Evaluation of Dementia: The Case for Neuroimaging All Mild to Moderate Cases

Yih-Yiow Sitoh,1 MBBS, MRCP, Kala Kanagasabai,2 MBBS, MMed (Fam Med), Yih-Yian Sitoh,3 MBBS, FRCR, Arul Earnest,4 MSc, Suresh Sahadevan,1 MBBS, FRCP

Abstract
Introduction: The aim of this study was to assess the usefulness of 4 clinical prediction rules, the neuroimaging guidelines from the Canadian Consensus Conference on Dementia (CCCAD) and the modified Hachinski’s Ischaemic Score (HIS) in identifying patients with suspected dementia who will benefit from neuroimaging. Materials and Methods: Two hundred and ten consecutive patients were referred to the memory clinic in a geriatric unit for the evaluation of possible dementia. Sensitivity, specificity and likelihood ratios (LR) were calculated for each of the prediction rules and the CCCAD guidelines, in terms of their ability to identify patients with significant lesions [defined firstly as space-occupying lesions (SOL) alone and secondly as SOL or strokes] on neuroimaging. Similar analyses were applied for the HIS in the detection of strokes. Results: When considering SOL alone, sensitivities ranged from 28.6% to 100% and specificities ranged from 21.7% to 88.4%. However, when strokes were included in the definition of significant lesions, sensitivities ranged from 16.2% to 79.0% and specificities ranged from 20.9% to 92.4%. The modified HIS had a similarly poor sensitivity and specificity (43.3% and 78.9% respectively). The LR for the clinical decision tools did not support the use of any particular instrument. Conclusions: Clinical decision tools do not give satisfactory guidance for determining the need for neuroimaging patients with suspected dementia, when the detection of strokes, in addition to SOL, is regarded as important. We recommend therefore that neuroimaging be considered for all patients with suspected mild or moderate dementia in whom the potential benefits of any treatment outweigh the potential risks.

Key words: Diagnostic medical imaging, Practice guidelines, Sensitivity and specificity

Introduction
Dementia has been reported to affect 4% to 13% of individuals above the age of 65, with the difference in prevalence rates being dependent on the screening tools used and the criteria adopted for the diagnosis of dementia.1,2 The evaluation of any individual presenting with suspected dementia has a threefold purpose: (1) to establish or exclude a diagnosis of dementia, (2) to identify conditions that may be amenable to interventions that may reverse or alter the progression of cognitive decline, and (3) to allow for prognostication.3 The requirement for neuroimaging as a routine component of the evaluation process has been widely debated, with proponents citing its requirement for the categorisation of dementia type and its usefulness in detecting space-occupying lesions (SOL) as well as silent strokes as some of the reasons for its necessity,4 and opponents citing the need for clinical judgement and cost considerations as major reasons for adopting a selective approach.5 Opponents to routine neuroimaging have cited their ability to “reliably” identify patients with SOL using clinical prediction rules as reasons for limiting imaging to those patients who fulfilled their respective criteria.6-8 However, the usefulness of such prediction rules are limited by the fact that they were mostly derived from highly selected populations and were designed solely for the detection of SOL (Table 1). Subsequent testing of such tools in different clinical settings have shown widely differing sensitivities and specificities.9 Concurrently, the impact of silent strokes, and possibly

1 Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore
2 Ang Mo Kio Hospital, Singapore
3 Department of Neuroimaging, National Neuroscience Institute, Singapore
4 Communicable Disease Centre, Tan Tock Seng Hospital, Singapore
Address for Reprints: Dr Yih-Yiow Sitoh, Department of Geriatric Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: syympc@pacific.net.sg

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white matter lesions (WML), on cognitive decline is increasingly being recognised.10-12 This, coupled with emerging evidence suggesting the possibility of modulating the progression of mixed dementia and vascular dementia,13,14 as well as the evidence concerning secondary preventive measures for strokes,15 suggest that neuroimaging may indeed have an important role to play in the evaluation of dementia, apart from the identification of SOL. This suggestion has been well attested to by studies conducted by Chui and Zhang16 and Massoud et al.17

In view of the above, we undertook a study to examine the clinical utility of the 4 clinical prediction rules previously studied by Martin et al,9 together with the clinical practice guidelines for neuroimaging that were drawn up by the Canadian Consensus Conference on Dementia (CCCAD).18 Similarly, the modified HIS was calculated (see below) for each of the patients using the data extracted. A neuroradiologist reviewed the CT brain scans of all the above patients and recorded the findings using a semi-structured protocol. All scans were evaluated dichotomously (present/absent) for SOL (hydrocephalus, meningoamas, sub-dural haematomas, sub-dural hygromas and other SOL), strokes i.e., small vessel infarcts or lacunes (defined as well-defined areas >2 mm with CT attenuation the same as cerebrospinal fluid; lesions with these characteristics but <2 mm were considered perivascular spaces) or large vessel infarcts, and white matter lesions (defined as ill defined and moderately hypodense areas of ≥5 mm on unenhanced axial CT brain scans in the periventricular, deep and subcortical white matter). The researchers were blinded to the findings of the neuroradiologist and vice versa.

Study Variables

Study variables collected included basic demographic data as well as information required in the different clinical prediction rules and guidelines (Table 2) as well as the modified HIS. The scoring for the latter was in accordance with the recommendations reported by Rosen et al19 (abrupt onset 2 points, stepwise deterioration 2 points, somatic complaints 1 point, emotional incontinence 1 point, history or presence of hypertension 1 point, history of strokes 2 points, focal neurological symptoms 2 points, focal neurological signs 2 points), to determine its utility in detecting strokes in this cohort of patients. In our study, patients with modified HIS scores of 3 or more were considered likely to have had strokes.

The study variables thus included the duration of cognitive decline, history of headache, presence or absence of focal signs and symptoms, speech disorders, papilloedema, history of head trauma, acuity of onset and pattern of progression, visual field defects, gait apraxia, use of anticoagulants or history of bleeding disorders, history of malignancy, urinary incontinence, history of stroke, hypertension, emotional incontinence and somatic complaints. In addition, scores on the Chinese Mini-Mental State Examination (C-MMSE)20 were recorded. In our study, patients were classified as having speech disorders if they had dysarthria or had been noted to have difficulty with naming objects or comprehending speech. Patients were deemed to have urinary incontinence if they had a history of urinary incontinence more than once weekly. Emotional incontinence was deemed to be present if the patients had a history of increasing agitation, inappropriate jocularity or had been noted to cry easily. Somatic complaints were defined as non-specific complaints that could not be attributed to any defined illness that the patients were suffering from.
Table 1. Clinical Prediction Rules for Neuroimaging: Clinical Setting and Patient Type

<table>
<thead>
<tr>
<th>Source</th>
<th>Clinical setting</th>
<th>No.</th>
<th>Patient type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradshaw et al⁶</td>
<td>Neuroradiology unit</td>
<td>500</td>
<td>Patients referred for evaluation of dementia. Referrals strictly from hospital specialists. Patients with predominantly psychotic features excluded.</td>
</tr>
<tr>
<td>Dietch⁷</td>
<td>Neuroradiology unit</td>
<td>200</td>
<td>Patients at least 50 years of age, who have had a neurologic examination and had findings suggestive of dementia studied. First 100 patients who were referred for neuroimaging and fulfilled specified inclusion criteria were compared with the first 100 patients who failed to meet one or more of the inclusion criteria.</td>
</tr>
<tr>
<td>Larson et al⁸</td>
<td>Outpatient clinic</td>
<td>107</td>
<td>Consecutive patients seen in outpatient clinic for the problem of suspected dementia.</td>
</tr>
</tbody>
</table>

Table 2. Variables Included in Clinical Prediction Rules

<table>
<thead>
<tr>
<th>Prediction rule</th>
<th>Variables included/Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradshaw et al⁶</td>
<td>Dementia &gt;1 month or &lt;1 year plus any of the following: headache, focal signs, speech disorder, papilloedema Neuroimaging recommended for patients who meet criteria.</td>
</tr>
<tr>
<td>Dietch⁷</td>
<td>Dementia present &gt;1 month, no head trauma in preceding week, gradual onset (&gt;48 hours), no history of strokes, no history of seizures, no history of urinary incontinence, no focal signs, no papilloedema, no visual field defects, no apraxia/ataxia of gait, no headache Neuroimaging not recommended for patients who meet all the criteria.</td>
</tr>
<tr>
<td>Larson et al⁸, high risk</td>
<td>Acute deterioration and recent onset (&lt;12 months) or mild dementia (C-MMSE &gt;20) Neuroimaging recommended for patients who meet criteria.</td>
</tr>
<tr>
<td>Larson et al⁸, low risk</td>
<td>No acute deterioration or have longer duration (&gt;36 months) and severe dementia (C-MMSE &lt;15) Neuroimaging not recommended for patients who meet criteria.</td>
</tr>
<tr>
<td>CCCAD guidelines</td>
<td>Age &lt;60, use of anti-coagulants or history of bleeding disorder, recent head trauma, history of carcinoma in sites that metastasize to brain, rapid unexplained decline (&lt;2 years), urinary incontinence and gait disturbance early in course of dementia, localising signs, gait ataxia Patients meeting any of the stated criteria should have neuroimaging.</td>
</tr>
<tr>
<td>Modified HIS</td>
<td>Abrupt onset (2 points), history of stroke (2 points), focal neurological signs (2 points), focal neurological symptoms (2 points), stepwise deterioration (1 point), hypertension (1 point), somatic complaints (1 point), emotional incontinence (1 point) Patients with total score ≤2 likely to have Alzheimer's disease.</td>
</tr>
</tbody>
</table>

Statistical Analysis

Patients were classified as either requiring or not requiring neuroimaging in accordance with the 4 clinical prediction rules and the CCCAD guidelines. The sensitivity and specificity for each of the instruments were then calculated in terms of the presence or absence of significant findings on neuroimaging. Significant findings were defined, firstly, as any SOL that may be amenable to surgical intervention (i.e., hydrocephalus, meningiomas, sub-dural haematomas, sub-dural hygromas and other SOL), and secondly, as SOL or strokes. The likelihood ratios for positive (LR+) and negative (LR−) “test results” were similarly calculated for both definitions of significant findings. In a separate analysis, sensitivity, specificity, and LR+ and LR− values were calculated for the modified HIS to determine its clinical utility in identifying patients with strokes. All analyses were done with the statistical programme STATA version 7.0 (Stata Corp., College Station, Tx).

Results

Of the 210 patients studied, 79 were male and 131 were female. There was no significant age difference between the 2 gender groups (males: mean age 72.5, standard deviation 9.8; females: mean age 74.7, standard deviation 7.9, P=0.2). SOL were found in 7 patients (2 meningiomas, 4 sub-dural hygromas and 1 metastatic deposit from cervical carcinoma). One hundred and twenty patients were found to have strokes on neuroimaging, out of which 70 (58.3%) did not have a previous history of strokes and did not demonstrate any focal neurological signs.

The neuroimaging findings are summarised in Table 3. If the prediction rule recommended by Bradshaw et al⁶ had been applied, 158 CT scans would have been avoided. However, 5 SOL and 85 strokes would have been missed. Similarly, 112 scans could have been avoided with the application of Dietch’s recommendations, but at the expense of missing 2 SOL and 51 strokes. The corresponding
Selective Neuroimaging for Suspected Dementia—Yih-Yiow Sitoh et al

Number of scans avoided and the number of lesions missed for the remaining prediction rules and guidelines are as follows: Larson et al\(^8\) (high risk) – 185 scans avoided, 4 SOL and 103 strokes missed; Larson et al\(^8\) (low risk) – 87 scans avoided, 3 SOL and 57 strokes missed; CCCAD guidelines – 44 scans avoided, no SOL and 26 strokes missed.

The sensitivity, specificity and likelihood ratios of the clinical prediction rules and the CCCAD guidelines are summarised in Table 4. The CCCAD guidelines had the highest sensitivity in detecting significant findings (SOL in isolation, as well as SOL or strokes). However, when the prediction rules and clinical guidelines were considered in terms of their likelihood ratios (which embrace the dimensions of both sensitivity as well as specificity), the LR+ ranged from 0.97 (Larson et al\(^3\) low risk) to 4.31 (Larson et al\(^8\) high risk) for SOL alone, and 0.80 (Larson et al\(^8\) low risk) to 2.13 (Larson et al\(^8\) high risk) for SOL or strokes. The corresponding LR− values ranged from 0 (CCCAD\(^9\)) to 1.04 (Larson et al\(^8\) low risk) and 0.58 (Dietch\(^7\)) to 1.39 (Larson et al\(^8\) low risk).

The modified HIS had a sensitivity of 43.3% (95% CI, 34.3, 52.7) and a specificity of 78.9% (95% CI, 69.0, 86.8) for detecting strokes in our patients when we used a cutoff of ≥3 to identify patients with higher vascular risk factors and hence, a greater risk of strokes. The corresponding LR+ and LR− values were 2.05 and 0.72, respectively. Using a modified HIS score of ≥3 to determine the necessity for neuroimaging, we would have missed 68 patients with strokes.

**Discussion**

An important element in the diagnostic approach to a patient presenting with suspected dementia is the...
identification of conditions, the treatment of which results in the reversal of the cognitive impairment, or the identification of conditions for which treatment may result in amelioration of the progression of cognitive decline. In the first instance, reversible dementias may be caused by metabolic or mood disorders, or SOL which may be amenable to surgical intervention (e.g., meningiomas, subdural collections and normopressure hydrocephalus). While the earlier group of conditions can be detected through careful clinical examination and blood investigations, the latter category can only be reliably diagnosed through neuroimaging. It is for this latter group that most of the clinical prediction rules cited in this study were proposed, with the common objective of facilitating a rational, more selective decision process for requesting brain scans.

Based on their original data sets, both Dietch et al. and Larson et al. were able to achieve 100% sensitivity in detecting SOL using their respective clinical prediction tools, with corresponding specificities ranging from 52.9% to 85.7%. However, when the same prediction tools were applied in the setting of an academic geriatric centre, Martin et al. found that the criteria formulated by Dietch had a sensitivity of 87.5% while that formulated by Larson and colleagues had a sensitivity of only 25%. More recently, in their review of clinical prediction rules for neuroimaging, Gifford and colleagues tested the different prediction rules and the CCCAD guidelines on a hypothetical population and arrived at similarly divergent sensitivities and specificities. Using sensitivity and specificity data collated by Gifford et al., the LR+ values for SOL would have ranged from 0.8 (Larson et al. low risk) to 2.13 (Larson et al. high risk) to 4.31 (Larson et al. high risk). This means that, at best, Larson’s “high risk” classification was 1.28 times more likely to be fulfilled in a person with a SOL than in a person without such a lesion. Conversely, the LR- value for the CCCAD guidelines was 0 in our study population, suggesting that patients who did not fulfill the CCCAD guidelines for neuroimaging were highly unlikely to have SOL within the brain.

It has been stated by Wasson and colleagues that “the ultimate measure of a clinical prediction rule is its effect on patient care”, and that in using such rules, “one should try to minimise the chance of serious error in patient care”. Similarly, Gifford et al. recommended that clinical prediction rules used for the assessment of dementia patients should possess a high sensitivity to minimise the proportion of false-negative findings. Our finding that the CCCAD guidelines have a high sensitivity and low LR− value in identifying patients with SOL concur with the results cited by Freter et al. and suggest that the CCCAD guidelines would be useful in identifying patients with SOL in the setting of a memory clinic for assessing patients with suspected dementia. The widely varying sensitivities, specificities for the other clinical prediction rules that were demonstrated by Martin’s group and reaffirmed in our study population, together with the relatively low likelihood ratios of the different “rules” suggest that they have limited usefulness in actual clinical practice.

Patients with SOL, however, constitute only a small percentage of all patients presenting with suspected dementia (3.3% in our study population, 3.1% in the study reported by Freter et al. and furthermore, the benefits of surgical intervention in such circumstances are not well substantiated, with patients suffering from mild cognitive decline being more likely to improve with intervention. Conversely, there is growing evidence concerning the importance of cerebrovascular disease in patients with dementia – Snowdon et al. demonstrated that strokes impact negatively on the cognitive function of patients with AD, while Vermeer et al. showed recently that silent brain infarcts more than doubled the risk of dementia and led to a steeper decline in cognitive function in patients who were so affected. In addition, we also recently reported that WML may impact negatively on functional outcomes in patients with dementia.

In view of these developments, we elected to study the utility of the clinical prediction rules and the CCCAD guidelines in detecting clinically significant lesions, using a definition that incorporated strokes in addition to SOL. As noted, the CCCAD guidelines had the highest sensitivity (79.0%). However, 26 patients with strokes were missed when the decision for neuroimaging was based on these guidelines. When strokes were incorporated within the definition of clinically significant lesions, Larson’s “high risk” criteria was found to have the lowest sensitivity (16.2%) and would have resulted in 99 strokes being missed. The LR+ values for the prediction tools ranged from 0.8 (Larson et al. low risk) to 2.13 (Larson et al. high risk).
risk\(^3\)), while the LR- values ranged from 0.58 (Dietch') to 1.39 (Larson et al., low risk). As can be seen, the performance of the clinical prediction rules and clinical guidelines in determining the need for neuroimaging were far from satisfactory when a more encompassing (but not unreasonable) definition of clinically significant lesions was applied.

To further assess the possibility of reducing the need for neuroimaging through the use of "clinical decision tools", we studied the ability of the modified HIS to detect brain infarcts in our study population. The HIS was derived from patient characteristics and cardiovascular risk factors and has been widely used, in both its original and modified forms, to differentiate patients with pure AD from those with VAD.\(^{24-26}\) It has been shown to be comparable to the criteria proposed by the National Institute of Neurological Disorders and Strokes and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN)\(^27\) or the Alzheimer’s Disease Diagnostic and Treatment Centers (ADTCT) of the State of California\(^28\) in its ability to exclude patients with pure AD. However, it has also been demonstrated that the HIS fares poorly in identifying patients with mixed dementia i.e., patients with AD and coexistent brain infaracts.\(^{24}\) In view of the fact that the HIS was based largely on known cardiovascular risk factors, we thought it reasonable to study its usefulness in predicting the presence of cerebrovascular disease. We had chosen to use the lower cutoff score of 3 or more (modified HIS) as the HIS has been shown to be more useful in identifying patients with pure AD and excluding vascular lesions at such a cutoff.\(^{24}\) As in the case of the other prediction rules, the modified HIS performed poorly in identifying patients with brain infarcts, with a sensitivity of 43.3% and an exclusion of 68% of patients with brain infarcts when the cutoff of \(\geq 3\) was applied.

Our study has shown that while some of the clinical prediction rules (especially the CCCAD guidelines) can be useful for detecting SOL, these same rules would generally have resulted in a sizeable proportion of patients with strokes (21.6% to 85.8%) being missed. However, given the importance of detecting underlying strokes in those presenting with possible dementia, these findings then lead to the question of whether neuroimaging should therefore be routinely recommended for all patients presenting for the evaluation of possible dementia. We believe this question is best answered by considering the relative merits of making such diagnoses, in terms of the relative benefits and risks associated with currently available treatment modalities for secondary stroke prevention. For example, while antiplatelet therapy is widely recognised to be effective in lowering the risk of recurrent strokes (2 recurrent strokes may be prevented for every 100 patients treated for 2 years), the risks associated with such treatment should not be overlooked (1 gastrointestinal bleed may be encountered in the same group of patients within the same period).\(^{29,30}\) Furthermore, it should be noted that the majority of patients presenting with possible dementia are elderly, and the risk of gastrointestinal haemorrhage from antiplatelet treatment increases with age.\(^{31,33}\)

Given the above context, we suggest that neuroimaging for the primary purpose of excluding the more commonly encountered strokes, should not be considered for those patients with advanced dementia in whom the prospects of improvement in cognition, functional status or quality of life would be slim. In this group, the topic of secondary stroke prevention would also lose its cogency, with the risks associated with antiplatelet use clearly outweighing benefits.

The same consideration will prevail when considering the need for neuroimaging for the primary purpose of excluding SOL. In this regard too, the time-line of 2 years that is stated within the CCCAD guidelines may be considered as an additional useful guideline: a patient with significant dementia of more than 2 years’ duration is thus very unlikely to benefit from any neuro-radiological evaluation for either SOL or strokes.

Our study is not without its limitations. Firstly, the retrospective nature of our study means that our patients did not undergo a strictly uniform protocol for neuroimaging, even though both scanners that were used applied scan parameters that were essentially identical except for a minimal difference in slice thickness supratentorially. However, it has previously been shown that use of different CT scanners with different scan protocols and slice thickness has not impeded scan evaluation.\(^{24}\) We have tried to minimise the resultant limitations by having all films reviewed by a single neuro-radiologist using a standardised qualitative assessment format.

Secondly, the ability of CT scans to detect ischaemic cerebrovascular disease lesions (ICVD) and the clinical significance of such lesions may be questioned. We acknowledge that CT imaging is less sensitive than magnetic resonance imaging (MRI) for the detection of ICVD. However, it is impractical to apply MRI for all patients presenting with suspected dementia and we propose that our findings may in fact underestimate the “miss rate” of silent infarcts.

Thirdly, we recognise that the retrospective nature of our study may affect the precision of our results. Retrospective power calculations based on the parameters for estimating sensitivities and specificities of prediction rules in detecting SOL indicated that we would be able to attain precisions (95% confidence level) ranging from ±18% to ±30% for our sensitivity values, and a precision of ±5% to ±7% for our specificity values. Similarly, for SOL or strokes, the
precision ranged from ±6% to ±9% for sensitivities, and ±6% to ±10% for specificities.

Conclusion

The currently established clinical decision tools (with the possible exception of the CCCAD guidelines) for the use of neuroimaging in the evaluation of patients with suspected dementia for detecting SOL are of limited utility. Application of such tools to determine the requirement for neuroimaging would result in a sizeable proportion of patients with strokes being missed. We recommend therefore that neuroimaging be routinely considered in the evaluation of patients with suspected dementia, as long as the potential benefits associated with possible subsequent treatment are judged to outweigh the associated risks. This approach will thus exclude patients who, when presenting to the clinician for the first time for problems related to possible dementia, are already advanced in their cognitive impairment, especially when the cognitive state has been steadily declining for at least 2 years.

Competing Interests

None identified.

REFERENCES

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