Systematic Review and Pooled Analysis of Published and Unpublished Validations of the ABCD and ABCD2 Transient Ischemic Attack Risk Scores

Matthew F. Giles, DPhil, MRCP; Peter M. Rothwell MD, PhD, FRCP, FMedSci

Background and Purpose—The ABCD system was derived to predict early risk of stroke after transient ischemic attack. Independent validations have reported conflicting results. We therefore systematically reviewed published and unpublished data to determine predictive value and generalizability to different clinical settings and users.

Methods—Validations of the ABCD and ABCD2 scores were identified by searching electronic databases, reference lists, relevant journals, and conference abstracts. Unpublished tabulated data were obtained where available. Predictive value, expressed as pooled areas under the receiver operator characteristic curves (AUC), was calculated using random-effects meta-analysis, and analyses for heterogeneity were performed by categorization according to study setting and method.

Results—Twenty cohorts were identified reporting the performance of the ABCD system in 9808 subjects with 456 strokes at 7 days. Among the 16 studies of both the ABCD and ABCD2 scores, pooled AUC for the prediction of stroke at 7 days were 0.72 (0.66 to 0.78) and 0.72 (0.63 to 0.82), respectively (P diff=0.97). The pooled AUC for the ABCD and ABCD2 scores in all cohorts reporting relevant data were 0.72 (0.67 to 0.77) and 0.72 (0.63 to 0.80), respectively (both P<0.001). Predictive value varied significantly between studies (P<0.001), but 75% of the variance was accounted for by study method and setting, with the highest pooled AUC for face-to-face clinical evaluation and the lowest for retrospective extraction of data from emergency department records.

Conclusion—Independent validations of the ABCD system showed good predictive value, with the exception of studies based on retrospective extraction of nonsystematically collected data from emergency department records. (Stroke. 2010;41:00-00.)

Key Words: TIA ■ ABCD score ■ ABCD2 score ■ risk ■ risk prediction ■ systematic review ■ meta-analysis

Stroke risk within the first week after transient ischemic attack (TIA) is 5% to 10%, depending on study population and methodology.1 The ABCD system (ABCD and ABCD2 scores2,3) is a prognostic system based on clinical data designed to predict stroke risk within 7 days after TIA to guide triage to specialist care, target secondary prevention, and inform public education. Use of the score has been recommended in national guidelines in North America, Europe, and Australasia.4–6

Usefulness of risk scores depends on predictive value and calibration,7 consistency of performance in different studies and settings,8 and ease of calculation. The ABCD score was derived and validated in specialist clinics in Oxfordshire, UK,2 and refined and revalidated as the ABCD2 score in clinic cohorts from Oxfordshire and emergency departments (EDs) and clinic cohorts from California.3 Additional validation by independent investigators from different specialties and healthcare settings is essential.7,8 Systematic reviews of stroke risk after TIA have shown that estimates of the early risk of stroke vary according to the clinical specialty, setting of evaluation,1 and method of data extraction.9 Multiple validations of the ABCD system have reported inconsistent results, ranging from excellent predictive value10 to little better than chance.11 However, in contrast to the original development studies, based on 266 early stroke outcomes,2,3 most validations have been underpowered, based on as few as 2 outcome strokes.12 The roles of additional clinical,13 etiologic,14 and radiological15–17 factors that might also be prognostic have been studied. Further, the function of the system as a diagnostic tool, distinguishing between TIA and TIA-mimics, has been questioned,18–20 as has its use in predicting stroke risk in the subacute phase after TIA.21

Therefore, we systematically reviewed all available validation studies of the ABCD and ABCD2 scores to determine their overall accuracy and any heterogeneity in relation to study methodology (eg, prospective face-to-face patient evaluation versus retrospective extraction of data from ED records). Where data were available, we studied the performance.
of the system in diagnosis compared with prognosis and over different intervals of follow-up.

**Methods**

We aimed to identify all studies of the ABCD and ABCD2 scores, irrespective of aims, design, or setting. PubMed, Ovid Medline, and EMBASE (2000 to July 2009) were searched using MeSH terms and text words: transient ischemic attack OR TIA OR amaurosis fugax AND prognosis OR outcome OR predict OR risk OR ABCD OR ABCD2. We hand searched reference lists of included studies, relevant reviews, and contents pages of journals from which most articles were identified. The final electronic search was conducted on July 15, 2009. To identify unpublished studies, we searched books of abstracts from the following conferences: Joint World Congress on Stroke 2006, World Stroke Congress 2008, American Heart Association International Stroke Conferences 2007 to 2009, and the European Stroke Conferences 2006 to 2009.

Any study of the application of the ABCD or ABCD2 scores in a cohort of TIA patients, with respect to prediction of stroke, was reviewed in full. Unpublished tabular data were requested from authors, if required. We excluded studies in which outcomes were only available by dichotomized or trichotomized scores (which are potentially data dependent).

Data were extracted on study method (dates, setting, specialty of diagnosing or evaluating clinician, follow-up, and outcome adjudication), patient characteristics, method of data extraction, and calculation of risk score, and numbers of patients and outcomes were stratified by ABCD and ABCD2 scores. Cohorts that included patients with TIA and TIA mimics were excluded, other than in analysis of diagnostic performance.

For each cohort, stroke risk and corresponding sensitivity and specificity were calculated for cut points over the interval(s) reported. Where possible, total risk was split between acute (0 to 7 days) and subacute (8 to 90 days) phases. Prognostic value was calculated from the area under the receiver operator characteristic curve with 95% CIs. Pooled areas under the curve (AUCs; 95% CI) were obtained by random-effects meta-analysis. AUCs were compared using independent samples t test.

Heterogeneity of AUCs was explored in relation to clinical specialty and setting of evaluation (neurologist versus non-neurologist) and methods of extraction of ABCD elements (face-to-face assessment versus retrospective extraction of data from clinical records). The proportion of overall heterogeneity accounted for by this subcategorization was determined by an inverse-variance weighted regression of AUCs. Analyses were done with SPSS 15.0.

**Results**

The electronic search yielded 2592 publications. After screening and exclusion of duplicates, 158 full reports were reviewed. Thirteen additional reports were identified by searching reference lists and abstract books. No additional studies were identified by hand searches of the 3 journals containing most studies (Lancet, Stroke, and Cerebrovascular Diseases). All publications were in English.

Unpublished data were obtained for 8 cohorts. Four cohorts containing TIAs and TIA-mimics were included in analyses of diagnostic performance only. Three studies with only dichotomized or trichotomized outcomes available were excluded. Data on prediction of early stroke risk after TIA by ABCD or ABCD2 scores were available for 20 cohorts (Tables 1 and 2): ABCD score in 18 cohorts (8470 subjects with 351 strokes at 7 days) and ABCD2 score in a different set of 18 cohorts (9436 patients with 442 strokes at 7 days).

Seven cohorts were published by Oxford or California researchers, and the remaining 13 by independent researchers (Table 1). Four cohorts were population based (including all patients from a predefined population). 8 were from EDs, 2 were from outpatient clinics, and 6 were from specialist neurovascular units. In 4, evaluation was by an ED physi-
were handled when complete data were unavailable.10,30

retrospective chart review, of which 2 reported how cases
were diagnosed by World Health Organization
definition.32

AUCs for prediction of stroke risk over 0 to 7 and 0 to 90
days. Figures 1 and 2 show funnel plots of AUCs plotted
for prediction of stroke risk over 0 to 7 and 0 to 90
days for the ABCD/ABCD2 scores for each set of 18 relevant studies. Using random-effects meta-analysis, pooled AUCs for prediction of TIA risk were 0.72 (0.66 to 0.78) (P = 0.001). Pooled AUCs for the ABCD2 score were 0.72 (0.66 to 0.78) (P = 0.001) for the ABCD and ABCD2 scores, respectively (P = 0.001). Pooled AUCs for the ABCD2 score for cohorts published by Oxford or California and independent investigators (ie, non-Oxford/California) were 0.77 (0.63 to 0.91) and 0.69 (0.64 to 0.74), respectively (P = 0.001). Results were similar for pooled AUCs for the ABCD score and when original derivation cohorts were excluded (data not shown).

Predictive value of the ABCD2 score for 7-day stroke risk varied significantly between studies (P = 0.001). However, using inverse variance-weighted regression of AUCs, 75% of variance was accounted for by study method (calculation of the score by face-to-face evaluation or neurology clinic records versus retrospective extraction of data from ED records), with pooled AUCs ranging from 0.74 (0.64 to 0.84) for face-to-face clinical evaluation or neurology clinic records to 0.68 (0.64 to 0.72) for retrospective extraction of data from ED records.

Figure 3 shows calibration of the ABCD2 score with observed stroke risks grouped according to clinical setting. Figure 4 shows the distribution of ABCD2 score, pooled according to study setting, with population-based and ED cohorts containing higher risk patients.

Table 3 shows predictive power of the ABCD score for stroke risk over 0 to 7 and 8 to 90 days after TIA for 15
studies providing relevant data (in 5, no outcomes were recorded during one of the periods). In 12 of the studies, the score had greater predictive power in the acute versus subacute phase. The pooled AUCs for stroke risk over 0 to 7 and 8 to 90 days were 0.71 (0.66 to 0.76) and 0.63 (0.57 to 0.69), respectively ($P$ diff=0.04). AUCs for the ABCD2 score were similar (data not shown).

Predictive power of the ABCD2 score was described in 4 cohorts of TIA and TIA mimics. $P$18–20 AUCs for prediction of TIA versus TIA-mimic were 0.73 (0.67 to 0.78), $P$2 0.75 (0.73 to 0.76), $P$18 0.75 (0.68 to 0.79), $P$19 and 0.80 (0.69 to 0.91).$P$20

**Discussion**

In a systematic review of 20 cohorts including 9808 subjects with 456 strokes at 7 days, the predictive power of the ABCD system for stroke within 7 days was good, with pooled AUCs of 0.72 (0.67 to 0.77) and 0.72 (0.63 to 0.80), respectively, for the ABCD and ABCD2 scores. Pooled AUCs for stroke prediction at 7 days were 0.72 (0.66 to 0.78) and 0.72 (0.63 to 0.82), respectively, for the ABCD and ABCD2 scores in the 16 cohorts reporting data for both scores.

It has been suggested that the system works either diagnostically$^{18–20}$ or by identifying TIAs caused by large artery
The system does have a diagnostic element, distinguishing between TIA and TIA-mimics, and it is likely that this partly explains its prognostic performance when applied to cohorts containing both TIAS and suspected TIAS with eventual non-neurovascular diagnoses. However, its diagnostic performance was limited, and predictive performance was maintained when applied to genuine TIAS only. Moreover, the system still predicts stroke reasonably well in a large multicenter pooled analysis of patients with diffusion-weighted imaging–positive TIA (M. Giles, unpublished data, 2010). Therefore, it is likely that the predictive power of the system is based on both diagnostic discrimination and identification of unstable cerebral ischemia. In the early phase, stroke risk is highest in patients with unstable vascular pathology, whereas in the later phase, stroke risk is determined by established vascular risk factors. The high AUC for the 0- to 90-day phase is predominantly driven by predictive power in the acute phase and implies that the score will overpredict risk in TIA patients who present after a delay.

There was significant heterogeneity between AUCs, with poorest performance in cohorts in which elements of the score were extracted retrospectively from review of ED clinical records. Method of extraction of the score elements accounted for 75% of overall heterogeneity. This may be explained in several ways. Direct clinical assessment of the patient is more accurate than retrospective extraction of data by review of clinical records. Expertise in diagnosing TIA may vary between clinical specialties, with misdiagnosis more common in EDs. Finally, in the United Kingdom, high-risk TIA patients are more likely to attend EDs than other healthcare services, and we found the greatest proportion of high-risk cases in ED cohorts, leading to an unrepresentative case mix and possibly reduced predictive power (Figure 4). However, irrespective of the explanation, retrospective extraction of the score from old records is not a likely modus operandi in routine clinical practice.

Our study has shortcomings. First, studies of performance of prognostic scores use inconsistent methodology, including inception criteria, clinical setting, score application, and treatments. We describe and acknowledge these potential limitations. Second, statistical methods for meta-analysis of AUCs are limited. Third, meta-analysis is susceptible to publication bias, but, arguably, nonconfirmatory studies are now more likely to be published. Fourth, there were no studies in which data were collected prospectively by face-to-face assessment by ED physicians or other nonspecialist...
of current guidelines.

Of course the ABCD system is not intended to be a substitute for clinical judgment and may perform less well in specific groups, such as young normotensive patients with arterial dissection or cerebral vasculitis. Development of supplementary versions of the score, with the incorporation of markers of vascular instability such as cerebral imaging, is likely to improve prediction of stroke for management in secondary care after initial triage. However, we have shown that the predictive power of the ABCD system in the generality of TIA patients in independent validations overall has been good, supporting the use of the score as recommended in current guidelines.

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Disclosures

None.

References


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The online version of this article, along with updated information and services, is located on the 
World Wide Web at: 
http://stroke.ahajournals.org/content/early/2010/02/25/STROKEAHA.109.571174.citation 

Data Supplement (unedited) at: 
http://stroke.ahajournals.org/content/suppl/2016/03/31/STROKEAHA.109.571174.DC1
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背景和目的: ABCD评分用于预测短暂性脑缺血发作(TIA)后早期卒中风险。多项独立的研究结果差异很大。因此我们系统性地回顾已发表或未发表的数据以衡量该评分系统的预测价值，从而推广到各级医院及使用者。

方法: 通过电子数据库、文献索引、相关杂志以及汇编摘要集来检索有关ABCD和ABCD2评分的文章。查询到的未发表数据也被纳入。预测价值用受试者工作特征曲线(AUC)汇总面积来表示，采用随机效应荟萃分析计算，异质性分析根据研究机构及方法学不同进行分类。

结果: 检索到20个关于ABCD评分的队列研究，共9808个受试者中456个7天内发生卒中。在16个包含ABCD和ABCD2的研究中，预测7天内卒中的汇总AUC分别为0.72(0.66-0.78)和0.72(0.63-0.82)(P差异=0.97)，而在所有队列研究中上述评分卒中的汇总AUC分别为0.72(0.67-0.77)和0.72(0.63-0.80)(P<0.001)。各研究中评分预测7天内卒中AUC分别为0.72(0.66-0.78)和0.72(0.63-0.82)(P差异=0.97)，但是5%的差异源于研究方法学和研究机构不同:即面对面的临床评估者汇总AUC最高，而回顾性收集急诊记录数据者汇总AUC最低。

结论: 独立的ABCD评分的研究结果显示其具有良好的预测价值，但是不包括回顾性非系统性的收集急诊记录数据的那些研究。

关键词: 短暂性脑缺血发作，ABCD评分，ABCD2评分，风险，风险预测，系统性回顾，荟萃分析

(Stroke. 2010;41:667-673. 倪俊 周立新 姚明译 高山校)
是否存在与研究方法相关的差异（如，前瞻性面对面地问诊或回顾性收集急诊记录）。可能的话，我们也评估该评分系统的诊断价值，并与预后价值以及不同随访间期的结果差异进行比较。

### 方法


所有关于 ABCD 或 ABCD2 评分的预测卒中风险的 TIA 患者队列研究均被纳入进行全面回顾分析。如果需要，我们向作者索取未发表的表格式数据。对于仅以将两分法或三分法显示结果的研究被排除（这种研究结果可能存在数据依赖性）。

我们收集了以下数据以进行汇总分析：研究方法（日期、数据来源、诊断或评估者的专业、随访以及结果判定）、患者特征、数据收集方法、危险评分的计算、采用 ABCD 和 ABCD2 评分进行分层的患者数以及结果。包括 TIA 和 TIA 样发作患者的队列研究仅被纳入进行诊断性能评估。如果需要，我们向作者索取未发表的表格式数据。

对于仅以将两分法或三分法显示结果的研究被排除（这种研究结果可能存在数据依赖性）。

### 结果

电子检索发现了 2592 篇文献。经筛选排查，最终纳入 158 篇文献进行回顾分析。通过检索参考文献和摘要汇编发现了另外 13 篇文献报道。手工检索收录大多数文献的 3 份主要杂志（Lancet, Stroke 以及...）
由于接诊医生的不同（单纯急诊医生诊断 TIA[2,29]或神经专科医生诊断 TIA[2]), 初步诊断的准确性有很大的差异。11项研究[2,12,15,16,24-28]由研究者直接对患者进行评分，而另外9项研究则通过回顾性分析进行评分，其中2项研究报道了当不能获取完整信息时的评分判定方法[10,30]。随访方式包括面对面评估、电话随访、利用病历审查以及搜索信息存储数据库。没有研究报道评分工具是否作为可能影响预后的因素而被纳入治疗决策中。自ABCD评分系统发表以来仅四项研究对此进行了探讨，但是在这项系统回顾纳入的研究中都没有对此进行报道。20项研究共纳入9808例患者，7天内发生卒中456人次；15项研究共计纳入7384例患者，90天内发生卒中507人次。两组研究只报道了7天和30天的结果[10,15]。表2显示了AUCs预测7天和90天卒中风险的结果。图1和图2所示的AUCs漏斗图显示了相应18个研究中ABCD/ABCD2评分和与之相对应的7天卒中风险。随机效应荟萃分析显示ABCD或ABCD2评分预测7天内卒中风险的汇总AUCs分别为0.72(0.67-0.77)和0.72(0.63-0.76)。
Giles et al      Systematic Review of the ABCD and ABCD2 TIA Risk Scores

0.80\((P<0.001)\)。对16项采用了两种评分体系的队列汇总AUCs分析显示，ABCD或ABCD2评分预测7天内卒中风险的汇总AUCs分别为0.72\((0.66-0.78;\ P=0.001)\)和0.72\((0.63-0.82;\ P<0.001)\)，\(P\)差异=0.97。牛津或加利福尼亚学者的研究和其他学者（即非牛津/加利福尼亚）的研究的ABCD2评分的汇总AUCs分别为0.77\((0.63-0.91)\)和0.69\((0.64-0.74)\)\((P\)差异=0.10)。排除衍生后续研究后，对ABCD评分的汇总AUCs分析的结果与此相似。

各研究关于ABCD2评分对于7天卒中风险的预测价值具有显著差异\((P<0.001)\)。但是，通过对AUCs进行逆差额加权回归显示75%的差异源于研究方法学（面对面评估或根据神经专科医疗记录评估和回顾急诊医疗记录评估），面对面评估或根据神经专科医疗记录评估的汇总AUCs为0.74\((0.64-0.84)\)，回顾急诊医疗记录评估为0.68\((0.64-0.72)\)。

图3显示按照临床数据来源进行分组，校正后的ABCD2评分和与之相对应的卒中风险。图4显示按照临床数据来源进行分组后，各组患者ABCD2评分的分布情况，发现高危患者多见于群体研究和
急性队列研究。

表 3 显示了 15 项研究关于 ABCD 评分对于 TIA 后 0-7 天和 8-90 天卒中的预测价值 (另外 5 项研究相关数据不全)。在这些研究中, 其中 12 项研究显示 ABCD 评分对于急性期卒中的风险预测优于亚急性期。急性期 (0-7 天) 和亚急性期 (8-90 天) 卒中风险的汇总 AUCs 分别为 0.71 (0.66-0.76) 和 0.63 (0.57-0.69) ($P$ 差异 =0.04)。ABCD2 评分的 AUCs 与此相似。

有 4 个关于 TIA 和样发作的队列研究描述了 ABCD2 评分的诊断预测价值 [2,18-20]。AUCs 对 TIA( 的 TIA 样发作) 的预测值分别为 0.73 (0.67 to 0.78) [2], 0.75 (0.73 to 0.76) [18], 0.75 (0.68 to 0.79) [19] 及 0.80 (0.69 to 0.91) [20]

讨论

在这项系统回顾和研究中, 共纳入了 20 个队列的 9808 名受试者, 其中 7 天内发生卒中事件 456 件, 研究发现 ABCD 系统具有良好的卒中的预测价值, ABCD 系统和 ABCD2 系统的汇总 AUCs 分别为 0.72 (0.67-0.77) 和 0.72 (0.63-0.80)。对 16 个已发表的队列研究分析发现, ABCD 和 ABCD2 系统预测卒中的汇总 AUCs 分别为 0.72 (0.66-0.78) 和 0.72 (0.63-0.82)。

研究还提示 ABCD 系统对于诊断 [18-20] 或鉴别由大动脉疾病所致的 TIA 也有一定作用。该系统确实有一些诊断意义, 可以鉴别 TIA 和类似 TIA 的发作。这可能也可以部分解释以下的现象, 我们发现在对既包含 TIA 同时也包含最终证实非神经血管疾病所致的 TIA 样发作的队列进行研究后, 该系统仍具有一定的预测价值 [18-20]。但是, ABCD 系统的诊断价值还是很有限的 [18-20], 其预测价值也只有在应用于真正的 TIA 上才比较可靠 [2]。此外, 一项多中心的大型汇总研究结果显示, 对于弥散加权像阳性 TIA 患者, ABCD 系统预测卒中也是非常可靠的 (M. Giles, 未发表数据, 2010)。因此, 决定 ABCD 系统预测价值大小的基础是诊断的准确性和鉴别不稳定的脑缺血。TIA 后的早期, 血管病理学上不稳定的患
者卒中风险高，而后期，卒中的风险取决于已存在的血管危险因素。0 到 90 天期间的 AUC 多出现于急性期，而在后期该评分可能会夸大卒中发生的风险。

各队列的 AUC 值之间存在着明显的异质性，ABCD 系统在回顾急诊的临床资料的研究中所显示的预测能力最差。75% 的异质性来自于对于所需评分参数的提取方法不同。这可能有以下几种解释。与患者进行面对面的直接临床评估获得的评分参数较对临床记录进行回顾所提取的参数准确得多。不同的临床专科医生对于 TIA 的诊断准确性是不同的，在急诊，TIA 很容易被误诊。最后，在英国，高危的 TIA 患者更多地到急诊就诊，而不是其它的医疗部门，并且我们的研究结果发现低危患者大部分出现于急诊队列中，这可能会导致由于对一些不典型病例的误诊而降低该系统的预测价值。无论如何，不管如何解释，通过回顾以往的记录中提取参数进行评分可能并不是一个有效的方法。

我们的研究存在一些缺陷。首先，这些评分系统所使用的方法学是不同的，包括纳入标准，患者来源，评分的应用和治疗。我们此前已经描述和确认了这些潜在的局限。其次，我们所用的 AUCs 荟萃分析的统计方法有一定的局限性。第三，荟萃分析方法易受出版偏移的影响，但可以说，目前通过验证未能获得阳性结果的研究更容易被发表。第四，这个评分系统是为急诊医生和其他非专业医生所设计的，但迄今尚无一项前瞻性的研究，其数据是来源于急诊或非专业医生面对面的评估。因此，将来由非专业医生对本评分系统进行验证是非常必要的。

当然，ABCD 评分系统并不能替代临床的判断，而且在对一些特殊患者其效能不佳，例如青年的不伴高血压的动脉夹层患者或脑血管炎患者。因此，对该评分系统应该进行适当的更新，例如结合判断血管不稳定的方法，如脑影像学的应用，能够提高卒中的预测价值，以制定更好地卒中二级预防策略。总之，我们的研究经过独立的验证后，已经很好地证实了 ABCD 评分系统在总的 TIA 人群中的预测价值，推荐在目前的指南中使用该评分系统。

参考文献(略)