# RAPID Progression: Tool for Screening Aggressive Course of Disease (ACD) in Alzheimer Dementia

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***Objective:*** *There is a need for a tool in clinical practice to assess the rate of progression of Alzheimer's disease (AD) patients. The present study purpose was to develop a tool for screening and progression assessing of AD patients with Aggressive Course of Disease (ACD).*
***Material and Method:*** *The Thai Realtime Assessment of Progression In Dementia (RAPID) was developed for screening AD patients with ACD through a caregiver questionnaire. At baseline and at a 6-month follow up visit, patients were tested by the Alzheimer's Disease Assessment Scale cognitive component (ADAS-Cog), while their caregivers completed the Thai RAPID. The tests were run by a team of psychiatrists in the Department of Psychiatry, Chulalongkorn Memorial Hospital.*
***Results:*** *Fifty patients with cognitive impairment were recruited. As a screening tool, the Thai RAPID cut-off point of 9-points yielded a fair sensitivity and specificity (0.625 and 0.643, respectively) for rapid progression as defined by 4 point or greater deterioration in ADAS-Cog. As a progression assessment tool, a cutoff point of 3-points yielded a good sensitivity and specificity (0.875 and 0.810, respectively).*
***Conclusion:*** *The present pilot study suggests that the Thai RAPID can be a valuable tool for the ACD screening and for progression assessment in AD patients.*

***Keywords:*** *ADAS-Cog, Aggressive course of disease, Alzheimer dementia, RAPID*

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Alzheimer's disease (AD) is the most common form of dementia among people over the age of 65 years. The course of AD is characterized by deterioration in cognitive abilities including learning new information, decision-making, language skills, and problems recognizing family and friends. The rate of AD progression can be highly variable between individual AD patients[1]. The general definition of an aggressive course of disease (ACD) is defined as "A significant deterioration in patient cognitive or functional status within a defined time period such as 6 to 12 months"[2]. Gauthier et al[2] estimated that at least one third of dementia patients may be regarded as experiencing ACD. The rate of disease progression, as measured by the rate of cognitive[3] or functional decline, might be more important than disease stage severity for predicting disease course. Rate of disease progression may be valuable not only for establishing a prognosis but also for predicting the level of responsiveness of patients with AD to the treatment[4]. Therefore, the ability to differentiate rates of progression may help both patients and caregivers to plan for the future, as well as potentially helping physicians to decide how to best manage their patients.

The Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) is considered as the "gold standard" for assessing cognition in clinical trials[5]. It assesses several cognitive domains, including memory, language and praxis where deficits are characteristically seen in AD. Total scores range from 0-70, where a higher ADAS-Cog score represents poorer cognitive performance. Therefore, a negative change from the baseline score reflects an improvement. Farlow et al[4,6] identified patients as rapidly progressing based on a greater than or equal to a 4-point deterioration in the ADAS-Cog score from baseline over 26 weeks. However, the ADAS-Cog was not designed specifically to evaluate severity of symptoms or course of the disease[7]. It is also not suitable for a clinical practice because of its complexity, as it requires 30-40 minutes to evaluate a patient with

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this test. There is a need for a simpler tool to briefly screen and assess disease progression in an AD patient as evaluated by the caregiver[2].

In March 2005, a working group met in Paris, France to discuss the concept of an aggressive course of AD. They considered the clinical importance of this concept and identified key "predictors" of the ACD. As a result, they designed a simple tool to help recognize patients experiencing an ACD through a quick caregiver interview. This led to the development of the Realtime Assessment of Progression in Dementia (RAPID) tool. The present report describes the development of the Thai RAPID tool for screening and progression assessing of AD patients with ACD. The cut-off point scores were identified by comparing the Thai RAPID score with the ADAS-Cog score as the gold standard.

**Materiel and Method**

The Thai RAPID was developed as a simple questionnaire to screen for ACD in patients through questioning their caregivers. The questionnaire consists of five questions regarding events that have occurred during the last six months. The caregivers have to complete each question related to the condition of the patients. The first three questions contain five-scale answers: "almost totally" (4 points), "quite a bit" (3 points), "moderately" (2 points), "slightly" (1 point) and "not at all" (0 point). They assess the rate of overall symptoms progression, the decrease of patients' ability to perform everyday activities and whether the caregivers notice the changes in personality or behavior of their patients, respectively. The remaining questions have to be answered with "yes" (1 point) or "no" (0 point). In the fourth question, the caregivers identify the underlying symptoms, which may affect the behavior of their patients. They are "memory loss", "visual hallucinations", "sleeping problems", "recurrent tremor", "poor appetite or weight loss", "confusion" and "psychosis or being paranoid or aggressive". The last question asks if the caregiver feels more stressed than previously. The total score ranges from 0-20 points.

The Thai RAPID study was conducted between October 2007 and January 2009. The present study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. Prior to the participation in the present study, all patients and caregivers gave written informed consent. At screening, the patients of the dementia clinic were assessed regarding their dementia severity by the investigator's clinical global impression and the Thai Mental State Examination (TMSE)[8], which is a translated and culturally modified Mini-Mental State Examination (MMSE). Patients with cognitive impairment, based on investigator's judgment or those who had TMSE score < 27, were enrolled. Severe dementia patients (TMSE < 10) were excluded, since they are not able to perform the ADAS-Cog. The principal caregiver of each patient had to be able to read or understand the Thai language. All patients received standard therapies through the present study period.

The Thai RAPID tool was applied to the patients at the Department of Psychiatry, Faculty of Medicine, King Chulalongkorn Memorial Hospital. The ADAS-Cog was given to the patients while the Thai RAPID was completed by their caregivers both at baseline and at the 6-month follow up evaluation.

The demographic data were analyzed at a descriptive level only. A 4-point or greater decline on the ADAS-Cog during 6 months was considered as ACD. A non-parametric receiver operating characteristic (ROC) curve analysis was performed to examine the ability of the Thai RAPID to discriminate between the patients with- and without ACD using a change in ADAS-cog score of 4 as the gold standard. All statistical analyses were carried out using SPSS 11.5 (SPSS Inc., Chicago).

To determine the usefulness of the Thai RAPID as a screening tool to predict an ACD in AD patients, the ROC analysis was applied to identify the cut-off point of the Thai RAPID score. In addition, the change of the Thai RAPID score during six months was calculated and analyzed to define the optimal cut-off point of the Thai RAPID progression assessment. Sensitivity and 1-specificity values were computed for each possible cut-off point in order to determine the most sensitive and specific cut-off point. The area under the ROC curve (AUC) was used to determine the accuracy of the tool in differentiating the patients with ACD. AUC values of less than 1.0 (perfect test) refer to excellent (> 0.9), good (> 0.8), fair (> 0.7) and poor (> 0.6) accuracy.

**Results**

The baseline characteristics are shown in Table 1. Fifty patients were recruited and included 18 males (36%) and 32 females (64%). The average age of 49 patients (one missing data) was 75.4 ($\pm$ 7.2) years old, with the range from 62 to 89 years old. At baseline,

**Table 1.** Baseline characteristics

| Characteristics | Results (n = 50) |
|---|---|
| Sample demographics | |
| Male (%) | 18 (36%) |
| Female (%) | 32 (64%) |
| Age (mean ± SD, year) | 75.4 ± 7.2 |
| Cognitive function | |
| TMSE (mean ± SD) | 23.70 ± 3.99 |
| ADAS-Cog (mean ± SD) | 16.43 ± 8.74 |

TMSE = Thai mental state examination; ADAS-Cog = Alzheimer's disease assessment scale-coqnitive component

the patients had a mean TMSE and ADAS-Cog score of 23.70 (± 3.99) and 16.43 (± 8.74), respectively. The majority of patients (94%) were classified as mild severity, which is defined by the TMSE score of greater than 18. The rest (6%) were classified as moderate severity, which is defined by the TMSE score of less than or equal to 18. At 6-month, eight subjects (16%) were assessed as an ACD due to the decline of the ADAS-Cog score of greater than or equal to 4 points versus baseline.

The mean Thai RAPID score at baseline was 7.54 (± 2.91) and at the 6-month follow-up was 8.32 (± 2.68). The coordinates of the ROC curve that were used to define the cut-off point of the Thai RAPID as a screening tool are shown in Table 2. The data indicate that a cut-off point of 9-point yielded a fair sensitivity (0.625) as well as specificity (0.643). The ROC curve presented in Fig. 1 shows that the accuracy of the Thai RAPID for predicting patients with ACD was fair (AUC = 0.744, 95% CI = 0.606-0.882). A 9-cut-off point indicated 20 patients (40%) with ACD.

With regard to the progression assessment during 6 months (Table 3), the Thai RAPID tool cut-off point of 3-point yielded good sensitivity (0. 875) and specificity (0.810). Analysis of the ROC curve as displayed in Fig. 2 shows that the discriminating accuracy of the Thai RAPID was good (AUC = 0.887, 95% CI = 0.795-0.979, p = 0.001). An increase of three points of the Thai RAPID score from baseline identified 15 patients (30%) with ACD.

**Table 2.** ROC curve co-ordinate for the Thai RAPID as a screening tool, using ADAS-Cog as the gold standard

| Cut-off point[a] | Sensitivity | 1-specificity |
|---|---|---|
| 1.00 | 1.000 | 1.000 |
| 3.00 | 1.000 | 0.976 |
| 4.50 | 1.000 | 0.952 |
| 5.50 | 1.000 | 0.881 |
| 6.50 | 1.000 | 0.762 |
| 7.50 | 1.000 | 0.429 |
| 8.50 | 0.625 | 0.357 |
| 9.50 | 0.500 | 0.262 |
| 10.50 | 0.375 | 0.167 |
| 11.50 | 0.250 | 0.143 |
| 12.50 | 0.000 | 0.048 |
| 15.00 | 0.000 | 0.024 |
| 18.00 | 0.000 | 0.000 |

[a] The smallest cutoff value is the minimum observed test value minus 1 and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values
RAPID = real time assessment of progression in dementia; ADAS-Cog = Alzheimer's disease assessment scale-coqnitive component; ROC = receiver operating characteristic

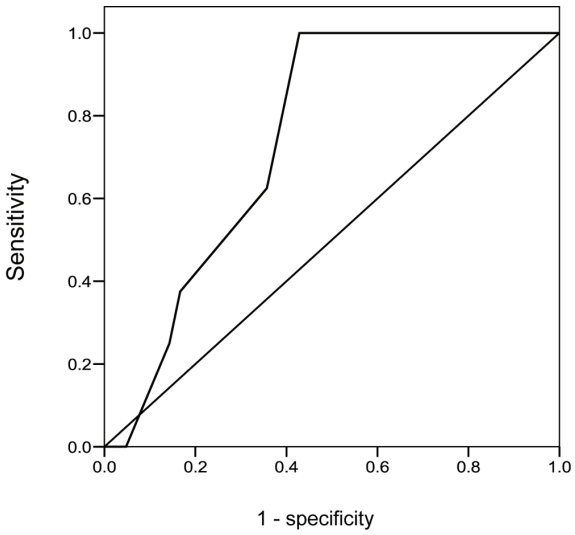


**Fig. 1** ROC curve for the Thai RAPID as a screening tool, using the ADAS-Cog as the gold standard

## Discussion

The ADAS-Cog has been widely used for assessing the progression in AD patients in clinical trials. Farlow et al[4,6] applied the ADAS-Cog to discriminate rapid progressors from the slow progressors. However, there is no standard tool to assess or predict which patients' disease is or will likely be rapidly progressive. Therefore, a simple tool that can be used in normal practice is needed.

**Table 3.** ROC curve co-ordinate for the Thai RAPID, as an assessment tool using ADAS-Cog as the gold standard

| Cut-off point[a] | Sensitivity | 1-specificity |
|---|---|---|
| -7.00 | 1.000 | 1.000 |
| -5.00 | 1.000 | 0.976 |
| -3.50 | 1.000 | 0.905 |
| -2.50 | 1.000 | 0.833 |
| -1.50 | 1.000 | 0.738 |
| -0.50 | 1.000 | 0.548 |
| 0.50 | 1.000 | 0.452 |
| 1.50 | 1.000 | 0.310 |
| 2.50 | 0.875 | 0.190 |
| 3.50 | 0.625 | 0.119 |
| 4.50 | 0.250 | 0.071 |
| 5.50 | 0.125 | 0.048 |
| 6.50 | 0.125 | 0.000 |
| 8.00 | 0.000 | 0.000 |

[a] The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values

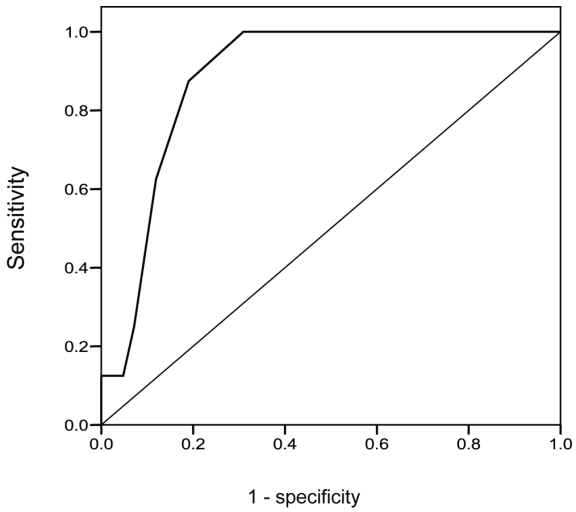


**Fig. 2** ROC curve for the Thai RAPID as an assessment tool, using the ADAS-Cog as the gold standard

The RAPID defines the perspective of caregivers, who usually accompany the AD patients. The tool may be completed in a shorter time compared to the ADAS-Cog. Furthermore, it offers an advantage in patients who are not able to read or understand the language, since the authors could predict or assess disease symptoms and their progression of the patient through their caregiver.

Although, short assessment scales such as the Thai RAPID might have a lower discrimination accuracy compared to the more comprehensive tools such as the ADAS-Cog, it is simpler and thus requires less time to complete. The accuracy of the Thai RAPID for screening purpose was fair, while its accuracy for assessing disease progression was better (AUC 0.625 vs. AUC 0.887, respectively). In comparison to the ADAS-Cog, the Thai RAPID indicated more AD patients with ACD (30 to 40% vs. 16%). This is closer to the previously estimated prevalence of ACD, which has been estimated to occur in approximately 33% of all AD patients[2].

Variation in results seen when applying the assessments of the ADAS-Cog and the Thai RAPID might be due to the differences in design, domain, and subjects tested with these tools. While the ADAS-Cog focuses on the cognitive functions, the Thai RAPID emphasizes the effect of the overall symptoms and daily life functions. Rockwood et al[9] suggested that, decline in ADAS-Cog score needs to be interpreted in the context of overall response and should not be weighted more highly, amongst other considerations, the preferences of patients and caregivers. Hence, the Thai RAPID could be utilized by physicians to screen and evaluate the progression of patients and to select a suitable treatment for patients in a clinical practice.

In this preliminary study, the numbers of subjects and assessment time were limited. Further research on the clinical utility of the Thai RAPID tool is required before applying the tool in the real-life practice.

## Conclusion

The Thai RAPID tool was developed for the prediction of an ACD in AD patients. A 9-point score of the Thai RAPID appears to be the optimal for ACD screening and a 3-point increase during 6 months appears to reliably indicate clinically significant progression. The present pilot study suggests that the Thai RAPID can be a valuable tool for the ACD screening and for progression assessment.

## Potential conflicts of interest

None.

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## *RAPID Progression:* เครื่องมือคัดกรองผู้ป่วยสมองเสื่อมโรคอัลไซเมอร์ที่มีการดำเนินโรคเร็ว

**นันทิกา ทวิชาชาติ, พวงสร้อย วรกุล, มาร์ติน ฟาร์โล**

***วัตถุประสงค์:*** *แบบทดสอบที่ใช้ประเมินอัตราการดำเนินโรคของผู้ป่วยโรคอัลไซเมอร์ เป็นเครื่องมือที่มีความจำเป็นในเวชปฏิบัติ การศึกษานี้มีวัตถุประสงค์เพื่อพัฒนาเครื่องมือคัดกรองและประเมินการดำเนินโรคของผู้ป่วยอัลไซเมอร์ที่มีการดำเนินโรคเร็ว*

***วัสดุและวิธีการ:*** *แบบทดสอบ RAPID ฉบับภาษาไทยได้ถูกพัฒนาเพื่อคัดกรองผู้ป่วยอัลไซเมอร์ที่มีการดำเนินโรคเร็ว โดยผู้ดูแลผู้ป่วยเป็นผู้ตอบแบบสอบถาม การศึกษาโดยทีมจิตแพทย์ภาควิชาจิตเวชศาสตร์ โรงพยาบาลจุฬาลงกรณ์ ผู้ป่วยทำแบบประเมินสัญญานพิสัยอัลไซเมอร์ (ADAS-Cog) ในขณะที่ผู้ดูแลทำแบบทดสอบ RAPID เมื่อแรกเข้าโครงการ และเดือนที่หก*

***ผลการศึกษา:*** *มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 50 ราย พบว่า คะแนน RAPID เท่ากับ 9 มีความไวและมีความจำเพาะปานกลาง (0.625 และ 0.643 ตามลำดับ) ในการใช้คัดกรองผู้ป่วยอัลไซเมอร์ที่มีการดำเนินโรคเร็ว แยกออกจากผู้ป่วยที่มีการดำเนินโรคปกติ ซึ่งวัดจากคะแนนประเมินสัญญานพิสัยอัลไซเมอร์ (ADAS-Cog) เท่ากับ 4 หรือมากกว่า และพบว่าคะแนน RAPID เท่ากับ 3 มีความไวและมีความจำเพาะดี (0.875 และ 0.810 ตามลำดับ) ในการใช้ประเมินการดำเนินโรคอัลไซเมอร์*

***สรุป:*** *แบบทดสอบ RAPID ฉบับภาษาไทยสามารถนำไปใช้คัดกรองและประเมินการดำเนินโรคของผู้ป่วยอัลไซเมอร์ที่มีการดำเนินโรคเร็วได้*