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# Prognostic value of the ABCD² score on long-term follow-up of transient ischemic attack using the new tissue-based definition

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### *Abstract*

The ABCD² score is validated for evaluating short-term stroke risk after transient ischemic attack (TIA); however, whether it is able to predict the long-term risk of vascular outcome remains uncertain. Recently a new tissue-based definition of TIA has been proposed. The ABCD² scores of 145 TIA patients admitted to our hospital were retrospectively calculated and stratified into two categories: ≤ 3 points (low risk); 4-7 points (moderate-high risk). At a median follow-up of 81 months, new vascular events were recorded. Follow-up data were available in 107 patients. Seventy one patients had a moderate-high ABCD² score. Sixty six patients experienced a cerebral ischemic event; 8 a myocardial infarction; 7 died of cerebrovascular or cardiovascular cause. Moderate-high ABCD² score was significantly associated with the further cerebral ischemic events (hazard ratio [HR], 1.755; 95% confidence interval [CI], 1.019 to 3.024) and with the combined endpoint (HR, 1.818; 95% CI, 1.079 to 3.063). Our study shows that the ABCD² score may also be used to predict long-term vascular outcome after tissue-based definition of TIA. Moderate-high ABCD² score is associated with an increased general vascular risk in the long-term follow-up after TIA.

## INTRODUCTION

After a transient ischemic attack (TIA), patients typically recover fully from their neurological deficits, but are at high risk of recurrent vascular events, such as ischemic stroke (IS) and coronary artery disease (CAD).[1,2] Whereas recurrence of cerebral ischemia dominates the short-term prognosis after TIA, cardiovascular disease becomes the major cause of death on long-term follow-up after TIA and IS.[2-4] Predicting and stratifying the risks of future vascular events after an initial TIA is therefore of clinically importance, and a simplified, 7-point ABCD² scoring system based on five clinical factors (age, blood pressure, clinical features, duration of symptoms, diabetes) has been proposed for this purpose.[5] If clinically validated, a simple assessment scale that can identify those TIA patients at higher risk of recurrent vascular events or death, would be helpful to guide subsequent treatment planning, and also raise patient awareness, which in turn might improve patient adherence to prevention strategies.[6] Early studies for evaluating short-term stroke outcomes after TIA have shown that high (6-7 points) and moderate (4-5 points) ABCD² scores were significantly associated with an increased risk at 2, 7 and 90 days, compared to low (0-3 points) ABCD² scores.[5] However, few studies have evaluated long-term risk of further vascular events after a TIA after 90 days.

The definition of TIA is also undergoing changes; recently, a new tissue-based definition proposed to classify TIA as a transient episode of neurologic dysfunction by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction.[7] Using neuroimaging criteria, this new pathophysiological definition may, by eliminating the confounding effects of small cerebral infarctions that might have been included in the previous arbitrary time-based definition (of transient symptoms lasting less than 24 hours), be more accurate in future studies of outcomes and risks in TIA.[7] A recent study of the early stroke risk and ABCD² score performance in tissue-defined TIA versus time-defined TIA supports the concept of tissue-based definition of TIA and stroke, at least on prognostic grounds.[8] In this study, we assessed the value of ABCD² score in predicting both cerebrovascular and cardiovascular recurrent

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events during long-term follow-up using the new tissue-based definition of TIA.

## METHODS

*Patient selection and data acquisition*

We retrospectively analyzed a consecutive series of patients with suspicion of stroke or TIA who had been admitted to the Stroke Unit of Huashan Hospital between January 2006 and December 2007. All patients presented to the outpatient or emergency department with a sudden onset of one or more of the following symptoms suspicious for a cerebrovascular event: hemiparesis, speech disorder, hemianopia, gait disturbance, vertigo, dysphagia, disturbance of consciousness, deviation of head and/or ocular symptoms. All research carried out in participating subjects was in compliance with the Helsinki Declaration.

These patients also underwent CT scan and MRI scan including diffusion-weighted imaging (DWI) sequences within 3 days after onset of symptoms. The neuroimaging records of all patients were reviewed by two senior neuroradiology specialists based on consensus reading to decide if a patient had cerebral infarction or TIA. Diagnostic criteria for cerebral infarction according to tissue-based diagnosis included DWI positive for hyperintensity on the isotropic b= 1000 scan and corresponding hypointensity on the apparent diffusion coefficient (ADC) map. These patients who were negative for cerebral infarction were considered positive TIA according to tissue-based diagnosis of TIA.[7]

The $ABCD^2$ score at time of admission was retrospectively calculated by evaluating medical records according to previously published criteria[5] as follows: age (≥60 years, 1 point); blood pressure on first assessment after TIA (systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg, 1 point); clinical features of TIA (unilateral weakness with or without speech impairment, 2 points; speech impairment without weakness, 1 point); duration of TIA symptoms (≥60 minutes, 2 points; 10-59 minutes, 1 point); diabetes (1 point). The $ABCD^2$ score was stratified into two categories (≤ 3 points, low risk; 4-7 points, moderate-high risk).[5]

In addition, vascular risk factors including medical history of hypercholesterolemia, CAD, heart failure (HF), atrial fibrillation (AF), smoking and family history of stroke were recorded. Hypercholesterolemia was defined as total cholesterol ≥6.0 mmol/L or current use of lipid-lowering medication. CAD was defined by the nomenclature and criteria for diagnosis of ischemic heart disease.[9] HF was defined by the American College of Cardiology/American Heart Association 2001 chronic HF guidelines.[10] AF was diagnosed as history of electrocardiographically (ECG) documented intermittent or persistent AF. Smoking was coded as positive if the patient was a current or former regular smoke. The patient with family history of stroke was the one whose immediate family had a history of stroke. In addition, diagnostic criteria for myocardial infarction (MI) included documented typical rise and gradual fall (Troponin T) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: ischemic symptoms (e.g. chest pain), development of pathological Q waves on ECG, or ECG changes indicative of ischemia (ST segment elevation or depression), either during admission or in medical reports from other hospitals.

In summary, the inclusion criteria for this study comprised the following factors: (1) patients with suspicion of stroke or TIA, (2) TIA diagnosis using the new tissue-based definition, and (3) patients whose $ABCD^2$ score could be calculated.

*Follow-up assessment*

During a median follow-up period of 81 months (range, 69 to 89 months), follow-up information was collected by an investigator blinded to $ABCD^2$ score. Patients or their relatives (if patients had died at the time of follow-up) were contacted and interviewed. The end points in the questionnaire included recurrent cerebral ischemic events (IS or TIA), cardiac ischemic events, and death from any cerebrovascular or cardiovascular cause (IS, intracerebral hemorrhage, MI, or HF); all the recurrent events occurred beyond first 3 months follow-up. In case of a suspected recurrent vascular event, confirmation was sought from the treating general physician or hospital records. Deaths from nonvascular cause were also documented. Patients with recurrent vascular events were compared against those without recurrent events; this latter group comprised the patients who only had one index TIA attack, and had no further cerebrovascular or cardiovascular events during follow-up.

*Statistical analysis*

For interpretation and summary of results, the $ABCD^2$ score was dichotomized into low scores (0-3 points) versus moderate-high scores (4-7 points). Differences in the distribution of baseline characteristics between groups were examined

using Chi-square test for categorical variables and Student's t-test for continuous variables. Cox proportional hazards regression models were carried out to detect the association between relative risk of recurrent cerebral ischemic events and combined endpoint of cerebral/cardiac ischemic events or death from cerebrovascular/cardiovascular cause and $ABCD^2$ score at baseline. Estimates derived from Cox proportional hazard regressions were presented as hazard ratios (HR) and 95% confidence intervals (CI). The data were analyzed with statistical software SAS version 9.2 (SAS institute, Cary, NC, USA).

## RESULTS

A total of 145 patients who were admitted during the study period fulfilled the inclusion criteria of tissue-based diagnosis of TIA. Follow-up data were available for 110 patients (75.9%); 35 were lost to follow-up after discharge from hospital and were excluded from analysis. At the time of follow-up, 10 patients (9.09%) had died for the following reasons: MI, 4 patients; IS, 1 patients; intracerebral hemorrhage, 2 patient; and 1 patient each died of pneumonia, lung cancer, and unexplained coma. These last 3 who died from nonvascular causes were also excluded from further analysis. (Figure 1)

Baseline characteristic of the study population of 107 TIA patients are shown in Tables 1 and 2. There were 84 men (78.50%) and 23 women (21.50%) (mean age, 62.03 ± 14.96 years). 36 patients (33.64%) had a low $ABCD^2$ score, 71 patients (66.36%) had a moderate-high score. The patients with moderate-high $ABCD^2$ score were significant older than patients with low scores ($P$ <0.05). Patients with moderate-high $ABCD^2$ score also had higher incidence of AF than those with low $ABCD^2$ score ($P$<0.05), but other factors like gender, smoking, hypercholesterolemia, CHD, HF, family history of stroke showed no statistically significant differences between groups.

Table 3 shows the comparison of risk factors between patients with and without recurrent vascular events. 31 patients (28.97%) did not have any recurrent vascular events, 66 patients (61.68%) had a cerebral ischemic event, and 76 patients (71.03%) had either recurrent cerebral/cardiac

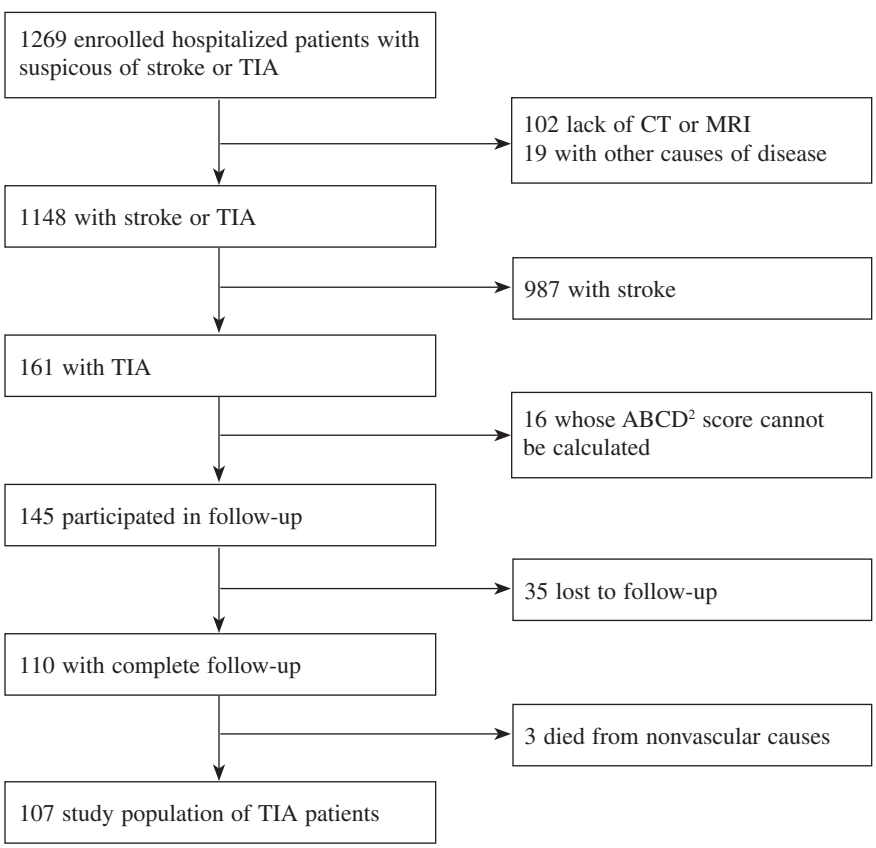


Figure 1. Selection of study patients

**Table 1: Single Items of ABCD² Score in study population (n=107)**

| Single item | n (%) |
|---|---|
| Age# | 62.03±14.96 |
| ≥60 years | 57(53.27) |
| SBP ≥140 mmHg /DBP ≥90 mmHg | 80(74.77) |
| Clinical features | |
| Unilateral weakness | 61(57.01) |
| Speech impairment without weakness | 26(24.30) |
| Duration of TIA symptoms | |
| 10-59 minutes | 24(22.43) |
| ≥60 minutes | 57(53.27) |
| Diabetes | 35(32.71) |

Data are presented as n (%) unless otherwise stated.
# mean ± standard deviation;
SBP= systolic blood pressure; DBP= diastolic blood pressure

ischemic events or death from cerebrovascular/ cardiovascular cause. At follow-up, 8 patients (7.27%) with moderate-high ABCD² score had suffered acute MI (median 49 months, range 4 to 81 months) after index TIA but none of the patients with a low ABCD² score was affected. Patients with recurrent vascular events had higher incidence of moderate-high ABCD² score compared with patients without recurrent vascular events ($P$ <0.05). Other factors like age, gender, smoking, hypercholesterolemia, CHD, HF, AF, family history of stroke showed no statistically significant difference.

Cox proportional hazards regression analysis showed that moderate-high ABCD² score increased the risk of recurrent cerebral ischemia and combined endpoint of cerebral ischemic events, cardiac ischemic events and death of cerebrovascular or cardiovascular cause ($P$<0.05 for both, Table 4).

**Table 2: Baseline Characteristics of Subjects who presented for follow-up**

| Variables | All subjects (n=107) | Low ABCD² Score (n=36) | Moderate- high ABCD² Score (n=71) | *P* value* |
|---|---|---|---|---|
| Age# | 62.03±14.96 | 51.42±11.7 | 67.41±13.54 | <0.001 |
| Follow-up# (month） | 80.17±5.64 | 81.03±5.73 | 79.73±5.59 | 0.264 |
| Female | 23(21.5) | 7(19.44) | 16(22.54) | 0.713 |
| Smoking | 38(35.51) | 14(38.89) | 24(33.8) | 0.603 |
| Hypercholesterolemia | 41(38.32) | 10(27.78) | 31(43.66) | 0.110 |
| CHD | 21(19.63) | 4(11.11) | 17(23.94) | 0.114 |
| HF | 1(0.93) | 1(2.78) | 0(0) | 0.158 |
| AF | 8(7.48) | 0(0) | 8(11.27) | 0.036 |
| Family History of stroke | 13(12.15) | 3(8.33) | 10(14.08) | 0.390 |

* Comparison of baseline characteristics between low ABCD² Score group and moderate-high group;
Data are presented as n (%) unless otherwise stated.
# mean ± standard deviation
CHD= coronary heart disease; HF= heart failure; AF= atrial fibrillation

**Table 3: Risk factor comparison between patients with and without recurrent vascular events on follow-up**

| Variables | Patients without recurrent vascular events (n=31) | Patients with recurrent vascular events (n=76) | *P* value |
|---|---|---|---|
| Moderate-high ABCD$^2$ scores | 14(45.16) | 57(75) | 0.003 |
| Age# | 60.03±15.2 | 62.84±14.89 | 0.381 |
| Follow -up#（month） | 80.74±4.76 | 79.93±5.98 | 0.504 |
| Female | 3(9.68) | 20(26.32) | 0.057 |
| Smoking | 10(32.26) | 28(36.84) | 0.653 |
| Hypercholesterolemia | 10(32.26) | 31(40.79) | 0.410 |
| CHD | 5(16.13) | 16(21.05) | 0.561 |
| HF | 0(0) | 1(1.32) | 0.521 |
| AF | 3(9.68) | 5(6.58) | 0.580 |
| Family History of stroke | 2(6.45) | 11(14.47) | 0.249 |

* Comparison between patients with cerebral ischemic event and patients without recurrent vascular events;
Data are presented as n (%) unless otherwise stated.
# mean ± standard deviation.
CHD= coronary heart disease; HF= heart failure; AF= atrial fibrillation

## DISCUSSION

We found that moderate-high ABCD$^2$ score is associated with an increased risk for vascular events up to 81 months after TIA. Several previous studies have suggested that the ABCD$^2$ score can predict the immediate and short term risks of stroke after a TIA: stroke risks for patients with moderate-high ABCD$^2$ scores at 2 days, 7 days, and 90 days were significantly higher than low

**Table 4: Univariate Cox proportional hazards regression analysis of risk factors for recurrent vascular events**

| Variables | Cerebral ischemic event | | | cerebral / cardiac ischemic events or death from cerebrovascular / cardiovascular cause | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *P* value | HR | 95%CI | *P* value |
| Moderate or high ABCD$^2$ scores | 1.755 | 1.019-3.024 | 0.043 | 1.818 | 1.079-3.063 | 0.025 |
| Age | 1.002 | 0.986-1.020 | 0.776 | 1.004 | 0.988-1.021 | 0.633 |
| Female | 0.799 | 0.415-1.541 | 0.503 | 0.723 | 0.406-1.286 | 0.270 |
| Smoking | 1.457 | 0.884-2.402 | 0.140 | 1.482 | 0.918-2.394 | 0.108 |
| Hypercholesterolemia | 1.401 | 0.844-2.324 | 0.192 | 1.202 | 0.76-1.902 | 0.431 |
| CHD | 1.271 | 0.658-2.455 | 0.475 | 1.421 | 0.805-2.506 | 0.225 |
| HF | 0.855 | 0.118-6.217 | 0.877 | 0.815 | 0.113-5.904 | 0.840 |
| AF | 0.924 | 0.288-2.967 | 0.894 | 1.104 | 0.441-2.763 | 0.832 |
| Family History of stroke | 1.037 | 0.526-2.045 | 0.916 | 0.883 | 0.461-1.694 | 0.709 |

CHD= coronary heart disease; HF= heart failure; AF= atrial fibrillation

$ABCD^2$ scores.[5,11,12] However, few studies have evaluated the $ABCD^2$ score in predicting long-term stroke and cardiac ischemia risk; our findings therefore extend the assessment of $ABCD^2$ score as a potential predictor of long-term recurrent events up to 81 months after a TIA. Furthermore, although stroke typically predominate the early recurrent events after TIA, the risk of cardiac events is also important, and studies have shown that the rate of MI is higher after TIA[2] and cardiovascular disease is the major cause of death on long-term follow-up after TIA.[2-4] Our findings of increased risk of combined recurrent events in patients with moderate-high $ABCD^2$ score is consistent with these studies. One of the important aims of prognostic tools like the $ABCD^2$ score is to identify those individuals who are at risk of developing a potentially avoidable recurrent event and to enable healthcare professionals to institute secondary stroke care and preventive treatments that are individualized to a particular patient's risk profile. The results of our present study suggest that the $ABCD^2$ score may predict not only the short-term stroke risk after TIA[5], but may also predict more generally the combined cerebrovascular and cardiac ischemic risks during long-term follow-up after TIA, and that secondary treatment should also include reduction of cardiac risks. However, further studies with large and representative patient cohorts are necessary to confirm this association and the efficacy of these secondary stroke care interventions.

The proportion of TIA patients with moderate-high $ABCD^2$ scores in our study is 66.36%, which is similar to the published literature.[5,13] However, the proportion of older patients and patients with AF was significantly higher in the moderate-high $ABCD^2$ score group compared to low $ABCD^2$ score (Table 2). Nevertheless, despite significantly older patients in the moderate-high $ABCD^2$ score group, we found that older age alone (Table 3) was not a significant predictor for recurrent events. Although age may be associated with MI after TIA[2], other studies have found no statistically significant predictive value.[13] Furthermore, a recent study found that neither age nor hypertension and diabetes was an independent predictor of subsequent cerebral ischemia or MI after TIA.[14] Since the $ABCD^2$ scoring system is based on five eponymous clinical components ( that is: age, blood pressure, clinical features, duration of symptoms, diabetes), as a whole it take into account these synergistic effects, including age, and thus the combined $ABCD^2$ score may be a better predictor than age alone. Hence, despite our patient sample being slightly biased, our results were consistent with published literature.[13,14] The effect of bias towards 8 patients with AF with moderate-high $ABCD^2$ score (and none with low score), and its possible effect on 8 patients who suffered MI on follow-up (again all in the moderate-high $ABCD^2$ score group and none in the low score group), is more difficult to explain. In our study AF was not a significant predictor of recurrent events partly due to small numbers, and Cox regression analysis was not possible because of the absence of events in the patient group with low $ABCD^2$ score. Although some studies have shown that AF might not be a significant predictor of recurrent events[13,14], MI may be an important cause of death after TIA, especially in later follow-up.[15,16] Hence, emphasis on prevention of cardiovascular events in TIA patients may be reasonable, especially since the assessment of coronary risk in these patients may not be adequately in busy clinical neurological practice. It seems prudent to suggest that further investigation may be warranted to assess the correlation between recurrent MI and cardiac events in patients with AF and TIA.

Our study made use of the new tissue-based definition of TIA, which was endorsed in 2009 by the American Heart Association/ American Stroke Association as it represents an improvement over previous definitions, since it is no longer based on the arbitrary 24-hour duration criterion and more importantly it is compatible with the pathophysiology (i.e. based on objective neuroimaging evidence of ischemia).[7] Increasing and widespread availability of CT and MRI scanners means that brain imaging can be used to stratify whether a particular episode of focal ischemic deficits was a TIA or a cerebral infarction.[7] A recent study of the early stroke risk and $ABCD^2$ score suggested that neuroimaging evidence of infarction in TIA patients may contribute 3 points to the prediction of stroke in the acute phase after initial TIA, and that separation of patients with true infarction from those without, may be valuable for a more accurate prediction of risk and better individualization of secondary stroke care.[8] We believe future studies should use the tissue-based definition.

The present study has several limitations. First, we acknowledge that the generalizability of our findings may be limited since this was a single-center small sample size study and all included subjects were Chinese. A larger, diverse patient cohort would have been necessary to improve the statistical power of the study. Second, the

$ABCD^2$ score was calculated retrospectively on the basis of medical records only and some follow-up was conducted as telephone interview only. This limitation could be overcome in future prospectively designed studies. Third, this study did not take into account the risk of future events associated with intracranial or extracranial artery stenotic or occlusive disease. Future studies should include for analysis neuroimaging data such as computer tomography perfusion (CTP), magnetic resonance-perfusion-weighted imaging (MR-PWI), and magnetic resonance/computed tomography angiography. The addition of the results of artery stenotic or occlusive and neuroimaging may improve the predictive value. Finally, this study did not compare the new tissue-based definition of TIA with the one after traditional time-based definition of TIA.

In conclusion, patients with moderate or high $ABCD^2$ scores are at increased risk of suffering from further vascular events during long-term follow-up up to 81 months after initial TIA. The association between moderate-high $ABCD^2$ score and recurrent vascular events was independent of other conventional vascular risk factors, and more aggressive intervention may be helpful in these patients.

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## DISCLOSURE

Conflict of interest: None

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