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Biomarkers of Motor Outcomes after Stroke

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Key Points

- Neurophysiological and neuroimaging biomarkers of the motor cortex and its descending pathways are related to subsequent upper and lower limb motor outcomes after stroke.
- Prediction tools combining neurophysiological biomarkers with clinical and demographic information have been validated for upper limb motor outcomes.
- Prediction tools have been developed for lower limb and walking outcomes and combine clinical and demographic information, but do not yet incorporate biomarkers.

Synopsis

Predicting motor outcomes after stroke based on clinical judgement alone is often inaccurate and can lead to inefficient and inequitable allocation of rehabilitation resources. Prediction tools are being developed so that clinicians can make evidence-based, accurate and reproducible prognoses for individual patients. Biomarkers of corticospinal tract structure and function can improve prediction tool performance, particularly for patients with initially moderate to severe motor impairment. Being able to make accurate predictions for individual patients supports rehabilitation planning and communication with patients and families.

Introduction

Motor impairment is common after stroke, affecting around half to three-quarters of patients.^{1,2} Recovery from motor impairment mainly occurs in the first three months after stroke.³⁻⁵ Further gains in activity capacity and participation can be achieved with ongoing adaptation and compensation.⁶ Minimising motor disability is essential for regaining independence in daily activities and participation in life roles.³

Accurate predictions of individual patients' motor outcomes can guide important decisions in the initial days after stroke, such as therapy goals and discharge destination.⁷⁻⁹ Predicting motor outcomes can also help patients and their families plan and make necessary arrangements for life after stroke.

Nature of the Problem

Predicting motor outcomes based on clinical impression alone can be difficult. For example, 20 experienced clinicians were asked to predict upper limb functional outcome for each of their 131 patients within a week of stroke, and their overall accuracy at six months was only 59%.¹⁰ Despite this, clinicians rate their clinical impression of the patient's likely functional outcome as the most important factor when deciding discharge destination from acute care.^{11,12} Differences between clinicians' impressions can produce wide variations in access to rehabilitation services. For example, a 3-fold variation in the rates of discharge to inpatient rehabilitation services was found by a large study of more than 31,000 stroke patients across 918 acute hospitals in the United States.¹³ This large variation persisted even when casemix and the availability of inpatient rehabilitation facilities were accounted for. These findings highlight the inaccuracy of predictions and variability in discharge decisions that arises when clinicians rely primarily on clinical impression. This variability is a potential source of inefficient allocation of rehabilitation resources, and inequitable access to rehabilitation services.^{11,13} One way to reduce variability in clinical decision-making is to use decision

support tools that combine clinical and demographic information with biomarkers in an evidence-based, systematic, and reproducible way.

Multivariable regression modelling has repeatedly identified several clinical and demographic variables associated with motor outcomes after stroke, including the patient's age, stroke severity evaluated with the National Institutes of Health Stroke Scale (NIHSS), and the severity of initial motor impairment. Unlike clinical variables, biomarkers provide information about underlying biological processes that are not readily discernible through clinical assessment and could be used to predict outcomes or response to treatment.⁹ Biomarkers that are strongly associated with motor outcome after stroke are provided in Box 1. In general, patients with more normal brain structure and function experience better motor outcomes after stroke, which is not surprising. Biomarkers are particularly useful for patients with initially severe motor impairment, to identify those with latent potential for recovery. Prediction tools that systematically combine biomarker information with clinical and demographic information can improve the accuracy of clinicians' prognoses and reduce variability in their decision-making.^{14,15} Desirable prediction tool characteristics are summarised in Box 2.

The purpose of this review is to summarise current methods for predicting motor outcomes for the upper limb, lower limb, and mobility after stroke, with a particular focus on the role of biomarkers. The strengths and limitations of current methods are identified, along with recommendations for future research.

Current Evidence – Upper Limb

Upper limb (UL) impairment is a frequent consequence of stroke that affects activity capacity and performance, independence, and participation in life roles.^{1,16} Early prediction of subsequent UL motor outcome can assist planning and tailoring of UL rehabilitation, and the management of patient, family, and clinician expectations. Upper limb prediction tools typically focus on UL outcome at either 3 or 6 months post-stroke, as most motor recovery occurs within this timeframe.¹⁷ The severity of initial UL impairment along with neurophysiological and neuroimaging biomarkers have consistently been shown to predict subsequent UL motor recovery and outcomes.¹⁸⁻²⁰

Prediction tools without biomarkers

Prediction tools have been developed that use clinical information alone to predict an individual's UL outcome after stroke. The advantage of these types of tools is that they capitalise on existing resources in terms of staff skill and time, and available equipment. Table 1 summarises five of these tools.²¹⁻²⁵ Some approaches use quick, simple bedside tests such as measures of upper limb strength. Other approaches incorporate selected single items from standardised assessments such as the Fugl-Meyer Upper Extremity assessment (FM-UE)²⁶ and the Action Research Arm Test (ARAT).²⁷ Many approaches use measures once, within days of stroke, while some use repeated measures over weeks post-stroke to make predictions iteratively.

Prediction tools without biomarkers can predict UL outcomes more accurately for patients with mild initial impairment than for patients with moderate to severe initial impairment.

Patients with some finger extension or grip strength within the first few days after stroke are highly likely to recover at least some motor function by 3 to 6 months post-stroke.^{21-23,28}

However, prediction tools that use clinical information alone cannot accurately identify which patients with moderate to severe initial UL impairment will recover at least some UL function.^{21-25,28} Repeating clinical assessments over the weeks following stroke could

improve prediction accuracy for these patients.^{22,24,25} But this may be too late to guide rehabilitation decision-making, and these models are currently most accurate for patients with mild initial UL impairment.^{24,25} Overall, predictions based on clinical information alone are least accurate for patients with initially moderate to severe UL impairment.

From a clinical utility perspective, the EPOS-UL model²¹ is currently the only externally validated clinical prediction tool.²⁸ However, this model has been criticized for its binary outcome, which limits clinical meaningfulness. An extended EPOS-UL model has been explored to address this, but requires further development.²⁸ Three tools²²⁻²⁴ offer more granular prediction categories, but are not yet validated. None of the clinical prediction tools have demonstrated positive clinical impact, and clinical implementation is not yet appropriate.

Prediction tools with biomarkers

Biomarkers of motor cortex and descending motor pathway integrity improve the accuracy of predictions for patients with moderate to severe initial UL impairment.^{14,18,19,29,30}

Neurophysiological measures

Prediction tools that include both clinical measures and neurophysiological biomarkers are summarised in Table 1. Electroencephalography (EEG) is a well-established tool in clinical practice, is relatively low cost, and is feasible within the acute stroke setting.³¹ EEG can be used to measure cortical activity and functional connectivity after stroke.³² Bihemispheric power spectral analysis is one of the most common and reliable analysis techniques.^{33,34} Using this technique Saes et al. found that a measure of theta frequency symmetry obtained within 3 weeks post-stroke added prognostic value when combined with FM-UE score to predict UL impairment at 6 months post-stroke.³⁵ The prognostic value of other early EEG measures, such as those derived from time-frequency analysis, evoked potentials, and EEG connectivity, is less clear.³⁶ A recent systematic review and meta-analysis including 12 UL-related studies concluded that EEG measures were associated with subsequent FM-UE

score, however this work is largely at the exploratory stage.³³ Currently there are no clinical prediction tools incorporating EEG biomarkers to predict an individual's UL outcome after stroke.

Transcranial magnetic stimulation (TMS) can be used to test the functional integrity of the corticospinal tract (CST).³⁷ TMS is a safe, painless, non-invasive technique that can elicit a motor evoked potential (MEP) in contralateral musculature when the CST is functionally intact. MEP status is a binary measure of MEP presence (MEP+) or absence (MEP-). MEP status can be readily obtained at a patient's bedside with no computation,^{38,39} and is the simplest MEP parameter that robustly correlates with UL motor outcome.⁴⁰⁻⁴² Typically, patients in whom MEPs can be elicited from affected UL muscles in the first days after stroke (MEP+) have better UL functional outcomes than MEP- patients.³⁹⁻⁴² Importantly, patients with initially severe UL impairment who are MEP+ are likely to have a good motor outcome, and this potential may go unrecognised without the UL MEP status biomarker.^{14,39} MEP absence in affected UL muscles in the first week after stroke indicates a patient is unlikely to regain fine motor control of the hand, which relies on a functional CST.²⁹ MEP- patients may regain gross movements of the UL, and even hand opening and closing, but not dexterous hand movement.⁴³ Several studies have found that combining UL MEP status with clinical assessments typically produces more accurate predictions than using either type of predictor alone.^{19,39}

To date, two UL prediction tools have combined TMS biomarkers with clinical assessments for predicting an individual's likely UL outcome. In 2017, Stinear et al. developed the PREP2 prediction tool, which predicts an individual's UL outcome at 3 months in one of 4 categories: excellent, good, limited, or poor.³⁹ The tool begins with the SAFE score, which is the combined Medical Research Council (MRC) strength grades for shoulder abduction and finger extension. If the SAFE score is ≥ 5 by day 3 post-stroke it is combined with the patient's age to predict an excellent or good UL outcome. If the SAFE score is < 5 then TMS is needed to determine UL MEP status within 7 days of stroke. Patients who are MEP+ are

predicted to have a good UL outcome. For MEP- patients, a binarised NIHSS score (< 7 , ≥ 7) obtained on day 3 post-stroke predicts either a limited or poor UL outcome.

Overall, PREP2 was accurate for 75% of patients, and most accurate for limited and poor predictions (85% and 90%, respectively).³⁹ Misclassification was most common between good and excellent categories, with predictions generally too optimistic. All MEP- patients had a limited or poor outcome, confirming the importance of CST functional integrity for achieving good functional outcomes.³⁹ Importantly, PREP2 predictions remained accurate for 80% of patients at 2 years post-stroke.⁴⁴

A criticism of PREP2 is that the timeframes for obtaining clinical and biomarker measures may not be feasible in all health care settings. If PREP2 is used outside the recommended timeframe at 2 weeks post-stroke then prediction accuracy falls from 75% to 60%, highlighting that the prediction tool needs to be used at the appropriate time to retain accuracy.⁴⁵ A strength of PREP2 is that it has been validated, and has demonstrated positive effects on clinical care such as increasing therapist confidence, enabling tailoring of therapy content, and shortening the length of inpatient stay.⁸

Hoonhorst et al. predicted the likelihood of achieving some return of dexterity (FM-UE ≥ 22) at 6 months post-stroke.⁴⁶ The model included binarised finger extension strength based on the relevant FM-UE item (0, ≥ 1), and binarised shoulder abduction strength using the relevant Motricity Index item (0, ≥ 9). These clinical measures were combined with abductor digiti minimi (ADM) MEP status obtained within 2 days and again at 11 days post-stroke. The models combining the clinical measures with ADM MEP status at these two timepoints had good overall accuracy, with areas under the curve of 0.83 and 0.91 respectively. The combined model was more accurate than ADM MEP status alone, but only at 11 days post-stroke, and it was no more accurate than a model using clinical measures alone. The authors concluded ADM MEP status is not required due to a negligible improvement in prediction accuracy. However, this could reflect the wide range of participants' initial UL impairment (FM-UE scores 3 - 50). Upper limb MEP status is of most value for patients with

moderate to severe initial UL impairment. The inclusion of patients with mild impairment may have diluted the predictive value of UL MEP status in the regression model. This highlights one of the potential limitations of regression models, where all variables are required to predict outcomes for all patients. However, some predictors, such as UL MEP status, are only relevant for a subset of patients. The models produced by Hoonhorst et al. are displayed as tables with probabilities of achieving favourable UL outcomes for all combinations of finger extension and shoulder abduction scores along with UL MEP status, but the predicted outcome is binary and its clinical meaningfulness is therefore questionable.

In summary, the most promising neurophysiological biomarker is UL MEP status obtained with TMS. Upper limb MEP status alone though appears to be an insufficient predictor of UL motor outcome. Combining UL MEP status with clinical measures improves prediction accuracy, particularly in tools where UL MEP status is only required for patients with moderate to severe initial UL impairment. To date, PREP2 is the only UL prediction tool to be validated and implemented within clinical practice, with evidence of positive clinical impact. However, TMS is not currently part of standard clinical care for stroke.

Neuroimaging measures

Several biomarkers obtained from structural and functional neuroimaging are associated with UL motor outcome after stroke. In general, greater disruption to typical brain structure or patterns of activation is associated with worse UL outcomes.¹⁴

Standard care clinical magnetic resonance imaging (MRI) can provide biomarkers of the structural integrity of the cortex and white matter pathways, and multivariable regression modelling has consistently identified associations between these biomarkers and motor outcomes. Lesion volume is broadly associated with motor outcomes, while lesion location and injury to the CST are biomarkers with more specific relevance to UL motor outcome.^{18,36,47} Typically, greater CST injury measured with neuroimaging in the first few days after stroke is associated with worse UL motor recovery and outcome at 3 months post-

stroke.⁴⁷⁻⁴⁹ In patients with severe initial UL impairment, Feng et al. found FM-UE score at 3 months post-stroke was more strongly associated with initial weighted lesion load than initial FM-UE score.⁴⁷ In contrast, in patients with moderate to severe initial UL impairment, Lim et al. found FM-UE score at ≥ 2 months post-stroke was more strongly associated with initial FM-UE than initial CST injury.⁵⁰ Differences in methodology, the cut-off for classifying severe stroke (FM-UE ≤ 10 vs < 35 respectively), and the different outcome timeframes may account for discrepancies. CST injury, when combined with initial FM-UE score, only accounted for about 10% of the variance in UL impairment outcome in patients with moderate to severe initial UL impairment.⁵⁰

MRI can also be used to obtain biomarkers of white matter microstructure characteristics of the CST. Diffusion tensor imaging (DTI) can derive metrics such as fractional anisotropy (FA), mean diffusivity, radial diffusivity and axial diffusivity, which have moderate to strong relationships with UL recovery and outcome.^{18,19} DTI measures of structures such as the posterior limb of the internal capsule (PLIC) at both the acute stage^{51,52} and 2 weeks post-stroke⁵³ are significant predictors of UL motor outcome at 3 months post-stroke. Typically, greater PLIC FA asymmetry is associated with less favourable UL motor recovery and outcomes.^{29,53} CST axial diffusivity measured within 24 hours after stroke may prove to be an alternative biomarker to FA for predicting UL motor outcome in the hyperacute phase.⁵⁴ The relevance of injury to non-primary motor cortex CST projections is less well-studied. However, relationships have been identified between UL motor outcome and measures of sensorimotor tract lesion load,³⁹ fibers originating from the premotor cortex,^{55,56} and cerebellar and corpus callosum tracts.⁵⁷ There is also some evidence that structural MRI biomarkers may outperform clinical assessment in prediction accuracy,^{19,53} but this may depend on how soon after stroke the images are acquired.⁵¹ Further research into structural biomarkers is warranted, however implementation in clinical care may be difficult if non-standard imaging techniques are used that currently require specialised skills to extract biomarker values.

Functional MRI (fMRI) provides another source of biomarkers, relating cortical activity and connectivity to motor outcomes after stroke. For instance, greater activation in the ipsilesional primary motor cortex, ipsilesional premotor cortex, and contralesional cerebellum activation while performing paretic UL motor tasks within the first week post-stroke are related to better UL outcome.^{36,58} The predictive value of resting state fMRI remains unclear.^{19,59}

In general, associations between neuroimaging biomarkers and UL motor outcome are observed at a group level using regression modelling. However, the ability to use these biomarkers to make accurate predictions for individual patients is limited by high variability and no clear cut-off values. Neuroimaging biomarkers may hold more value when combined with clinical and/or demographic information, or other biomarkers, compared to when used alone.^{18,19}

The optimal imaging biomarker may vary depending on UL MEP status.⁵⁷ The original PREP prediction tool in 2012 was the first approach to include a neuroimaging biomarker, PLIC FA asymmetry index, in a sequential manner following SAFE score and UL MEP status to predict an individual's UL motor outcome.⁵³ The PLIC FA asymmetry index was used to predict either a limited or poor outcome for MEP- patients. Overall accuracy was moderate at 64%, and PREP has been superseded by PREP2³⁹ and therefore is not included in Table 1. The subsequent development of PREP2 found that sensorimotor tract lesion load was a more accurate predictor than CST lesion load and PLIC FA asymmetry index.³⁹ Further, PREP2 replaced sensorimotor tract lesion load with day 3 NIHSS score, as the latter had equivalent prediction accuracy and is easier to obtain.

In summary, neuroimaging biomarkers of CST injury and white matter integrity are related to subsequent UL motor outcomes. To date there has been little integration of neuroimaging biomarkers within clinical prediction tools for UL motor outcome, and there are currently no validated tools incorporating neuroimaging biomarkers. Further prospective studies

combining promising neuroimaging biomarkers with clinical and demographic information or other biomarkers are recommended.

Current Evidence - Lower limb

The likelihood of recovering independent walking has significant implications for discharge planning and long-term support needs after stroke. Thus, most lower limb (LL) prediction studies focus on the binary outcome of independent walking or not rather than walking pattern, speed, or endurance. The Functional Ambulation Categories (FAC) is the most commonly used outcome assessment with a category of $\geq 4/5$ indicating independent walking. Age,⁶⁰⁻⁶³ initial stroke severity,^{60,62} LL strength,^{61,63-66} and trunk control or balance^{61,63-66} are consistently identified as variables associated with subsequent independent walking after stroke. These variables have typically been identified through large-scale regression models, providing a basis from which to develop prediction tools.

Prediction tools for independent walking after stroke fall into two categories: predicting achievement of independent walking by a specific timepoint post-stroke such as 3 or 6 months;⁶⁵ or predicting time taken to achieve independent walking in weeks or months.⁶¹

Tools that predict independent walking at discharge from rehabilitation are not considered in this review, as discharge criteria often relate to mobility, creating a circular argument (Box 1).¹⁵

Prediction tools without biomarkers

Two prediction tools using only clinical and/or demographic variables to predict independent walking are outlined in Table 1. The EPOS-LL model predicts the probability of independent walking by 3 months post-stroke using the sitting component of the Trunk Control Test (TCT) and the lower limb Motricity Index (LL-MI).⁶⁵ EPOS-LL is currently the only externally validated prediction tool for the lower limb.⁶⁵ The ability to sit for 30 seconds unsupported (TCT) and a LL-MI score $\geq 25/100$ predicts independent walking by 3 months post-stroke with up to 86% accuracy.⁶⁵ EPOS-LL used multiple assessments over time from 1 to 9 days post-stroke and predictions improved with time post-stroke. Model accuracy at day 1 post-

stroke was 64% but increased to 83% at day 3 post-stroke and 86% by day 9. Although EPOS-LL performs well overall, its specificity ranges from 55 - 73%, which indicates the tool is less able to identify those patients who will not achieve independent walking than those who will. The EPOS-LL study did not include age as a potential variable despite older age being identified as a factor in remaining non-ambulant or taking longer to achieve independent walking after stroke.⁶⁵ It is also unclear whether patients were allowed to use walking aids for the FAC assessment at 3 months post-stroke.

The EPOS-LL development and validation studies had different outcome timepoints of 6 months (development)⁶⁶ and 3 months (validation)⁶⁵ post-stroke with very similar findings. This supports previous work identifying that most patients who achieve independent walking do so within the first 3 months post-stroke,⁶⁰⁻⁶³ with a much smaller number achieving independent walking between 3 and 6 months.⁶¹

The TWIST studies also identified trunk control and lower limb strength as important clinical predictors for independent walking.^{61,64} The TWIST prediction tool uses clinical and demographic variables at 1 week post-stroke to predict time taken to achieve independent walking after stroke.^{61,64} TWIST combines age (< 80 years), knee extension strength ≥ 3 out of 5 (MRC strength grades) and a Berg Balance Test score of < 6, 6 – 15 or ≥ 15 out of 56 to predict the likelihood of independent walking at 4, 6, 9, 16 and 26 weeks post-stroke.⁶¹ TWIST performs well overall with accuracy ranging from 83 – 86%. However, specificity and negative predictive value at 6 months post-stroke were poor due to a very small number of participants achieving independent walking between 16 and 26 weeks post-stroke.⁶¹ The TWIST prediction tool has been internally validated with bootstrapping and goodness of fit calculations.

The TWIST and EPOS-LL studies had relatively large sample sizes (93 and 124 respectively) and viewed together, these studies indicate that similar variables predict both independent walking at 3 months post-stroke and time taken to achieve independent walking. Age and standing balance (Berg Balance Test) are predictors in TWIST but not

EPOS-LL, indicating these may be important factors for achieving independent walking in the first weeks post-stroke but may have less influence on achievement of walking at 3 or 6 months.

Neurophysiological measures

Similar to the UL, the relationships between EEG and walking outcomes are at an early stage of exploration. A recent meta-analysis and systematic review identified only 2 studies investigating EEG as a predictor for walking outcomes with contradictory results.³³ There are currently no prediction tools for walking outcomes incorporating EEG biomarkers.

TMS can be used to assess the functional integrity of the CST to the LL. Lower limb MEPs are usually recorded from the paretic tibialis anterior muscle. The predictive value of LL MEPs is not clear due to small sample sizes^{64,67,68} and few studies obtaining MEP status within 10 days of stroke.^{64,69} In general, patients with LL MEPs experience better walking outcomes than those without MEPs.^{67,68,70,71} There are no prediction tools developed for the LL that include MEP status.

Only one study has combined LL MEP status or MRI measures with clinical variables in the process of developing a prediction tool.⁶⁴ The TWIST development study combined LL MEP status, CST lesion load, and a range of demographic and clinical variables in a single analysis. Sitting balance and hip extensor strength were stronger predictors of time taken to achieve independent walking than either LL MEP status or CST lesion load. Caution should be used in interpreting these results as the sample size was very small (TMS n = 25; MRI n = 30). There are also some possible technical and neuroanatomical explanations for this finding that CST biomarkers do not add value over clinical predictors for walking after stroke.

There are unique challenges with LL TMS. The LL motor cortex is situated within the medial longitudinal fissure and is therefore more difficult to effectively stimulate. From a neuroanatomical perspective, motor control of the lower limb is less reliant on CST function than the UL, and LL MEP status may therefore be less relevant. The most important clinical

predictors for independent walking after stroke are trunk control (sitting balance) and proximal leg strength. Axial and proximal lower limb muscles are controlled by bilateral descending pathways, which support recovery of independent walking despite disruption to the CST.⁷²⁻⁷⁴ Further work combining TMS with clinical and demographic variables should be conducted with larger sample sizes.

Neuroimaging measures

Very few studies have used MRI measures early after stroke to predict walking outcomes. Sample sizes are small and study design is highly variable, making it difficult to draw conclusions. Overall, participants with less structural CST damage measured with DTI achieve better walking outcomes at 6 months post-stroke.⁷⁵⁻⁷⁸ One of these studies also identified a relationship between the ratio of ipsilesional-to-contralesional CST FA at the level of the pons and walking performance (FAC) at 6 months.⁷⁷ An intact CST predicts independent walking, however walking outcomes for patients with damage to the CST can be highly variable. There are currently no prediction tools for walking recovery after stroke that combine MRI and clinical measures.

As control of walking is not solely reliant on CST integrity, imaging studies have begun to explore non-CST neural pathways as potential biomarkers for walking recovery.⁷⁸

Independent walking is associated with FA measures of ipsilesional CST, ipsilesional corticoreticulospinal tract, and contralesional cerebellar peduncles.⁷⁸ These findings indicate that subcortical motor networks contribute to walking recovery after stroke. The contributions of cortical and subcortical networks beyond the CST warrant further investigation.

Discussion

Accurate predictions for motor outcomes after stroke can improve rehabilitation planning by clinical teams and help patients and their families adjust to life after stroke. This review has found that predictions can be made for patients with initially mild upper limb impairment using clinical and demographic information. However, CST biomarkers are needed to make accurate predictions for patients with initially moderate to severe upper limb impairment, and these biomarkers can be combined with clinical and demographic information in prediction tools. Upper limb MEP status is a simple and robust CST biomarker that has been incorporated in the PREP2 prediction tool. PREP2 has been validated and implemented, with demonstrable clinical impact. The role of CST biomarkers is less clear for predicting independent walking after stroke, as clinical and demographic information can be combined in prediction tools to accurately predict both whether and when a patient will safely walk independently again. However, there is relatively less literature on biomarkers for walking recovery, sample sizes are small, and study design is variable. Future research could usefully explore neuroimaging biomarkers of non-M1 CST white matter projections, particularly for walking outcomes after stroke. Measures of non-motor functions such as vision, sensation, attention, and cognition could also be further investigated to see whether they improve the accuracy of prediction tools for motor outcomes.^{79,80}

The implementation of prediction tools needs to be considered during their development and validation.^{81,82} Implementation is likely to be easier when prediction tools have the characteristics summarised in Box 2. Prediction tools also need to be applicable to a wide range of patients, with evidence of accuracy and relative advantage over clinical judgement. Further considerations are clinicians' appetite for change, and the resources and training needed to support accurate and sustainable use of prediction tools in clinical practice. While therapists typically agree that having prediction information is valuable,^{82,83} there are barriers to implementing the biomarkers identified in this review. TMS is not widely available, and MRI measures require sophisticated analyses. Therapists identify the need for specific

equipment and training, along with a lack of time, as barriers to implementation,^{82,84} and addressing these barriers early in tool development can facilitate subsequent use in routine clinical care. Identifying adaptable components of prediction tools, such as the time windows for obtaining predictor information, may also facilitate implementation. Finally, implementation goes beyond the use of a tool to generate a prediction; it requires the thoughtful communication and effective use of prediction information to guide clinical care.

Summary

CST biomarkers obtained within days of stroke are strongly related to subsequent motor outcomes. MEP status is particularly important for patients with initially moderate to severe UL impairment, and can be efficiently obtained and interpreted using the PREP2 prediction tool. In contrast, CST biomarkers have not yet been incorporated in prediction tools for independent walking outcomes, as these can be predicted using clinical and demographic variables.

Clinics Care Points

- Predicting motor outcomes using clinical information alone is often inaccurate for patients with initially moderate-severe motor impairment, and contributes to potentially inefficient and inequitable use of rehabilitation resources.
- The UL MEP status biomarker obtained within 1 week of stroke can accurately identify whether a patient with initially moderate-severe UL motor impairment will recover individuated finger movement by 3 months post-stroke.
- Prediction tools for UL motor outcome are more accurate when they combine clinical and demographic variables with the MEP status biomarker, particularly for patients with moderate to severe initial UL impairment.
- At present, CST biomarkers do not add value to clinical prediction tools for recovery of independent walking.

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Table 1: Prediction tool characteristics

Tool	Reference	n	Baseline severity	Clinical predictors	Biomarkers	Predicted outcome	Statistical method	Model type	Validation study	Clinical impact study
CLINICAL Upper Limb										
EPOS-UL	Nijland et al. 2010 ²¹	156	NIHSS median 7, IQR 4 – 14 FM-UE median 21, IQR 4 – 56 UL MI median 39, IQR 0 – 76 ARAT median 1.5, IQR 0 – 41	FE task in FM-UE 0 or ≥ 1 within 72h SA task in MI 0 or ≥ 9 within 72h Both predictors also obtained on d5 and d9	None	Binarised UL dexterity at 6m based on ARAT score < or ≥ 10	Logistic Regression	Table	Yes, at 3m ²⁸	No
SALGOT	Alt Murphy et al. 2022 ²²	94	NIHSS median 6, IQR 3 – 11 FM-UE median 39, IQR 4 – 58	ARAT grasp 2.5 cm cube < or ≥ 2 on d3 Grip strength dynamometry 0 or > 0 kg on d3 FM-UE SA or SE within flexor synergy 0 or ≥ 1 on d3	None	One of 5 categories of UL function at 3m based on ARAT score: full, excellent, good, limited, or poor	Logistic Regression	Decision tree	No	No
Not named	Barth et al. 2022 ²³	49	90% of NIHSS 0 – 15 59% of SAFE scores ≥ 5	SAFE score < or ≥ 5 at time of consent, mean d7, range d2 – 14 Age < or ≥ 80 y NIHSS < 9, 9, or ≥ 10 at 48h	None	One of 4 categories of UL function at 3m based on ARAT score: excellent, good, limited, and poor	Correct classification rate	Decision tree	No	No
Not named	van der Vliet et al. 2020 ²⁴	412	NIHSS range 0 – 21 66% ≥ 9 on SA task in MI 45% ≥ 0 on FE task in FM-UE	FM-UE total score/s within 26w	None	One of 3 categories of UL impairment within 26w based on FM-UE score: good, moderate, or poor, with % likelihood of	Longitudinal mixture (dynamic)	Web-based application	No	No

						achieving predicted category				
Not named	Selles et al. 2021 ²⁵	450	NIHSS mean 8, SD 5 FM-UE mean 25, SD 22 ARAT mean 14, SD 19 UL MI mean 38, SD 34	ARAT score/s within 26w SA score/s from MI and FE score/s from FM-UE within 26w	None	ARAT score within 26w	Longitudinal mixture (dynamic)	Web-based application	No	No
CLINICAL AND NEUROPHYSIOLOGY COMBINED Upper Limb										
PREP2	Stinear et al. 2017 ³⁹	207	95% NIHSS 0 – 15 68% SAFE score ≥ 5	SAFE score $< \text{or} \geq 5$ on d3 Age $< \text{or} \geq 80$ y NIHSS $< \text{or} \geq 7$ on d3	FDI or ECR MEP status using TMS between d3-7	One of 4 categories of UL function at 3m based on ARAT score: excellent, good, limited, or poor	CART	Decision tree	Yes	Yes ⁸
Not named	Hoonhorst et al. 2018 ⁴⁶	51	NIHSS not reported FM-UE median 8, IQR 3 – 50 UL MI arm median 18, IQR 0 – 70 37% had FE 53% had SA	FE task in FM-UE 0 or ≥ 1 at ≤ 48 h or d11 SA task in MI 0 or ≥ 9 at ≤ 48 h or d11	ADM MEP status using TMS on ≤ 48 h or d11	Binarised UL outcome at 6m based on FM-UE score $< \text{or} \geq 22$	Logistic Regression ROC curve	Table	No	No
CLINICAL Lower Limb										
EPOS-LL	Veerbeek et al 2011 ⁶⁶	154	NIHSS not reported LL MI median 44.5 IQR 33 – 65 Berg Balance scale median 5/56 (1 – 23) Sitting balance yes 68% FM-LL median 17, IQR 7 – 25 TCT median 62, IQR 25 – 87	LL MI $< \text{or} \geq 25$ TCT sitting balance $< \text{or} \geq 25$ Both predictors at < 72 h, d5, and d9	None	Independent walking (FAC ≥ 4) at 6m	Logistic Regression	Table	Yes, at 3m ⁶⁵	No

			FAC median 0, IQR 0 – 2 Barthel Index median 6, IQR 2 – 10							
TWIST	Smith 2017 ⁶⁴	41	NIHSS median 8, range 1 – 11 LL MI median 48, range 0 – 92 FAC median 0, range 0 – 2	TCT < or > 40 on d7 MRC hip extension strength < or ≥ 3 on D7	None	Time taken to achieve independent walking (FAC ≥ 4) at 6w, 12w, or dependent at 12w	CART	Decision tree	No	No
Revised TWIST	Smith 2022 ⁶¹	93	NIHSS median 8, range 1 – 24 LL MI median 59, range 1 – 100 FM-LL median 19, range 7 - 29	Age < or ≥ 80y MRC knee extension strength < or ≥ 3 on d7 Berg balance test < 6, 6 – 15, ≥ 16 on d7	None	Time taken to achieve independent walking (FAC ≥ 4) at 4w, 6w, 9w, 16w, 26w, or dependent at 26w	Cox multivariate regression. Calibration plots and discrimination (C statistic)	Probability table Suggested interpretation	No	No

ADM, Abductor digit minimi; ARAT, Action Research Arm Test; CART, classification and regression tree; e, day; ECR, Extensor Carpi Radialis; EPOS, Early Prediction of Functional Outcome After Stroke; FAC, functional ambulatory category; FDI, first dorsal interosseous; FE, finger extension; FM-LL, Fugl-Meyer Lower Limb assessment; FM-UE, Fugl-Meyer Upper Extremity assessment; h, hours; IQR, interquartile range; LL, lower limb; m, months; MEP, motor evoked potential; MI, Motricity Index; MRC, Medical Research Council; NIHSS, National Institutes of Health Stroke Scale; PREP2, Predict Recovery Potential 2; ROC, receiver operating characteristic; SA, shoulder abduction; SAFE, shoulder abduction and finger extension; SALGOT, Stroke Arm Longitudinal Study at Gothenburg University; SD, standard deviation; SE, shoulder elevation; TCT, Trunk Control Test; TMS, transcranial magnetic stimulation; TWIST, Time to Walking Independently after Stroke; UL, upper limb; w, weeks. All times are relative to stroke onset.

Boxes

Box 1 Biomarkers associated with motor outcomes after stroke

Neurophysiological

Motor evoked potential (MEP) status. Transcranial magnetic stimulation can be used to elicit MEPs as a biomarker of corticospinal tract function. Patients in whom MEPs can be elicited from affected muscles in the first days after stroke are considered MEP+, and generally have better UL and LL motor recovery and outcomes than patients who are MEP-.

Electroencephalography (EEG). EEG can be used to measure hemispheric symmetry of EEG power spectrum metrics in specific frequency bands, such as theta band frequency. Patients with more symmetrical EEG power spectra generally have better UL motor recovery and outcomes than those with large asymmetries.

Neuroimaging

Corticospinal tract (CST) injury. Standard care clinical Magnetic Resonance Imaging (MRI) can be used to obtain biomarkers of stroke-related injury to the CST. Patients with more CST injury typically have poorer UL and LL motor outcomes.

Fractional anisotropy (FA). MRI can be used to obtain FA asymmetry index as a measure of microstructural integrity of the CST. When measured at the level of the posterior limb of the internal capsule, greater asymmetry between hemispheres is associated with poorer UL motor outcomes.

Box 2 Desirable characteristics of prediction tools for motor outcomes after stroke¹⁵

1. Designed for use within days of stroke so that predictions can inform rehabilitation and discharge planning.
2. Predict outcome at a specific later timepoint, such as three months post-stroke when recovery from impairment is mostly complete. This is preferable to predicting an outcome at discharge because discharge often depends on achieving a specific outcome, and the prediction can therefore become circular.
3. Predict something meaningful for the patient and their family. A binary prediction, such as a “good” or “bad” outcome, is not informative enough for patients to anticipate how stroke will affect a myriad of daily activities. At the other extreme, precisely predicting a score can lack meaning because patients find it difficult to translate an exact assessment score to real-world utility. Between these two extremes are categorical predictions for levels of function in daily activities, and these might be more informative for patients and families.
4. Combine a relatively small number of variables in a way that is easily remembered and used. Online apps or simple decision trees are more likely to be used by clinicians than complex regression equations.
5. Externally validated with demonstrated positive clinical impact.