Multidomain post-stroke cognitive impairment: development and validation of a clinical prediction model

Andrea Kusec, Kym I E Snell, Nele Demeyere

Summary

Background Post-stroke cognitive impairment (PSCI) is highly prevalent across multiple domains. Individualised PSCI prognosis has mainly been researched using dementia-specific outcomes instead of stroke-specific outcomes, and existing models often use predictors not routinely available in electronic health records. We aimed to develop and externally validate clinical prediction models for overall PSCI via use of a stroke-specific cognitive outcome, using acute PSCI and data routinely collected in stroke care.

Methods In this prediction model development and validation study, we used data from a cohort of participants with stroke who were consecutively recruited from the acute stroke ward of the John Radcliffe Hospital (Oxford, UK) for the Oxford Cognitive Screening Programme (OCS-Recovery study). Participants completed the Oxford Cognitive Screen (OCS; comprising 12 subtasks covering six cognitive domains) acutely and at the 6-month follow-up. The outcome was binarised (impaired *vs* unimpaired). The selected predictors for the logistic regression models were available in electronic health records and conceptually relevant to post-stroke cognition. Logistic regression models were fitted with mandatory clinically relevant predictors (age, sex assigned at birth, stroke severity, education, stroke hemisphere, and acute PSCI) and data-driven predictors (acute mood difficulties, length of stay in acute care, and multimorbidity). We conducted backward elimination on multiply imputed data to remove non-significant ($p>0·10$) data-driven predictors. Internal validation used bootstrapping to obtain optimism-adjusted performance estimates. The same internal validation procedure was followed for a continuous prediction model, using proportion of OCS tasks impaired as the outcome. For external validation, we used the OCS-Care dataset, comprising data from a stroke cohort with mild severity PSCI. Performance measures included discrimination (eg, C-statistic), calibration, and goodness-of-fit. Overall binary PSCI model performance was further evaluated within subgroups by age range, sex assigned at birth, first versus recurrent stroke, and acute PSCI severity.

Findings Between March 20, 2012, and March 9, 2020, 430 participants recruited to the OCS-Recovery study completed the OCS acutely and at 6-months after stroke. All participants attempted the OCS, with 400 (93%) completing at least ten of 12 subtasks. The overall binary PSCI model had good optimism-adjusted performance (C-statistic 0·76 [95% CI 0·71–0·80]), with similar external validation performance (0·74 [0·68–0·80]). Model performance did not vary by sex assigned at birth but was best in adults younger than 60 years (0·76 [0·62–0·86]) with moderate-to-severe acute PSCI (0·72 [0·60–0·81]).

Interpretation Stroke-specific cognition prediction models can offer more meaningful PSCI prognoses than models focused on cognitive decline. Our binary and continuous overall PSCI models show promise in terms of generalisability across different stroke cohorts. Future recalibration of domain-specific models would be beneficial.

Funding UK National Institute for Health and Care Research.

Lancet Healthy Longev 2026

Published Online
https://doi.org/10.1016/j.lanhl.2026.100820

Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK (A Kusec PhD, Prof N Demeyere PhD); **Department of Applied Health Sciences, School of Health Sciences, University of Birmingham, Birmingham, UK** (K I E Snell PhD); **National Institute for Health and Care Research Birmingham Biomedical Research Centre, Birmingham, UK** (K I E Snell)

Correspondence to:
Prof Nele Demeyere, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK
nele.demeyere@ndcn.ox.ac.uk

Introduction

Stroke is the leading cause of long-term physical and cognitive disability worldwide.[1] The prevalence of 1-year post-stroke cognitive impairment (PSCI) has been estimated at up to 55%,[2] with rates of 45%[3] to 80%[4] in chronic stroke. PSCI negatively affects patients[5] and their caregivers or families[5] and has considerable economic costs.[6]

Clinical prediction models have been developed to improve PSCI prognostication, chiefly post-stroke cognitive decline and dementia.[7,8] However, PSCI does not necessarily cause cognitive decline or dementia, with research showing some patients have stable, chronic cognitive impairment or even show continued improvement.[9] New definitions of PSCI acknowledge the complex interplay of declining brain health, focal brain injury, and cognitive recovery, with outcomes including decline, stability, and improvement. PSCI is highly prevalent across multiple cognitive domains of language, memory, attention, numeracy, executive function, and praxis.[10] These impairments have previously been studied in isolation, despite research indicating differing recovery rates across domains.[10]

Existing prediction models of post-stroke dementia[11–13] perform poorly in PSCI,[14] possibly because specific

Research in context

Evidence before this study

We searched PubMed, PsycInfo, OVID, and other relevant databases from inception until Sept 1, 2024, with the terms "stroke", "risk prediction", "clinical prediction", "cognitive outcomes" and "risk factors" for English-language articles only. This search yielded available evidence of existing post-stroke cognition models that were either adapted from dementia patient cohorts or used cognitive decline-related outcome measures. However, post-stroke cognitive impairment (PSCI) does not always result in cognitive decline. There are no models that estimate chronic PSCI using a stroke-specific cognitive outcome. Furthermore, existing models are impractical in clinical practice because they use specialised risk factors that are not routinely available in medical records or are not regularly collected and recorded in electronic health records (eg, MRI-based connectivity metrics and blood-based biomarkers).

Added value of this study

Our study provides a practical clinical prediction model for estimating 6-month PSCI that outperforms other available models and uses risk factors routinely available in UK electronic health records because of their requirement for collection by stroke care services. From this model, we have developed a Cognition Calculator that can be further developed and evaluated for acceptability by health-care professionals. We have also provided initial evidence that domain-specific prediction models that include subtypes of cognitive impairment such as language, memory, and attention might offer even more informative prediction outcomes.

Implications of all the available evidence

Evidence from this study and other relevant research shows that models of PSCI and post-stroke cognitive decline should be considered and developed separately to yield precise predictive information. Developing models that make use of routinely available health record data could increase the uptake and scope of prediction models. Our findings lay the groundwork for the development of pragmatic prediction tools to be evaluated and implemented in clinical practice in the future.

cognitive domains have different relationships to functional outcomes. Newer models have attempted to improve PSCI prediction but remain focused on traditional clinical and demographic predictors (eg, age and stroke severity).[14,15] A 2024 meta-analysis (n=160 783) of PSCI predictors reported that acute cognition was by far the strongest predictor of chronic PSCI,[15] indicating the importance of baseline cognitive performance in developing accurate prediction models.[16] However, existing PSCI prediction models do not routinely include acute cognition as a predictor. With early PSCI assessment now recommended by national and international guidelines,[17,18] acute cognitive data are becoming more routinely available and are being used in PSCI prognostication.

Existing PSCI prediction models often assess acute and long-term cognition via dementia screening tools (eg, Mini Mental State Examination). These are not suitable for left hemisphere stroke due to an over-reliance on verbal abilities. A stroke-specific cognitive screen such as the Oxford Cognitive Screen (OCS)[19] minimises confounding from language and motor impairments and is strongly associated with 6-month cognitive recovery.[10] In this study, we aimed to develop and externally validate clinical prediction models of 6-month PSCI outcomes using acute cognitive information via a stroke-specific tool.

Methods

Study design and participants

In this prediction model development and validation study, we used cohort data collected from the Oxford Cognitive Screening Programme (OCS-Recovery study). This cohort comprised participants consecutively recruited from the acute stroke ward of the John Radcliffe Hospital, Oxford, UK and Abingdon Community Hospital, Abingdon, UK. OCS-Recovery data were collected locally across two Oxfordshire National Health Service hospitals by researchers from the Translational Neuropsychology Group at the University of Oxford.

Programme inclusion criteria were stroke diagnosis (first ever or recurrent) ascertained via CT or MRI scan, age 18 years or older, ability to remain alert for 20 min or longer, and ability to provide informed consent. Stroke severity (ascertained via the National Institute of Health Stroke Scale [NIHSS]) and other stroke-related details (eg, lesion hemisphere and first *vs* recurrent stroke) were obtained from electronic health records. Race or ethnicity data were not available in the development or validation cohorts. All participants provided written informed consent to take part. The OCS-Recovery study was approved by the South Central–Oxford C Research Ethics Committee (reference 18/SC/0550).

Study outcome measure

Overall PSCI was assessed using the OCS,[19] a measure of stroke-specific cognition across multiple cognitive domains affected by stroke. Participants completed the OCS acutely and at 6 months after stroke. The OCS comprises 12 subtasks forming six cognitive domains: language (picture naming, semantics, and sentence reading), memory (orientation, verbal recall, and episodic recognition), spatial attention (broken hearts cancellation task), numeracy (number writing and calculation), praxis (gesture imitation), and executive function (mixed trails). Subtask scores are binarised as impaired (1) or unimpaired (0) relative to cutoff scores from a normative sample. A domain

impairment was defined as the presence of any impairment in any subtask within that domain.

Potential predictors

For the PSCI prediction model, we selected predictors that were likely to be available in electronic health records on deployment and be conceptually relevant to post-stroke cognition, including eight clinically relevant predictors (age at stroke, sex assigned at birth, NIHSS scores, years of education, first *vs* recurrent stroke, type of stroke [ischaemic *vs* haemorrhagic], stroke hemisphere, and acute cognitive impairment [acute proportion of OCS subtasks impaired]).[15] Haemorrhagic stroke included intracerebral haemorrhage but not traumatic or subarachnoid haemorrhage. Stroke hemisphere included an undetermined category for instances of unclear lateralisation (based on CT or MRI scan data) or inconclusive clinical presentation. We also considered four data-driven predictors that are available in electronic health records (length of stay in acute care, independence before admission [defined as not requiring paid or family carer support >2 h per week], presence of mood difficulties during acute care [as reported by clinical records during stay], and Charlson Comorbidity index). These predictors covered prestroke factors (ie, education-based cognitive reserve, independence status, comorbidity, age, and sex assigned at birth) and post-stroke factors (ie, NIHSS, first *vs* recurrent stroke, type of stroke, hemisphere, acute cognition, mood, and length of stay) conceptually relevant to cognition.

Sample size justification

Sample size sufficiency was evaluated on the basis of events fraction, total sample size, number of predictor parameters, and a target shrinkage factor of more than 0·90 to minimise overfitting.[20] Event fraction rates and assumed apparent Nagelkerke's R^2 performance (0·30) were based on previous OCS programme analyses.[10] For the overall PSCI model, the minimum sample size required was 393 participants.

Management of missing data

Those with complete versus incomplete data 6 months after stroke were compared in terms of predictor variables. To increase statistical power and reduce bias, multiple imputation was conducted across 20 imputed datasets (due to 28·8% missingness in acute NIHSS scores) with 50 iterations. Data were assumed missing at random, given that the variable with the highest missingness rate (NIHSS) was historically unavailable in electronic health records in earlier recruitment periods. Only predictor variables were imputed, given that missingness is not likely to occur in the outcome variable at deployment.[21] Missingness of predictor variables (eg, of stroke severity information) is likely to occur on model deployment, meaning that imputation would be necessary.[21] Sensitivity analyses were conducted to investigate the influence of missing information (appendix pp 8–10). A detailed account of participant attrition has been published previously.[10]

Model development and internal validation

The models included overall PSCI severity (total proportion of OCS subtasks impaired at 6 months after stroke; linear regression continuous outcome model) or PSCI presence in any domain (logistic regression binarised outcome model). Because of the potential drawbacks associated with removal of clinically relevant (albeit statistically non-significant) predictors,[22] backward stepwise elimination was only used to remove non-significant ($p>0·10$) data-driven predictors. These clinically relevant predictors were considered mandatory in model development (irrespective of statistical significance) because of previous research showing the association of clinical predictors with 6-month PSCI[15] as well as the conceptual importance and face validity of such predictors for clinicians using the model on deployment. Models developed across 20 imputed datasets were compared with complete case data.

Each model had 12 potential predictors, forming an initial model. Following predictor selection, performance was estimated with clinically relevant predictors and only significant data-driven predictors were retained, forming the final model. Predictor selection per model was repeated with bootstrapping across 1000 iterations. We took this dual approach to model development to allow updating of models following future external validation and recalibration efforts—ie, identification of new predictors, or predictors previously identified as conceptually relevant becoming routinely available in electronic health records.

We evaluated the apparent final model performance (ie, with non-significant data-driven predictors removed) using discrimination (model's ability to correctly identify individuals with and without 6-month PSCI, estimated via area under the curve [binary outcome models only] and C-statistic), calibration measures (calibration-in-the-large [CITL], calibration slope, calibration plots, Brier scores, and observed-over-expected ratio), and goodness-of-fit measures (adjusted R^2 for the continuous PSCI model; Nagelkerke's R^2 for the binary PSCI models). Pooled (across imputed datasets) β values, coefficients, and performance statistics are reported per model. Pooling was conducted using Rubin's rule.

Optimism-adjusted performance estimates were obtained via bootstrapping each model on multiply imputed data across 1000 samples, comparing the performance of each bootstrapped model with the original sample. The average difference (optimism) was deducted from the original model (apparent performance), providing optimism-adjusted performance measures. The model-specific optimism-adjusted calibration slope was used as a uniform shrinkage factor and was multiplied with model regression coefficients to correct for potential overfitting.[23,24] Model intercepts were re-estimated with the shrunken regression coefficients to ensure CITL for the shrunken model. Risk groups were created using tenth decile groups on prediction model estimates for visualisation purposes via calibration plots. 95% CIs for adjusted and Nagelkerke's R^2 estimates across all types of prediction models are not

See Online for appendix

typically calculated as they are descriptive measures rather than an estimand; hence, our results do not report these data. Full details of final model formulas for continuous and binary PSCI models are provided in the appendix (pp 4–8).

External validation

The OCS-Care dataset[9] was used for external validation. Like the OCS-Recovery cohort, the UK OCS-Care cohort was assessed for PSCI acutely and after 6-months with the OCS (a detailed comparison of OCS-Recovery and OCS-Care demographics is provided in the appendix [p 2]). Model predictors were collected from electronic health records. The OCS-Care dataset was collected, processed, and stored independently across 37 hospitals in England by stroke ward research nurses and occupational therapists. OCS-Care data were managed independently by Keele University's Clinical Trails Unit. In parallel with the OCS-Recovery dataset, missing OCS-Care predictor variables were imputed via multiple imputation across 20 iterations. In terms of minimum sample size requirements,[25] this dataset was sufficient to estimate a C-statistic of 0·80 (CI width 0·20); precise calibration slope estimates would have required a much larger dataset.

The pooled shrunken model coefficients obtained through internal validation were applied to the OCS-Care data to estimate performance to both the binary logistic and continuous models. Performance measures (calibration slope, CITL, C-statistic, R^2, and Nagelkerke's R^2) were estimated and pooled across the 20 imputed OCS-Care datasets using Rubin's rules. Overall binary PSCI model performance was further evaluated within subgroups by age range, sex assigned at birth, first versus recurrent stroke, and acute PSCI severity.

Exploratory domain-specific prediction models

We developed exploratory logistic domain-specific prediction models using the same development and validation methods as applied for the overall PSCI model to inform future development of domain-specific models (appendix p 10). Minimum sample sizes were not met for the individual subdomains of language (1000 participants), memory (1016 participants), attention (638 participants), praxis (2912 participants), numeracy (2524 participants), and executive function (1724 participants).

Statistical analysis

Analyses were done in R version 4·4·0. Baseline descriptive statistics were first summarised. R packages used included rms, psfmi, mice, and pmvalsampsize.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants were recruited to the OCS-Recovery cohort between March 20, 2012, and March 9, 2020. Participants completed the OCS acutely (mean 4·4 days [SD 4·5] after stroke; n=866) and at 6 months after stroke (n=430). Attrition from acute to 6 months was due to loss to follow-up (n=149), participant death (n=82), declining follow-up (n=76), being too unwell to take part (n=72), having moved out of the area (n=36), having had an incomplete assessment (n=16), or not being seen due to COVID-19 restrictions (n=5).[10] As reported previously,[10] those lost to attrition versus those retained differed in terms of having greater stroke severity and greater acute cognitive impairments; additionally, those with no cognitive impairment were more likely to be lost to attrition than those with any cognitive impairment. The demographic and clinical characteristics of the OCS-Recovery cohort are in table 1. Acutely, 323 (75·1%) of 430 participants completed all OCS subtasks, with 400 (93·0%) completing at least ten subtasks, indicating the feasibility of the OCS. At 6 months, all 430 participants provided outcome data for our continuous and logistic PSCI models, with 370 (86·0%) completing all subtasks and 409 (95·1%) completing at least ten subtasks.

Participants with missing 6-month PSCI data were more likely to have higher acute PSCI (p<0·0001), be older (p=0·027), and have acute impairments in language (p=0·0011), memory (p=0·0006), or numeracy (p=0·0049) than were those without missing PSCI data. NIHSS missingness was not related to demographic factors (p>0·05 for all factors; appendix pp 8–9).

In the multivariable continuous model of proportion of OCS tasks impaired at 6 months after stroke, the strongest clinically relevant predictors included higher age (pooled β=0·002 [95% CI 0·001–0·003]; p=0·37) and a greater proportion of acute OCS tasks impaired (0·367 [0·306–0·429]; p<0·0001; appendix p 3). In bootstrapped and complete case data, the only data-driven predictor retained was requiring carer support before admission (0·099 [0·048–0·151], p=0·0002), which improved variance explained in complete case data (F=3·69, p=0·026). The optimism-adjusted performance of the continuous overall PSCI model was good to excellent (calibration slope 0·96, CITL –0·01, mean squared error 0·02, adjusted R^2=0·34; table 2). Pooled shrunken coefficients for the final overall continuous and binary PSCI models are provided in the appendix (p 3).

In the multivariable binary model (figure 1), higher age at the time of stroke (pooled odds ratio 1·04 [95% CI 1·02–1·06]; p=0·0005), bilateral hemisphere lesions (0·38 [0·16–0·91]; p=0·0301), fewer years of education (0·94 [0·88–1·01]; p=0·076), and a greater proportion of acute OCS tasks impaired (45·39 [12·16–169·43]; p<0·0001) were associated with risk of 6-month PSCI (appendix p 3). No data-driven predictors were retained for the binary PSCI model. The final optimism-adjusted estimates showed good performance (C-statistic 0·76 [95% CI 0·71 to 0·80],

	Participants (n=430)
Sex assigned at birth	
Male	230 (53·5%)
Female	200 (46·5%)
Age, years	
Mean (SD)	73·8 (12·5)
Range	18–95
Education, years	
Mean (SD)	12·3 (3·6)
Range	0–23
Stroke type	
Ischaemic	362 (84·2%)
Haemorrhagic	68 (15·8%)
Lesion hemisphere	
Left	153 (35·6%)
Right	168 (39·1%)
Bilateral	34 (7·9%)
Undetermined from scan	75 (17·4%)
First or recurrent stroke	
First	292 (67·9%)
Recurrent	138 (32·1%)
Acute NIHSS score	
Mean (SD)	6·8 (6·1)
Range	0–30
Acute OCS	
Proportion of OCS tasks impaired, mean (SD)	0·27 (0·24)
Range of OCS tasks impaired	0–1
Language impairment	195/429 (45·5%)
Attention impairment	177/391 (45·3%)
Executive function impairment	113/380 (29·7%)
Memory impairment	170/428 (39·7%)
Number impairment	178/428 (41·6%)
Praxis impairment	112/419 (26·7%)
Any domain impairment	352/430 (81·9%)
6-month OCS	
Proportion of OCS tasks impaired, mean (SD)	0·16 (0·18)
Range of OCS tasks impaired	0–0·80
Language impairment	138/428 (32·2%)
Attention impairment	184/416 (44·2%)
Executive function impairment	98/400 (24·5%)
Memory impairment	137/430 (31·9%)
Number impairment	85/420 (20·2%)
Praxis impairment	79/403 (19·6%)
Any domain impairment	295/430 (68·6%)

Data are n (%) unless otherwise specified. NIHSS=National Institute of Health Stroke Scale. OCS=Oxford Cognitive Screen.

Table 1: **Participant demographics**

	Model performance (95% CI)	Average optimism (95% CI)*	Optimism-adjusted performance (95% CI)
Overall PSCI (continuous)			
Calibration slope	1 (0·88 to 1·12)	0·04	0·96
CITL	0·00 (–0·0001 to 0·0001)	–0·01	–0·01
MSE	0·02 (–0·05 to 0·08)	0·00	0·02
Adjusted R^2	0·38 (0·31–0·45)†	0·04	0·34
Any domain impairment (binary)			
C-statistic	0·78 (0·73 to 0·83)	0·02 (0·02 to 0·03)	0·76 (0·71 to 0·80)
Calibration slope	1·03 (0·85 to 1·22)	0·10 (0·09 to 0·11)	0·93 (0·75 to 1·11)
CITL	0·0001 (–0·04 to 0·04)	1·17 (0·91 to 1·35)	–1·17 (–1·39 to –0·95)
Brier score	0·17 (0·15 to 0·19)	0·05 (0·04 to 0·05)	0·12 (0·10 to 0·14)
O:E	1 (1 to 1)	0·01 (–0·06 to 0·06)	0·99 (0·94 to 1·06)
Nagelkerke's R^2	0·27†	0·06 (0·06 to 0·07)	0·21†

CITL=calibration-in-the-large. MSE=mean squared error. O:E=observed-over-expected ratio. PSCI=post-stroke cognitive impairment. *At the time of writing, the R package rms does not calculate bootstrapped CIs for average optimism and optimism-adjusted performance for clinical prediction models with a continuous outcome variable. †CIs for R^2 estimates across all types of prediction models are not typically calculated in prediction as they are descriptive measures rather than an estimand; for the adjusted R^2, the CI across the imputed datasets is provided.

Table 2: **Performance metrics for all final continuous and binary models pooled across 20 imputed datasets**

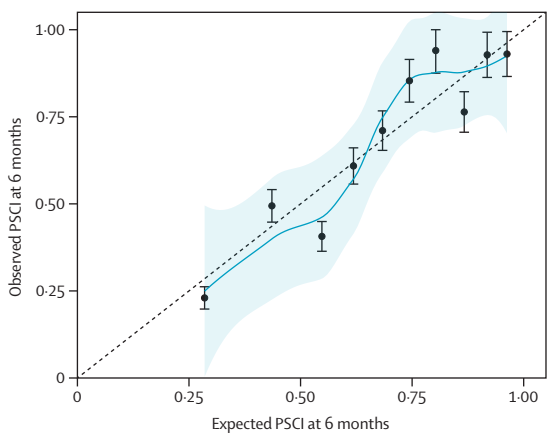

Figure: **Calibration plot of any PSCI at 6 months across 20 imputed datasets**
0 indicates no impairment; 1 indicates any impairment. A calibration plot with complete cases is provided in the appendix (p 18). Points indicate risk groups by decile with 95% CIs of each risk group shown as whiskers. The shaded area indicates the pointwise 95% CI around the Loess smoother applied to the calibration curve. PSCI=post-stroke cognitive impairment.

calibration slope 0·93 [0·75 to 1·11], CITL –1·17 [–1·39 to –0·95], Brier score 0·12 [0·10 to 0·14], Nagelkerke's R^2=0·21; table 2).

In sensitivity analyses to assess the influence of missing information, there were no notable differences in predictor selection for the continuous or binary overall PSCI models (appendix pp 18–19). Unadjusted relationships between predictor and outcome variables for the overall PSCI models are provided in the appendix (pp 22–23).

The external validation cohort (OCS-Care)[9] comprised 264 patients with a median age of 68·9 years (IQR 16·6), recruited between July 31, 2014, and Jan 31, 2017. The mean NIHSS score within this cohort was 2·8 (SD 6·1), constituting mild stroke severity. 147 (55·6%) OCS-Care participants had at least one cognitive impairment at 6 months, versus 187 (70·8%) with at least one cognitive impairment acutely.[9] For the binary model, the C-statistic was (0·74 [95% CI 0·68 to 0·80]) with the external data (table 3). Overall, model discrimination, calibration, and goodness-of-fit for both binary and continuous models were not substantially discrepant in the validation cohort,

	Model performance (95% CI)*
Overall PSCI (continuous)	
Calibration slope	1·26 (1·03 to 1·49)
CITL	–0·08 (–0·04 to –0·12)
MSE	0·01 (0·009 to 0·017)
Adjusted R^2	0·46*
Any domain impairment (binary)	
C-statistic	0·74 (0·68 to 0·80)
Calibration slope	1·10 (0·73 to 1·48)
CITL	–0·13 (–0·42 to 0·15)
Nagelkerke's R^2	0·22*

OCS-Care[9] data were used for external validation. CITL=calibration-in-the-large. MSE=mean squared error. PSCI=post-stroke cognitive impairment. *CIs for R^2 estimates across all types of prediction models are not typically calculated in prediction as they are descriptive measures rather than an estimand.

Table 3: **Model performance following external validation across 20 imputed datasets**

	C-statistic (95% CI)	Calibration slope (95% CI)	Nagelkerke's R^2
Sex assigned at birth			
Male	0·76 (0·67 to 0·83)	1·29 (0·72 to 1·86)	0·24
Female	0·76 (0·66 to 0·84)	1·27 (0·67 to 1·88)	0·18
Age, years			
<60	0·76 (0·62 to 0·86)	1·70 (0·72 to 2·67)	0·28
>60	0·64 (0·49 to 0·77)	1·07 (0·09 to 2·04)	0·11
>70	0·65 (0·50 to 0·78)	0·64 (–0·09 to 1·37)	0·06
>80	0·71 (0·54 to 0·84)	1·24 (0·15 to 2·33)	0·15
First ever stroke	0·75 (0·67 to 0·81)	1·24 (0·77 to 1·70)	0·24
Recurrent stroke	0·73 (0·57 to 0·84)	0·97 (0·14 to 1·81)	0·13
Mild acute PSCI	0·62 (0·51 to 0·71)	0·79 (0·15 to 1·43)	0·03
Moderate-to-severe acute PSCI	0·72 (0·60 to 0·81)	0·99 (0·38 to 1·61)	0·14

PSCI=post-stroke cognitive impairment.

Table 4: **Subgroup analysis of overall binary cognitive model performance with the external validation dataset**

suggesting good model performance across cohorts (table 3).

In subgroup analyses conducted with the binary overall PSCI model in the external validation dataset (table 4), performance did not vary by sex assigned at birth (C-statistic 0·76 [95% CI 0·67–0·83] for male and 0·76 [0·66–0·84] for female) or first versus recurrent stroke (0·75 [0·67–0·81] for first ever stroke and 0·73 [0·57–0·84] for recurrent stroke). Model performance varied by age group (0·76 [0·62–0·86] for participants aged <60 years, 0·65 [0·48–0·78] for participants aged >60 years, 0·65 [0·50 –0·78] for participants aged >70 years, 0·71 [0·54–0·84] for participants aged >80 years) and by level of acute PSCI (0·62 [0·51–0·71] for mild acute PSCI and 0·72 [0·60–0·81] for moderate-to-severe acute PSCI).

Given the promising performance of the binary overall PSCI model, we developed an online risk calculator, allowing further independent evaluation in future research. The tool allows entry of raw values for each key predictor, resulting in a percentage likelihood of domain-specific PSCI impairment at 6 months after stroke.

For the **PSCI online risk calculator** see https://ocs-strokecogpredictor.shinyapps.io/

The optimism-adjusted performances of the exploratory domain-specific models of PSCI were either similar to the overall PSCI models (C-statistic 0·77 for language and 0·73 for attention) or had lower performance (C-statistic range 0·60–0·71 for memory, numeracy, executive function, and praxis [appendix pp 17–18]). In external validation, language and attention models showed good discrimination and goodness-of-fit; however, calibration was poor across all domains, particularly in memory, numeracy, executive function, and praxis. Full details of the exploratory domain-specific models, including external validation, are in the appendix (pp 10–21).

Discussion

We developed and externally validated overall PSCI prediction models using acute cognitive information from a stroke-specific screen alongside established PSCI predictors. To our knowledge, this study is the first to use acute cognitive data and a stroke-specific measure of PSCI in clinical prediction model development. We additionally explored creating domain-specific prediction models to be developed further in future research.

Our models provided good explanatory power, with even the domain-specific models performing better than existing models of post-stroke cognitive decline and dementia (C-statistic range 0·53–0·66).[14] Promisingly, the overall binary PSCI model performed similarly with external and internal data, suggesting that this model could be used across different stroke cohorts. The performance of the binary PSCI model showed some variation within subgroups, with a better performance in younger age groups (<60 years) and those with moderate-to-severe acute PSCI. These findings are in line with domain-specific PSCI prediction being indicative of stroke-specific focal cognitive changes and their recovery rather than of overall, non-stroke-specific brain health-related cognitive outcomes (eg, dementia or cognitive decline).

For external data, CITL estimates were consistently negative, suggesting a small systematic overprediction of 6-month PSCI risk. This is likely because the development data comprised a moderate-to-severe stroke cohort, whereas the external data comprised a milder stroke cohort. Additionally, the calibration slopes were larger for external data than in internal data, potentially indicating overshrinkage. This prediction model should further be recalibrated across a range of stroke severities.

Age, sex assigned at birth, years of education, NIHSS scores, recurrent stroke, and stroke type contribute to PSCI[15] and should be included in recalibrations of these models. Novel predictors should also be considered—our modelling approach includes data-driven predictors to allow for routine model updating. This approach identified potential predictors for recalibration (ie, requiring carer support before a stroke and comorbidity) that are currently

excluded from PSCI prediction modelling.[7,14,26] Crucially, to facilitate future implementation, we only selected predictors available in electronic health records, whereas many PSCI models include predictors not routinely available at deployment.[7,8,14] In the UK, selection of predictors—eg, acute cognitive assessment—should be guided by those included in the National Clinical Guideline for Stroke,[18] which are likely to be available. Other biopsychosocial predictors (eg, white matter hyperintensities and socioeconomic status) and clinical predictors (eg, amount or intensity of neurorehabilitation offered) might improve model performance but could be less available or have considerable economic considerations. For example, although imaging-based data improve PSCI prediction models,[27] behavioural data (eg, cognitive assessments) are considerably more affordable and feasible to implement.[28] The OCS is currently a standard first-line screening tool in the UK, but evaluating the model's scalability will depend on wider international implementation. Furthermore, incorporating measures of pre-stroke cognitive ability might enhance model performance.

As is typical for electronic health record data, NIHSS scores had large amounts of missingness. Imputation methods should be considered at deployment.[21] Given predictor missingness, collecting qualitative feedback on model usability would aid future implementation.

Clinical prediction models using acute cognitive information might offer more meaningful PSCI prognoses than published prediction models of post-stroke cognition,[11–14] as evidenced by their better performance. Although PSCI rates are highest during acute stroke, early PSCI might be reversible,[29] and information about likely 6-month outcomes is valuable to patients who have had a stroke. Qualitative research suggests that focusing solely on cognitive decline as a possible PSCI outcome (eg, as per the study by Hbid and colleagues[7]) might cause undue concern or, at best, be irrelevant.[30] Stroke survivors and families commonly report wanting personalised information about managing cognitive changes.[30] Our models are an essential first step to providing person-specific cognitive trajectories.

A notable strength of this study was its use of a stroke-specific PSCI outcome measure rather than a score reflecting overall cognitive decline or dementia. The minimisation of confounds associated with the OCS, together with its brief administration time and the information it provides on the cognitive domains compromised in stroke make it a credible candidate for PSCI model development.

Our overall PSCI model performed well and offers an improvement on cognitive decline-focused models, but domain-specific models could provide still further personalised detail. The low prevalence of some domain-specific outcomes (ie, numeracy, executive function, and praxis) restricted domain-specific model development. Although highly common acutely, these impairments are less prevalent in chronic stroke and, therefore, require substantial sample sizes for sufficient development. Future domain-specific models could also consider how combinations of specific cognitive impairments influence performance. Specific combinations of impairment (eg, language and executive function) could affect outcomes differently, given the differential correlations between cognitive domains.[10] Developing within-domain models (eg, a sentence-reading model *vs* a language impairment model) might also be helpful, given varying recovery within domains.[3,10] Furthermore, predictor selection should be carefully considered. Baseline cognition best explains long-term PSCI risk,[15] with established predictors other than age explaining little variance.[10,26] Less-frequently researched PSCI domains (eg, numeracy and praxis) might particularly benefit from data-driven predictors. As is typical for new prediction models, recalibration of our models is required. Our cohort's high attrition might affect model estimates, event probabilities, and model generalisability. Although subgroup analyses with external data showed similar performance in severe stroke, bias from high attrition could be explored further in future studies. Data collection for future recalibration should target patients who have had severe strokes and those with no cognitive impairment and could consider propensity score adjustment. Our models were derived from a mixed cohort of patients with first ever and recurrent strokes and ischaemic and haemorrhagic strokes and are not applicable to subarachnoid haemorrhage. Future recalibration should explore whether performance differs in patients with first ever versus recurrent stroke, ischaemic versus haemorrhagic stroke, and subarachnoid haemorrhage versus intracerebral haemorrhage due to the potentially differing cognitive profiles of patients with these conditions. A linear regression model best aligns with the additive contribution of predictor variables; however, recalibration of our continuous outcome model should explore alternative regression models for proportion-based outcomes.

In conclusion, we show that a domain-specific model including acute cognitive information improved prediction of 6-month PSCI, with initial external validation in a milder cohort. Our model development process allows for future inclusion of novel data-driven predictors. This prediction model of stroke-specific cognition has the potential to offer more meaningful PSCI prognoses, including domain-specific cognitive recovery, compared with existing models focused on domain-general decline.

OCS_Stroke_Cognition_Predictor/

Contributors

ND conceived the study and was responsible for protocol development, ethical approval, overseeing patient recruitment, project administration, and funding acquisition. AK researched the literature and conducted all formal analyses, visualisation, data curation, and writing of the original and final drafts. ND and AK verified the data. KIES provided oversight on methodological design and statistical and analysis support. All authors interpreted the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed and edited the manuscript and approved the final version.

Declaration of interests

ND is a developer of the Oxford Cognitive Screen, which is licensed through Oxford University Innovations, but does not currently receive

any remuneration from its use. ND declares having received research grants from the Stroke Association; industry funding and consultancy payments from Brain Stimulation; honoraria for lectures, invited talks, and travel in the UK, Norway, Australia, and Japan; and having unpaid committee roles on a trial steering committee (C-SIGHT), a funding committee (NIHR RfPB), and the Federation of the European Societies of Neuropsychology (Stroke Topic Chair). AK declares unpaid committee membership for the UK & Ireland Stroke Psychology Network and the Organisation for Psychological Research into Stroke. KIES declares no competing interests.

Data sharing

De-identified data collected for this study, with a corresponding data dictionary, are freely available for public research use via an application to Dementias Platform UK, with approval for use provided by Nele Demeyere. Applications are processed via https://www.dementiasplatform.uk/. Analysis code is available via the Open Science Framework.

For the **analysis code** see https://osf.io/3pc5k/

Acknowledgments

This study was delivered through the UK National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, which provided funding for ND (Advanced Fellowship NIHR302224), AK (Development and Skills Enhancement Award NIHR305153), and KIES. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The authors thank all participants and members of the Oxford Translational Neuropsychology Group for contributions to recruitment and testing.

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