(3):19. doi: 10.3390/geriatrics2030019. PMID: 31011029; PMCID:
496 PMC6371182.
497
498
- 499 12. Stephan BCM, Kurth T, Matthews FE, Brayne C, Dufouil C. Dementia risk prediction
500 in the population: are screening models accurate? *Nat Rev Neurol*. 2010;6:318–326.
501
- 502 13. Lim JS, Oh MS, Lee JH, Jung S, Kim C, Jang MU, Lee SH, Kim YJ, Kim Y, Park J,
503 Kang Y, Yu KH, Lee BC. Prediction of post-stroke dementia using ninds-csn 5minute
504 neuropsychology protocol in acute stroke. *Int Psychogeriatr*. 2017;29:777–784.
505
- 506 14. Kandiah N, Chander RJ, Lin X, Ng A, Poh YY, Cheong CY, Rae Cenina A, Nkouibert
507 Assam P. Cognitive impairment after mild stroke: development and validation of the
508 SIGNAL2 risk score. *J Alzheimers Dis*. 2016; 49:1169–1177. doi: 10.3233/JAD-
509 150736.
510
- 511 15. Chander RJ, Lam BYK, Lin X, Ng AYT, Wong APL, Mok VCT, Kandiah N.
512 Development and validation of a risk score (CHANGE) for cognitive impairment after
513 ischemic stroke. *Sci Rep*. 2017; 7:12441. doi: 10.1038/s41598-017-12755-z
514
- 515 16. Tang EY, Amiesimaka O, Harrison SL, Green E, Price C, Robinson L, Siervo M,
516 Stephan BC. Longitudinal Effect of Stroke on Cognition: A Systematic Review. *J Am*
517 *Heart Assoc*. 2018 Jan 15;7(2):e006443. doi: 10.1161/JAHA.117.006443. PMID:
518 29335318; PMCID: PMC5850140.
519
- 520 17. Tilling K, Sterne JA, Wolfe CD. (2001). Estimation of the incidence of stroke using a
521 capture-recapture model including covariates. *Int J Epidemiol.*;30:1351–1359;
522 discussion 1359.
523
- 524 18. Hodkinson HM. Evaluation of a Mental Test Score For Assessment of Mental
525 Impairment in the Elderly. *Age Ageing*. 1972;1:35–40.
526
- 527 19. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of
528 cognitive impairment by Mini-Mental State Examination versus the Montreal
529 Cognitive Assessment in patients with transient ischemic attack and stroke: a
530 population-based study. *Stroke*. 2010;41:1290–1293.
531
- 532 20. Elias MF, Sullivan LM, D’Agostino RB, Elias PK, Beiser A, Au R, Seshadri S,
533 DeCarli C, Wolf PA. Framingham stroke risk profile and lowered cognitive
534 performance. *Stroke*. 2004;35:404–409.

- 535
536 21. Piotrowicz, K., Romanik, W. et al. (2019). The comparison of the 1972 Hodkinson's
537 Abbreviated Mental Test Score (AMTS) and its variants in screening for cognitive
538 impairment. *Aging clinical and experimental research*, 31(4), 561–566.
539 doi:10.1007/s40520-018-1009-7
540
- 541 22. Pendlebury ST, Rothwell PM. (2009). Prevalence, incidence, and factors associated
542 with pre-stroke and post-stroke dementia: a systematic review and meta-analysis.
543 *Lancet Neurol.*;8:1006–1018.
544
- 545 23. Crichton S. (2016). Methods for handling missing data in a population-based cohort
546 study. PhD Thesis, King's College, London (University of London).
547
- 548 24. Breiman, L. Random Forests. *Machine Learning* **45**, 5–32 (2001).
549 <https://doi.org/10.1023/A:1010933404324>
550
- 551 25. Wood, S. (2017). *Generalized Additive Models*. New York: Chapman and Hall/CRC,
552 <https://doi.org/10.1201/9781315370279>
553
554
- 555 26. Vickers AJ and Elkin EB. Decision curve analysis: a novel method for evaluating
556 prediction models. *Med Decis Making* 2006; 26: 565–574.
557
- 558 27. Fitzgerald M, Saville BR, Lewis RJ. (2015). Decision curve analysis. *JAMA* 313:
559 409–410.
560
561
- 562 28. Jitapunkul S, Pillay I, Ebrahim S. (1991). The abbreviated mental test: its use and
563 validity. *Age and ageing* 20(5): 332-336.
564
- 565 29. Harvan JR, . Cotter VT. (2006). An evaluation of dementia screening in the primary
566 care setting. *J Am Acad Nurse Pract* 18(8): 351-360.
567
- 568 30. Pernecky R, et al. (2006). Mapping scores onto stages: mini-mental state examination
569 and clinical dementia rating. *Am J geriatric psych* 14(2): 139-144.
570
- 571 31. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural
572 history of clinically identifiable subtypes of cerebral infarction. *Lancet*.
573 1991;337:1521–1526.
574
- 575 32. Rajan KB, Aggarwal NT, Wilson RS, Everson-Rose SA, Evans DA. Association of
576 cognitive functioning, incident stroke, and mortality in older adults. *Stroke*.
577 2014;45:2563–2567.
578

- 579 33. Toole JF, Bhadelia R, Williamson JD, Veltkamp R. Progressive cognitive impairment
580 after stroke. *J Stroke Cerebrovasc Dis.* 2004;13:99–103. Douiri A, Grace J, Sarker S,
581 Tilling K, et al. (2017). Patient-specific prediction of functional recovery after stroke.
582 *International Journal of Stroke* 12(5): 539-548.
- 583 34. Ben Assayag E, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Hallevi H, Shopin L,
584 Auriel E, Giladi N, Mike A, Halevy A, Weiss A, Mirelman A, Bornstein NM,
585 Hausdorff JM. Gait measures as predictors of poststroke cognitive function: evidence
586 from the TABASCO study. *Stroke.* 2015;46:1077–1083.
- 587
- 588 35. Tene O, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Hallevi H, Shopin L, Auriel E,
589 Mike A, Bornstein NM, Assayag EB. Depressive symptoms following stroke and
590 transient ischemic attack: is it time for a more intensive treatment approach? Results
591 from the TABASCO cohort study. *J Clin Psychiatry.* 2016;77:673–680.
- 592
- 593 36. Levine DA, Haan MN, Langa KM, Morgenstern LB, Neuhaus J, Lee A, Lisabeth LD.
594 Impact of gender and blood pressure on poststroke cognitive decline among older
595 Latinos. *J Stroke Cerebrovasc Dis.* 2013;22:1038–1045.
- 596
- 597 37. Ghosal MK, Burman P, Singh V, Das S, Paul N, Ray BK, Hazra A, Banerjee TK, Basu
598 A, Chaudhuri A, Das SK. Correlates of functional outcome among stroke survivors in a
599 developing country—a prospective community-based study from India. *J Stroke*
600 *Cerebrovasc Dis.* 2014;23:2614–2621.
- 601
- 602 38. Comijs HC, Kriegsman DM, Dik MG, Deeg DJ, Jonker C, Stalman WA. Somatic
603 chronic diseases and 6-year change in cognitive functioning among older persons. *Arch*
604 *Gerontol Geriatr.* 2009;48:191–196.
- 605
- 606
- 607 39. Wagle J, Farner L, Flekkoy K, Wyller TB, Sandvik L, Eiklid KL, Fure B, Stensrod B,
608 Engedal K. Cognitive impairment and the role of the apoe epsilon4-allele after stroke—a
609 13 months follow-up study. *Int J Geriatr Psychiatry.* 2010;25:833–842.
- 610
- 611 40. Dik MG, Deeg DJ, Bouter LM, Corder EH, Kok A, Jonker C. Stroke and
612 apolipoprotein E epsilon4 are independent risk factors for cognitive decline: a
613 population-based study. *Stroke.* 2000;31:2431–2436.
- 614
- 615 41. Rowan EN, Dickinson HO, Stephens S, Ballard C, Kalaria R, Kenny RA.
616 Homocysteine and post-stroke cognitive decline. *Age Ageing.* 2007;36:339–343.
- 617
- 618 42. Douiri A, Grace J, Sarker SJ, Tilling K, McKeivitt C, Wolfe CD, Rudd AG. Patient-
619 specific prediction of functional recovery after stroke. *Int J Stroke.* 2017 Jul;12(5):539-
620 548. doi: 10.1177/1747493017706241. Epub 2017 Apr 25. PMID: 28440112.
- 621

622 43. Abdel Douiri , Christopher McKeivitt, et al. (2013). Long-Term Effects of Secondary
623 Prevention on Cognitive Function in Stroke Patients. *Circulation*, 128(12):1341-1348
624 10.1161/CIRCULATIONAHA.113.002236
625 44. Nasreddine, Z.S., Phillips, N.A., Bédirian, V., et al. (2005). The Montreal Cognitive
626 Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal*
627 *of the American Geriatrics Society*, 53: 695-699.
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Table1: Baseline post stroke characteristics of patients including sociodemographic, past medical history, case mix, and stroke subtypes

	Development cohort (1995-2010)		Validation cohort (2011-2018)	
Cognitive Impairment	Intact (%)	Impaired (%)	Intact (%)	Impaired (%)
	1468	1000	736	204
Age, mean (SD)	66.84 (14.61)	74.10 (12.90)	69.60 (15.40)	70.50 (15.31)
Sex				
female	824 (56.13%)	540 (54%)	279 (38%)	98 (48.04%)
Male	644 (43.87%)	460 (46%)	457 (62%)	106 (51.96%)
Ethnicity				
White	1044 (71.12%)	732 (73.2%)	412 (56%)	95 (46.57%)
Black	346 (23.57%)	219 (21.9%)	278 (38%)	95 (6.37%)
Other	63 (4.29 %)	44 (4.4%)	43 (0.6%)	13 (6.37%)
Missing	15 (1.02%)	5 (0.5%)	3 (0.41%)	1 (0.5%)
Socioeconomic group				
Manual	831 (56.61%)	621 (62.1%)	218 (29.62%)	59 (28.92%)
Non-manual	533 (36.31%)	207 (20.7%)	222 (30.16%)	47 (23.04%)
Unknown	2 (0.14%)	2 (0.2%)	1 (0.14%)	0 (0%)
Missing	102 (6.95%)	170 (17%)	295 (40.08%)	98 (48.04%)
Pre-stroke vascular risk factors				
Transient ischemic attack				
No	1285 (87.53%)	858 (85.8%)	666 (90.5%)	179 (87.75%)
Yes	173 (11.78%)	129 (12.9%)	57 (7.74%)	22 (10.78%)
Missing	10 (0.68%)	13 (0.13%)	13 (1.77%)	3 (1.47%)
Atrial fibrillation				

No	1310 (89.24%)	787 (78.7%)	602 (81.79%)	156 (76.47%)
Yes	148 (10.08%)	198 (19.8%)	115 (15.63%)	44 (21.57%)
Missing	10 (0.68%)	15 (0.15%)	19 (2.58%)	4 (1.96%)
Hypertension				
No	517 (35.22 %)	301 (30.1%)	245 (33.29%)	62 (30.39%)
Yes	944 (64.31 %)	691 (69.1%)	484 (65.76%)	140 (68.63%)
Missing	7 (0.48%)	8 (0.8%)	7 (0.95%)	2 (1%)
Diabetes mellitus				
No	1188 (80.93%)	775 (77.5%)	540 (73.37%)	133 (65.20%)
Yes	271 (18.46%)	217 (21.7%)	189 (25.68%)	67 (32.84%)
Missing	9 (0.61%)	8 (0.8%)	7 (0.95%)	4 (2%)
Hypercholesterolemia				
No	895 (60.97%)	512 (51.2%)	428 (58.15%)	113 (55.4%)
Yes	310 (21.12%)	163 (16.3%)	298 (40.5%)	86 (42.16%)
Unknow	263 (17.92%)	325 (32.5%)	10 (1.36%)	5 (2.45%)
Current Smoker				
No	491 (33.45%)	365 (36.5%)	306 (41.60%)	90 (44.12%)
Yes	481 (32.77%)	308 (30.8%)	246 (33.42%)	59 (28.92%)
Unknown	473 (32.22%)	270 (27%)	180 (24.46%)	48 (23.53%)
Missing	23 (1.57%)	57 (0.57%)	4 (0.54%)	7 (3.43%)
Drinker				
No	504 (34.33%)	399 (39.90%)	336 (45.65%)	120 (58.82%)
Yes	931 (63.41%)	531 (53.10%)	392 (53.26%)	79 (38.72%)
Missing	33 (2.24%)	70 (7.00%)	8 (1.08%)	5 (2.45%)
Antiplatelet prior to stroke				
No	1089 (74.18%)	735 (73.50%)	686 (93.20%)	177 (86.76%)
Yes	209 (14.23%)	181 (18.10%)	38 (5.16%)	23 (11.27%)
Missing	170 (11.58%)	84 (8.40%)	12 (1.63%)	4 (1.96%)
Family history of stroke				
No	161 (10.96%)	76 (7.60%)	430 (58.42%)	133 (65.19%)
Yes	114 (7.76%)	30 (3.00%)	242 (32.88%)	33 (16.17%)
Missing	1193 (81.26%)	894 (89.40%)	64 (8.69%)	38 (18.63%)
Stroke severity (Case-mix)				
Glasgow coma scale (GCS)				
Severe (<8)	21 (1.43%)	69 (0.69%)	6 (0.82%)	8 (3.92%)
Moderate (9-12)	38 (2.59%)	173 (17.3%)	31 (4.21%)	25 (12.25%)
Mild (13-15)	1375 (93.66%)	739 (73.9%)	678 (92.12%)	162 (79.41%)
Missing	34 (2.32%)	19 (0.19%)	21 (2.85%)	9 (4.41%)
Urinary incontinence				
No	1180 (80.38%)	424 (42.4%)	633 (86%)	130 (63.73%)
Yes	251 (17.10%)	555 (55.5%)	82 (11.14%)	67 (32.84%)
Missing	37 (2.52%)	21 (0.21%)	21 (2.85%)	7 (3.43%)
Stroke subtype				

Infarct	1286 (87.60%)	817 (81.7%)	629 (85.46%)	179 (87.75%)
Haemorrhagic	169 (11.51%)	161 (16.1%)	106 (14.40%)	25 (12.25%)
Missing	13 (0.89%)	22 (0.22%)	1 (0.14%)	0 (0%)

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Table 2: predictive values and likelihood ratios for classifying each cognitive impairment score of interest.

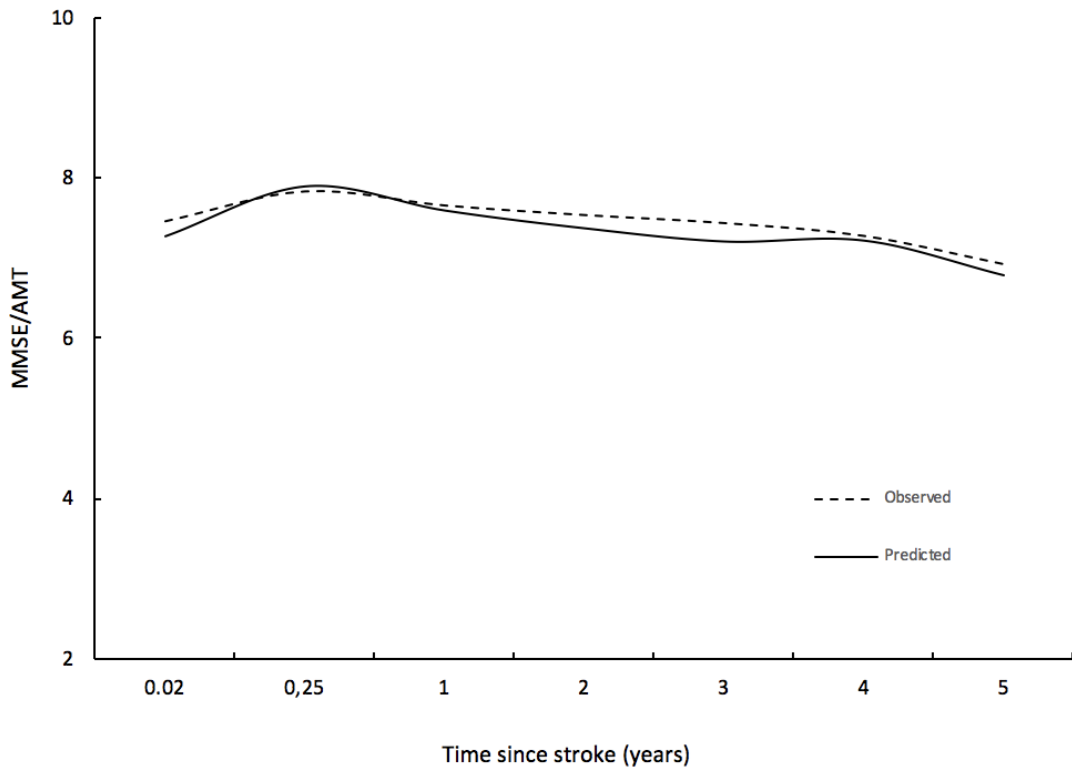
Measure	3 months	1 year	5years
(cut-off=4)			
Prevalence	10% [8- 12]	9% [7- 11]	6% [4-7]
Overall prognostic performance			
Overall performance (Brier)	7%	7%	8%
Discrimination (AUC)	88.5% [85-90]	89.6% [86-92]	87% [85-91]
Prognostic performance at a cut-off			
Sensitivity	62% [52-71]	58% [48-68]	59% [46-71]
Specificity	93% [91- 94]	92% [90-94]	90% [88-92]
Clinical utility at cut-off			
PPV	49% [41- 58]	42% [33-50]	27% [20- 35]
NPV	96% [94-97]	96% [94- 97]	97% [96 -98]
LR+	8.75 [6.68 -11.46]	7.29 [5.57-9.54]	6.10 [4.61-8.05]
LR-	0.41 [0.32- 0.52]	0.45 [0.36 - 0.57]	0.46 [0.34- 0.61]
DOR	21.30 [13.51- 33.57]	16.03 [10.10 - 25.45]	13.35 [7.76- 22.96]
Youden	0.54 [0.43-0.65]	0.50 [0.38 - 0.62]	0.50 [0.34 - 0.63]
(cut-off=8)			
Prevalence	32% [29-35]	39% [36-42]	42% [39- 45]
Overall prognostic performance			

679	Overall performance (Brier)	17%	19%	20%
680				
681	Discrimination (AUC)	80% [76-81]	77% [73-78]	75% [72-78]
682				
683	Prognostic performance at a cut-off			
684				
685	Sensitivity	78% [73-82]	74% [70-78]	72% [68-76]
686				
687	Specificity	72% [68-75]	65% [61-68]	65% [61-69]
688				
689	Clinical utility at cut-off			
690				
691	PPV	56% [52-61]	58% [53 - 62]	60% [55-64]
692				
693	NPV	87% [85-90]	79% [76 - 83]	76% [73- 80]
694				
695	LR+	2.75 [2.42 - 3.12]	2.10 [1.87 - 2.36]	2.05 [1.82 - 2.31]
696				
697	LR-	0.31 [0.25 - 0.37]	0.40 [0.34 - 0.47]	0.43 [0.37 - 0.51]
698				
699	DOR	8.99 [6.67-12.11]	5.24 [4.01 - 6.84]	4.74 [3.66 - 6.15]
700				
701	Youden	0.50 [0.41- 0.57]	0.39 [0.31- 0.46]	0.37[0.29 -0.47]

702 AUC : area under the curve; LR : likelihood ratio; DOR : diagnostic odds ratio; NPV : negative predictive
703 value; PPV : positive predictive value.

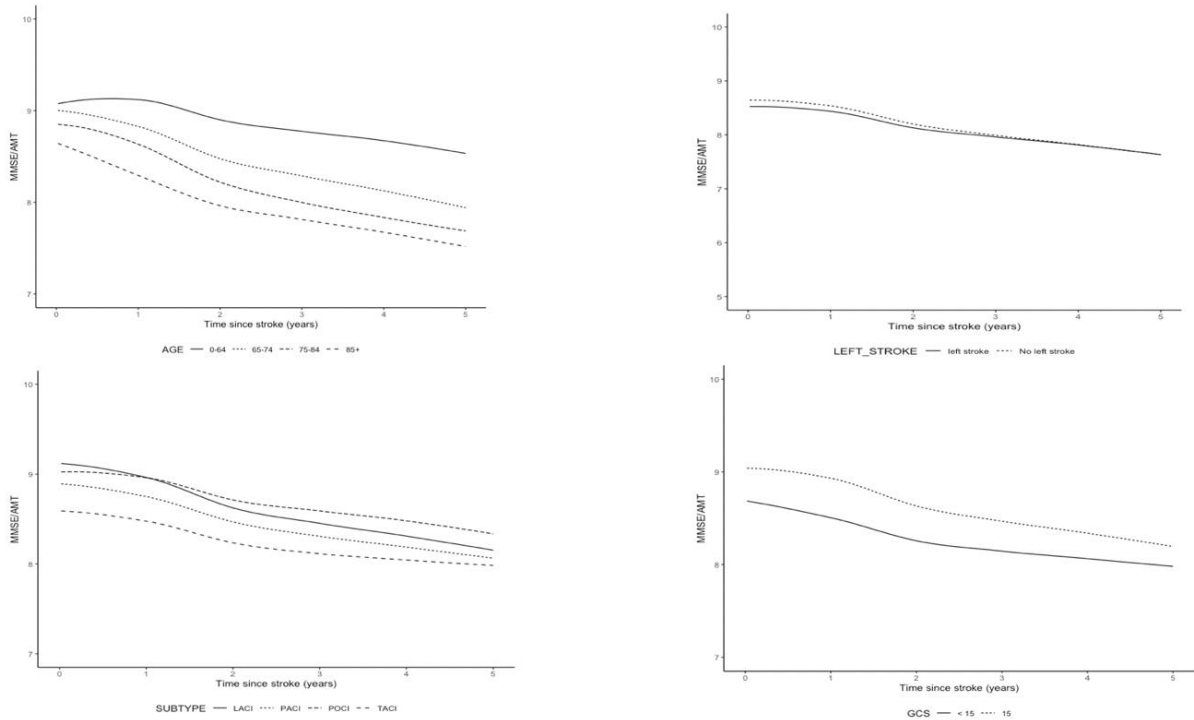
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Figure 1. Average predicted trajectories compared to the average observed cognition score after stroke up to 5 years



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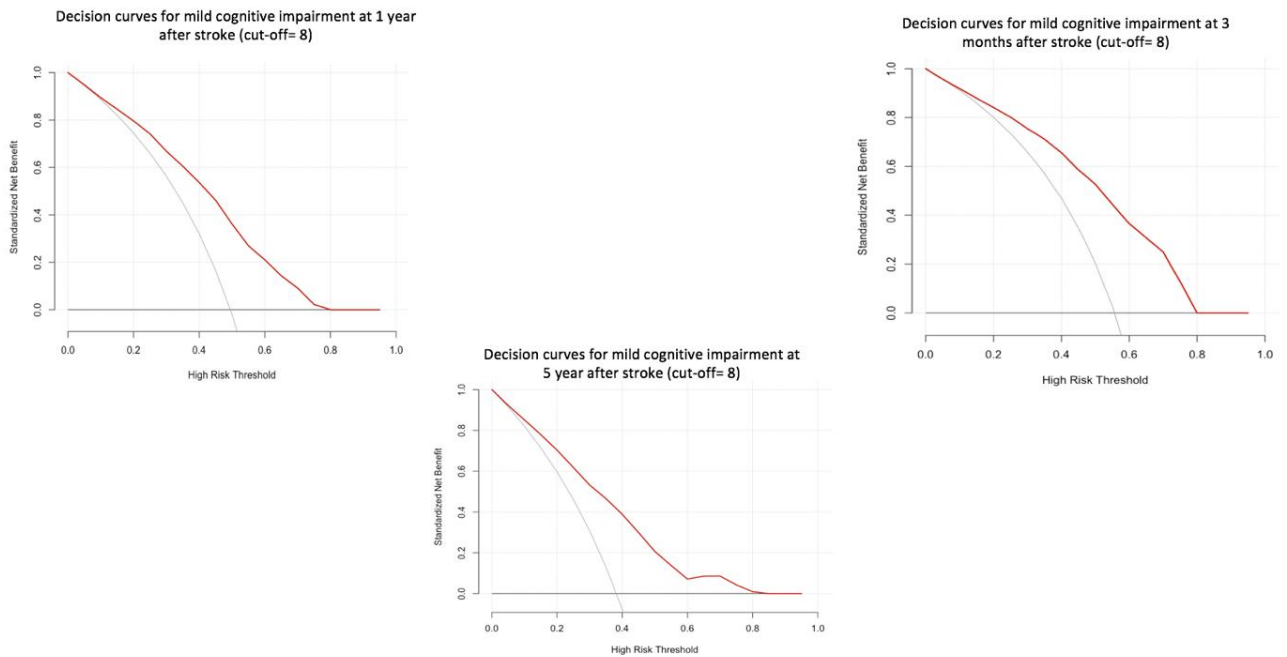
Figure 2. Average predicted recovery patterns after stroke stratified by age, stroke subtype, GCS, and left-stroke. GCS: Glasgow coma score.



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Figure 3. Decision curves for recovery curves to predict mild cognitive impairment in stroke survivors at three months, 1 and 5 years. Red line: Prediction model. Grey line: assume all are cognitively impaired. Black line: assume all are not cognitively impaired.



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Figure legends

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Figure1. Average predicted trajectories compared to the average observed cognition score after stroke up to 5 years

Figure 2. Average predicted recovery patterns after stroke stratified by age, stroke subtypes, GCs, and left-stroke. GCS: Glasgow coma score.

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Figure 3. Decision curves for recovery curves to predict mild cognitive impairment in stroke survivors at three months, 1 and 5 years. Red line: Prediction model. Grey line: Assume all are cognitively impaired. Black line: assume all are not cognitively impaired.

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List of Tables:

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