

## **Critical Review:**

### **What Patient Factors Predict Outcome in Mild Stroke?**

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Speech-language pathologists commonly work with patients who have experienced stroke to facilitate their reacquisition of swallowing and language skills. A significant minority of patients with mild ischemic stroke present with poor functional outcomes; however, little is known about what factors predict outcome in mild stroke. This critical review evaluates existing studies identifying potential prognostic indicators in mild stroke. The research provides suggestive evidence for several predictors of poor outcome in mild stroke patients including: etiological subtype (large vessel occlusion, cardioembolism), poor cognitive screening results, and the presence of aphasia. Knowledge of prognostic factors of poor outcome allows for better understanding of medical decisions and more effective caseload prioritization for speech-language pathologists and other professionals working with this population.

#### ***Introduction***

Stroke is a pervasive, disabling condition throughout world. In Canada, stroke is the third leading cause of death (Statistics Canada, 2011) and an estimated 50,000 new cases arise each year (Hakim, Silver, & Hodgson, 1998) representing a significant health care cost of \$3.6 billion a year (Public Health Agency of Canada, 2009). According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, the etiology of ischemic stroke can be divided into the following subtypes: large-artery atherosclerosis/occlusion, small artery occlusion, cardioembolism, stroke of other determined cause, and stroke of undetermined cause (Adams et al., 1993).

Patients presenting with stroke symptoms that result in a low National Institute of Health Stroke Scale (NIHSS) score are generally considered to be mild. Many patients presenting with mild stroke symptoms are expected to have a good prognosis and, therefore, are precluded from intravenous thrombolysis treatment with recombinant tissue plasminogen activator (tPA) as the risks of treatment may be considered to outweigh the potential benefits (Nedeltchev, *et al.*, 2007). However, mild stroke survivors present with a wide range of functional outcomes including a significant minority who experience permanent neurological deficits or death (Nedeltchev, *et al.*, 2007). The factors that may predict poor functional outcome in mild stroke are not well known. Knowledge of predictive factors could assist health care practitioners in making informed decisions about whether a patient may be an appropriate candidate for treatment such as tPA.

#### ***Objectives***

The primary objective of this paper was to find and evaluate existing studies investigating potential predictive factors of outcome after mild ischemic stroke.

#### ***Methods***

##### Search Strategy

Research articles pertaining to the question of interest were identified by searching the PubMed, EMBASE, and CINAHL databases using the following key terms: predict\* OR prognos\* AND mild stroke AND rankin AND outcome.

##### Selection Criteria

The abstract of each of the articles retrieved using the above search strategy was perused for inclusion and exclusion criteria. Articles that examined patient-related factors predicting outcome in mild stroke (as described using at least the modified Rankin scale (mRS), a commonly used seven-point scale characterizing level of disability and dependence upon assistance) were included. Articles were excluded if they: assessed the efficacy of an intervention strategy; did not examine patients with mild stroke independently from patients with strokes of other levels of severity; or looked at non-patient factors (e.g. time from symptom onset to admission).

##### Data Collection

Six papers were determined to fit the above criteria and were therefore included in this critical review. Of these articles, two were prospective cohort studies and four were retrospective cohort studies.

## Results

Of the six studies investigating predictive factors of outcome in mild stroke, four were retrospective cohort studies. The retrospective design presents a limitation in that it was not specifically designed to answer the research question.

### *Physiological Predictors of Outcome*

In a retrospective cohort study, Nedeltchev *et al.* (2007) analyzed factors influencing outcome in 123 patients with mild ischemic stroke (NIHSS score  $\leq 3$ ) and 39 with rapidly improving symptoms (NIHSS score improved by  $\geq 4$  points from initial evaluation to time of decision whether to administer thrombolysis) who did not receive thrombolytic treatment solely because of their mild or rapidly improving symptoms. Functional outcome was measured at 3 months post-stroke by clinical examination or telephone interview using the mRS. Favourable outcome was defined as mRS of 0-1, and unfavourable outcome was defined as mRS of 2-6. A stroke neurologist analyzed the patients' CT (computed tomography) or multimodal MRI (magnetic resonance imaging) images to determine their stroke etiology. In the whole group, proximal vessel occlusion was a predictor of poor outcome, where patients with this symptom were 7 times more likely to have an unfavourable outcome at 3 months. In the subgroup of patients with mild symptoms, no predictors of clinical outcome were found. In the rapidly improving subgroup, a baseline NIHSS score of  $\geq 10$  was the best predictor of unfavourable outcome at 3 months.

Positive aspects of this study include the relatively large sample size ( $n=162$ ), the measurement of outcome at 3 months (rather than just at discharge from hospital), and appropriate statistical analysis. However, this study also presented with some limitations including the lack of information regarding baseline/pre-stroke level of functioning, and the fact that the neurologists collecting outcome information at follow-up were not blinded to the clinical history of the patients. This study presents level 2b evidence and provides suggestive evidence that 25% of patients with mild or rapidly improving stroke symptoms have unfavourable outcomes at 3 months and that the best predictors of poor functional outcome for these patients are an NIHSS score of  $\geq 10$  upon admission and persisting proximal vessel occlusion.

In a retrospective cohort study, Rajajee *et al.* (2006) investigated the predictive value of early neurologic deterioration (END – increase in NIHSS score of  $\geq 4$  in 48 hours following admission) with or without infarct expansion (IE – identified by MRI) in patients with

mild (NIHSS  $\leq 4$ ) or rapidly improving stroke symptoms (NIHSS  $\leq 4$  that had improved from a more severe deficit). Patients were included if they received multimodal MRI, including diffusion-weighted imaging, and were eligible for thrombolytic treatment. Through appropriate statistical analysis using the Fisher exact two-tail test, the study indicated that persisting large-vessel occlusion was a predictor both of ENDIE and of poor functional outcome at discharge (mRS  $\geq 3$ ). Limitations of this study include the measurement of functional outcome only at discharge. Longer-term outcomes of patients post-stroke may provide a more realistic picture of their functional outcome. Furthermore, their definition of rapidly improving symptoms (NIHSS  $\leq 4$  that had improved from a more severe deficit) was not quantified in terms of time period over which the improvement occurred or amount of change, indicating selection of these patients may not have been reliable. The authors of this study also did not perform appropriate statistical analysis to address their actual research question (i.e. determining the impact of ENDIE on incidence of poor functional outcome). This study presents level 2b evidence suggesting predictive ability of persisting large-vessel occlusion for ENDIE and poor outcome in mild and rapidly improving stroke.

Hao *et al.* (2013) completed a prospective cohort study exploring the effect of various etiologic subtypes on prognosis at 3 months in 680 patients with mild stroke (NIHSS  $\leq 3$ ). Stroke etiology was determined according to the TOAST criteria (Adams *et al.* 1993). The researchers performed appropriate logistic regression analyses, which were adjusted for potential confounding factors (e.g. age, NIHSS score, vascular risk factors) in order to determine the influence of etiologic subtype on outcome. It was determined that stroke due to cardioembolism was an independent predictor of poor outcome (mRS  $> 2$ ) and small vessel occlusion was an independent predictor of good outcome at 3 months (mRS  $\leq 2$ ). Furthermore, they found that age, history of intracerebral hemorrhage, and complications during hospital stay were independent predictors of poor outcome across etiologic subtypes.

Strengths of this study include the prospective design, blinding of the outcome assessors to patient information, and inclusion of patient characteristics, such as history of stroke, in the collection and analysis of data. Despite the large sample size utilized in this study, a few factors may impact the generalizability of these results to the general population of mild stroke patients. For example, all patients were recruited at a single hospital in China, which may not represent the whole Chinese population, or the North American population. Furthermore, the study included patients

that were admitted to hospital within 30 days of symptom onset. This delay in hospital admission means that what occurred during the initial period post-stroke was variable among patients and unaccounted for in the study design; thus, it could have affected the patients' outcomes without the knowledge of the researchers. The work presented by Hao *et al.* (2013) represents level 2b evidence suggesting the predictive value of etiologic subtypes in mild stroke indicating cardioembolism as a predictor of poor outcome and small vessel occlusion as a predictor for good outcome.

#### *Cognitive and Communication Factors as Predictors of Outcome*

Dong *et al.* (2013) conducted a prospective cohort study analyzing the predictive value of the NIHSS and cognitive screening instruments, Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), in 400 patients with mild stroke (79.8%) or TIA (20.2%). The majority of patients (64.9%) had good functional outcomes ( $mRS \leq 1$ ). In the remaining patients, several demographic factors were found to be associated with poor functional outcome at 3-6 months ( $mRS \geq 2$ ) including: age, sex, ethnicity, level of impairment pre-stroke, time to assessment, and number of cardiovascular risk factors. Furthermore, patients with large artery occlusion and cardioembolic stroke had poorer functional outcome. The authors then performed appropriate hierarchical regression analysis adjusting for these predictive factors to determine the predictive value of the baseline NIHSS, MoCA, and MMSE scores. It was found that each of these scores was significantly predictive of functional outcome at 3-6 months for patients with NIHSS scores of  $> 2$ , and that each the MoCA and the MMSE added significant prediction of functional outcome in addition to the baseline NIHSS. However, for patients with NIHSS scores of  $\leq 2$ , none of the three baseline measures could predict functional outcome at 3-6 months.

One limitation of this study was the inclusion of patients within a relatively long period of time between symptom onset and hospital admission (up to two weeks). Another limitation was the lack of definition of mild stroke in terms of NIHSS score. They reported that the median NIHSS score of the cohort was 2 and that 79.8% had mild stroke (which was not further defined). The mean NIHSS score for patients with poor outcome was 5.04 ( $SD=3.68$ ), which is higher than the cut-off score for many studies examining mild stroke (e.g. Hao *et al.*, 2013; Rajajee *et al.*, 2006; Nedeltchev *et al.*, 2007). The remaining 20.3% of the patients were reported to have had transient ischemic attacks (TIA), which may have had different etiology, progression,

and/or outcome than mild stroke. Therefore, although the studied population largely consisted of patients with mild stroke, it was a heterogeneous group in terms of severity and warrants caution in interpreting the results. This study performed by Dong *et al.* (2013) represents level 2b evidence suggesting the predictive value of the admission NIHSS, MMSE, and MoCA scores in functional outcome in mild stroke.

In their 2013 study, Wendt *et al.* aimed to assess the frequency, type, and degree of functional impairment in mild stroke patients with neurological deficits. They retrospectively examined the data of 172 stroke patients with mild stroke who received tPA. They considered two definitions of mild stroke:  $NIHSS \leq 4$  and  $NIHSS \leq 3$ . At 3 months, 74% of all patients had a favourable outcome ( $mRS \leq 1$ ). The remaining 26% presented with unfavourable outcomes ( $mRS > 1$ ) at 3 months despite tPA treatment. They also found that despite low NIHSS scores, language impairment was considered to be the most frequently occurring disabling symptom in mild stroke, followed by distal paresis and gait disorder. Therefore, they suggested that the admission NIHSS score alone is not appropriate for discriminating between minor and non-minor stroke.

A strength of this study was the inclusion of mild stroke patients who had been treated with tPA. However, inclusion of a control group that had not been treated with tPA may have provided more information regarding the effect of tPA on functional outcome in mild stroke. Furthermore, statistical analysis comparing the characteristics of patients with poor outcome to those with good outcome and/or comparing the relative frequency of neurologic symptoms between these two groups would have added strength to the level of evidence presented in this study. This is a level 2b study providing suggestive evidence for language impairment as a frequent disabling symptom in strokes characterized by low NIHSS scores.

In a retrospective cohort study by Nesi, Lucente, Nencini, Fancellu, and Inzitari (2013), the data of patients with mild stroke ( $NIHSS$  score  $\leq 6$ ,  $n=128$ ) who were eligible for thrombolytic treatment were analyzed to investigate whether any presenting feature predicted poor outcome. At 3 months, 15.6% of patients ( $n=20$ ) had an unfavourable outcome. Through appropriate univariate logistic regression analysis, the NIHSS score was not found to correspond to outcome; however, aphasia was found to be significantly related to poor outcome. Furthermore, the patients with aphasia who were treated with tPA showed better outcomes than those presenting with aphasia who were not treated with tPA.

A strength of this study was the inclusion of patients that were and were not treated with tPA. A caveat of this study is that the definition of mild stroke, as an NIHSS score of  $\leq 6$ , indicates the inclusion of patients that were relatively more severe than the other studies included in this critical review. In addition, the sample sizes of patients with unfavourable outcome and of patients with aphasia were small ( $n=20$  and  $n=22$ , respectively). If these samples had been larger, trends in differences within these groups may have become statistically significant allowing for the identification of further predictive factors of outcome. This study presents level 2b evidence suggesting that aphasia predicts poor outcome and that outcome in patients presenting with aphasia is better when treated with tPA.

### Discussion

The results of the six research studies evaluated in this critical review present compelling, level 2b+, evidence that the presence of aphasia and the etiological subtypes of large vessel occlusion and cardioembolism are predictive factors of poor outcome in mild stroke and a suggestive, level 2b, evidence that poor cognitive screening results are predictive factors of poor outcome in mild stroke. In addition, there is suggestive evidence that small vessel occlusion is a predictor of good outcome. However, there are some limitations within these research studies that must be considered.

Firstly, each study had variations in their inclusion criteria resulting in the analysis of slightly different populations. For example, each study defined mild stroke differently, ranging from an NIHSS score of  $\leq 2$  to  $\leq 6$ . This difference is important to consider when attempting to compare studies as each included a marginally different population of stroke patients in their samples.

In addition, the articles included patients who were admitted to hospital within different time periods from stroke onset (**6 hours or less**: Nesi *et al.*, 2013; Rajajee *et al.*, 2006; Wendt *et al.*, 2013; **1 day or less**: Nedeltchev *et al.*, 2007; **within weeks**: Dong *et al.*, 2013; Hao *et al.*, 2013). Those that included patients that were admitted to hospital weeks after stroke onset risk including variability that was unaccounted for among patients during the initial period post-stroke. Furthermore, there is the potential that patients with late admission to hospital could include patients with rapidly improving symptoms that were characterized as mild upon admission but may have had more severe symptoms upon symptom onset, and differences between the mild and rapidly improving populations may exist. Indeed, the study by Nedeltchev *et al.* (2007) indicated differences in prognostic factors between the

two populations. Therefore, the potentially unidentified presence of patients with rapidly improving symptoms (or other unknown variables) may present a confounding factor in the identification of predictive indicators unique to the mild stroke population, particularly within the populations examined in the studies performed by Dong *et al.*, 2013 and Hao *et al.*, 2013.

The NIHSS score has previously been shown to predict outcome in stroke (Kwakkel, *et al.*, 2010). However, based on the findings of Dong *et al.*, 2013, and Nesi *et al.*, 2013, the NIHSS may be less sensitive and may lose its predictive value at the lower end of the scale. Further research into the prognostic value of NIHSS in mild stroke should be performed. The development of a method of interpretation of low NIHSS scores or use of a different tool for determining severity in mild stroke may warrant consideration in order to better predict outcome in these patients. Some researchers have already suggested, and implemented, performing simple functional tests in the emergency room in order to detect potentially disabling deficits (e.g. in communication or usage of the dominant hand) in addition to standardized measures such as the NIHSS (Kohrmann *et al.*, 2009).

There is already some evidence suggesting that treatment with tPA is safe and results in good functional outcome in mild stroke (Nesi, *et al.*, 2013; Kohrmann, *et al.*, 2009; Urra *et al.*, 2013); however, randomized clinical trials need to be performed to further investigate the safety and efficacy of tPA treatment in mild stroke. In particular, future research may include investigating the benefit of tPA treatment in mild stroke patients with identified prognostic factors of poor outcome, such as aphasia.

### Clinical Implications

Knowledge of prognostic factors of poor outcome allows for better understanding of medical decisions and more effective caseload prioritization for speech-language pathologists and other professionals working with stroke patients. Mild stroke as described by a low NIHSS score does not necessarily indicate a good prognosis and may not be the best indicator for inclusion or exclusion for treatment with tPA. Furthermore, if aphasia is a predictor of poor outcome, speech-language pathologists may have a role in assessing language abilities of acute stroke patients and participating in treatment decision making.

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