EDITORIAL



# Screening for Cognitive Impairment, Being Cognizant of the Liminal Deities and Demons

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In patients with transient ischemic attack (TIA) and minor stroke, one in five patients have persistent cognitive impairment (CI) at 3 months.[1] This proportion may reach up to 60% in patients with moderate to severe stroke and multiple associated vascular comorbidities. According to the latest estimates, there are 405,000 individuals in Canada experiencing the effects of stroke,[2] and with the most conservative approximation, a total of 100,000 may be having CIs of varying grades, some diagnosed and treated, others are not. Furthermore, Vascular CI may be progressive and invariably affects recovery from stroke in a multifactorial process. Canadian Stroke Best Practices recommendation suggests that all patients with TIA and Stroke should be considered high risk for CI and may be screened with a standardised test like Montreal Cognitive Assessment (MoCA).[3] MoCA is continuous 30 points scale devised to screen mild CI. The proposed cut-off values for diagnosis of vascular dementia (16.5–24) and vascular mild CI (26–27) have been variable with varying sensitivities (77%–92%).[4] The specificity of MoCA for diagnosing vascular dementia is higher >90% compared to diagnosing vascular mild CI < 80%. Lack of uniform threshold value and equivocal clinical validity is an obstacle in consistent implementation of a cognitive screening tool in patients with TIA and stroke.[5]

Zaidi et al.[6] propose a novel approach with differential tiering of cut-off value for MoCA and sequential additional cognition speed processing testing for accurate categorisation of patients with possible vascular CI. A total of 161 patients after median of 11 months after an index event, with a mean ± standard deviation (SD) of 14.6 ± 2.9 years of education and MoCA score >18, were recruited. A >1.5 SD variation from normative data in multidomain neuropsychological assessment scores was considered as the gold standard for diagnosis of vascular CI. The authors derive a tiered cut-off values for low probability of CI (>27), high probability of CI (<24), and indeterminate probability of CI (24–27). Patients with indeterminate probability were further categorised with symbol digit modalities test (SDMT), coding score, and learning score. This approach led to accurate classification of 79% of patients across the entire sample. This indeed is an incremental step bolstering the utility of cognitive screening tool thus leading to early diagnosis with detailed assessment. However, this is a very selective group of patients, which may affect reproducibility of results, and one in five patients can still be misclassified thus preventing appropriate referral and management.

The approach described in the article has improved the discriminant function of MoCA but has brought forth important shortcomings of using frequentist binary approach. Application of cut-off values makes screening tools easy to use in the clinic; nevertheless, it has an inherent fallacy of having false positive and false negative allocations. This is further compounded due to "*reference standard bias*" which assumes that the neuropsychological assessment is gold standard which is far from truth.[7] A clinical diagnosis with multidomain neuropsychological assessment may have a wide range of sensitivity from 39%–98% and specificity from 33%–100% compared to neuropathological diagnosis of Alzheimer's disease with strong negative correlation (−0.79).[8] This is contrary to our presumption that gold standard test has a 100% sensitivity and 100% specificity, thus making a trade-off of *imperfect reference test* and effect thereof. The second issue is assumption of "*conditional independence*" of two tests that the diagnostic error due to the imperfect – reference test is independent of the diagnostic test being assessed.[9] MoCA, SDMT, and neuropsychological assessment apply similar principles of multidomain cognitive testing and hence are not independent tests. A possible example of independent test would be imaging- or blood-based biomarker. The two issues discussed above can be partially mitigated when the sensitivity and specificity of imperfect reference standard (like neuropsychological test) are known, with help of "*correction methods*."[10]

A pragmatic approach would be to use Bayesian rules (applying the knowledge of pre-test probability, likelihood ratio, and post-test probability) as an extension to the proposed scoring system by Zaidi et al.[6] for classification of stroke patients with CI.[11] The pre-test probability of patients attending the stroke clinic having CI is modified by the presence of *clinical* (increasing age, severe neurological deficits at baseline, presence of delirium, aphasia, neurological comorbidities like epilepsy and mental health issues) and *imaging* variables (infarct volume and markers of small vessel disease, perivascular spaces, microbleeds, brain atrophy, and white matter hyperintensities) (Figure 1).[12] Presence and progression of white matter hyperintensity on magnetic resonance imaging increases the odds of CI by 1.9 times and 6 times, respectively.[12,13] Once we have a pre-test probability, subsequently the positive and negative likelihood ratio of MoCA with three-tiered score to classify low or high probability of CI (5.4 and 0.18, respectively) can guide the trajectory of post-test probability. In the indeterminate group, addition of SDMT, coding and learning scores further improve the classification to high or low probability of CI. Further research is needed to quantify the magnitude and interaction of clinical and imaging modifiers with the cognitive screening tools.

To conclude, universal cognitive assessment in patients with stroke, TIA, and covert stroke with a rapid screening test like

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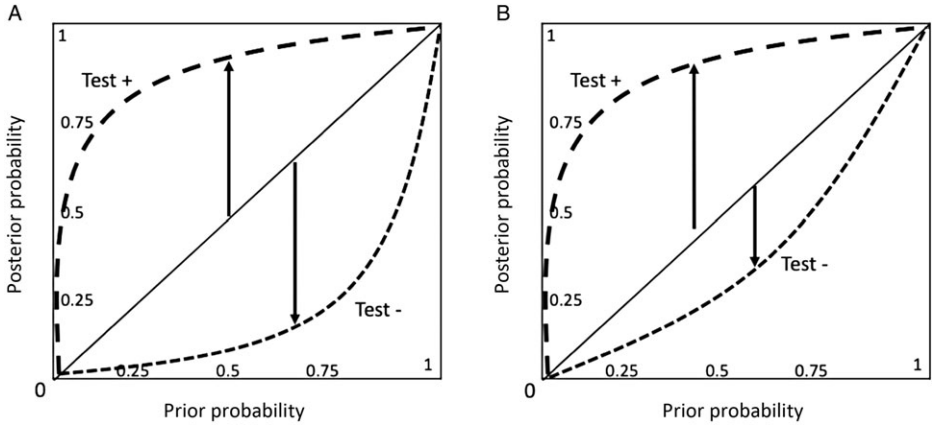


***Figure 1:*** *Effect of small vessel disease burden on prior (pre-test) probability and posterior (post-test) probability for cognitive screening tool. (A) In patients without small vessel disease, the likelihood of high and low probability of cognitive impairment is symmetrical; it is governed by the test characteristics alone. A three-tiered approach would be appropriate. (B) In patients with varying small vessel disease burden, the likelihood of high and low probability of cognitive impairment is asymmetrical. A negative test (high scores in Montreal Cognitive Assessment) is less likely associated with low probability of cognitive impairment due to good cognitive and brain reserve.*

MoCA, SDMT in a tiered pattern is feasible and aids early diagnosis and treatment. However, the screening must be administered with a Bayesian approach with anchoring and adjusting heuristics to determine accurate pre-test probability and thus maximise post-test probability for appropriate classification of CI. Even if the patient is categorised as low probability of CI due to high scores of the screening tool, if the pre-test probability for CI is high, they should be referred for detailed cognitive evaluation so the chances of misclassification are reduced.

## Disclosures

The authors have no conflicts of interest to declare.

## Statement of Authorship

CV, drafted manuscript, review of literature; BJ, critical review and revision of the manuscript, review of literature, analysis; MK, concept critical review and revision, analysis, figure, review of literature review.

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