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Validity of the International HIV Dementia Scale as Assessed in a Socioeconomically Underdeveloped Region of Southern China: Assessing the Influence of Educational Attainment

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SUMMARY

In 2012, more than 80,000 cases of HIV infection were recorded in the Southern Chinese minority autonomous region of Guangxi Zhuang, where the occurrence of HIV-associated dementia remains high. The International HIV Dementia Scale is a relatively simple-to-administer screening scale for HIV-associated neurocognitive disorders. However, clinical experience in utilizing the scale with large Chinese samples is currently lacking, especially among individuals with limited formal schooling. In this study, a full neuropsychological evaluation the gold standard was conducted to identify the incidence/prevalence of HIV-associated neurocognitive disorders in a socioeconomically underdeveloped region of Southern China and to locate the optimal cut-off scale value using receiver operating characteristic curves. The highest Youden index of the scale was 0.450, with a corresponding cut-off point of 7.25. The sensitivity and specificity were 0.737 and 0.713, respectively. These results suggest that the scale is an effective and feasible screening tool for HIV-associated neurocognitive disorders in poorer regions of China with fewer well-educated residents.

1. Introduction

HIV-associated neurocognitive disorders (HAND) remain prevalent, especially in regions like Guangxi Zhuang, a minority autonomous region in Southern China, where the total number of infections was estimated to be over 80,000 in 2012. Although the incidence of HIV dementia (HAD) has been halved with the use of antiretroviral therapy (ART), its prevalence remains high. Therefore, appropriate brief screening tools are needed in order to facilitate the timely initiation of HAD treatment. The International HIV-associated Dementia Scale (IHDS) was developed in 1995 to screen for HAND[1], and many studies since 2005 have shown the effectiveness of this scale as a screening tool and have demonstrated its satisfactory sensitivity and specificity in a variety of populations.

For example, the sensitivity and specificity of the scale were recorded at 80% and 55% for a Ugandan sample.[2–5] In both American and Spanish-speaking populations,[3–6] the IHDS was also shown to be an effective tool in screening for HIV-associated dementia. Because of its relative ease of use, the IHDS may be applied in regions of Europe and Africa where English is not the first language. According to Antinori, who further studied and revised the HIV Dementia Scale (HDS) and the IHDS, the latter can be used in place of standard neuropsychological tests typically used to diagnose HAND, especially in areas where resources are limited, such as developing countries like Africa and China[7].

However, the outcomes of psychological testing tools are influenced by a range of cultural, linguistic, and regional factors. Validity must be demonstrated in relation to the specific sociocultural environments in which the individuals who are screened with these instruments live. Thus far, the sensitivity and specificity of HAND screening tools such as the IHDS have not been reported for China's vast population. Few studies have examined the administration or use of this scale in a predominantly Chinese-speaking society. As previous research has demonstrated that the results of cognitive function tests may be influenced by the

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subjects' sociocultural status,[8] the diagnostic values of these instruments may vary depending on associated factors, such as the educational levels of the screened individuals.

One of the researchers of the present study, TingTing Zhao, and her research team found 200 cases of HIV infection in 2011 while researching its prevalence in the mountains of Southwest China.[9] When the results were analyzed while controlling for educational background, the diagnostic cut-off score of the IHDS appeared to be 8.25. However, when sociocultural differences or influences were factored in, the prevalence of infection in groups of individuals with different educational levels varied, with different diagnostic cut-off values being identified for each group. Analyzing the IHDS scores of those who had a high school, secondary school, or higher level of education, Zhao and her colleagues found that the scale's diagnostic cut-off was 8.25, whereas this value was 7.25 for individuals with a primary school education.[9]

These results caused us to question the use of a single cut-off point in screening individuals for HAND using the IHDS. More specifically, we were curious about (1) the scale's efficacy in screening for HAND in a Chinese population, (2) its optimal cut-off point when used to screen for HAND in individuals with low levels of education, and (3) whether the IHDS is more efficient in screening for HAND compared to established scales such as the Mini Mental State Examination (MMSE).

This study thus evaluated the diagnostic cut-off of the IHDS in screening for HAND in the multi-ethnic minority autonomous region of Guangxi Zhuang in Southern China, where economic and educational development lag behind those of many of China's other regions. Several studies have shown that although the MMSE is sensitive to cortical dementia, it is only 50% sensitive to diagnosing subcortical dementia, such as AIDS-related dementia.[1] However, the MMSE has been used for many years in China and is the most commonly used cognitive screening tool by clinicians. Our study, therefore, sought to compare the diagnostic values of both the IHDS and MMSE in a large sample of Chinese individuals whose educational levels were lower than those of residents/populations of China's more developed regions.

2. Methods

2.1. Subjects

This study was part of a larger study on HAND conducted in the Guangxi Zhuang autonomous region of Southern China. To summarize, the potential research sample (n = 345, age 18–65 years) was recruited from three health care centers (the Fourth People's Hospital of Nanning, Guangxi Longtan Hospital and the First affiliated hospital of Guangxi Medical University) providing medical services to HIV infected patients. Data collection took place between February 2011 and August 2012. The final research sample, consisted of 230 HIV-infected patients (Figure 1: Flow chart of screening process). We used the following criteria for exclusion from our HIV/AIDS population: (1)Severe physical disease preventing the completion of the study;(2)Nervous system diseases that might lead to cognitive function decline, such as nervous system opportunistic infections, intracranial tumors, history of head trauma, and cerebrovascular diseases;(3)Severe depression, anxiety, or other mental illness affecting cognitive functioning; (4) Other systematic diseases that could damage cognitive functioning, such as thyroid dysfunction; (5) Those whose CSF syphilis antibodies were positive (+) and/or who were unwilling to cooperate with the lumbar puncture; and (6) Presence of achromatopsia or hypochromatopsia.

All participants attended two full study sessions, during which detailed sociodemographic, neuromedical, neuropsychological, and laboratory measures were administered. The evaluations took

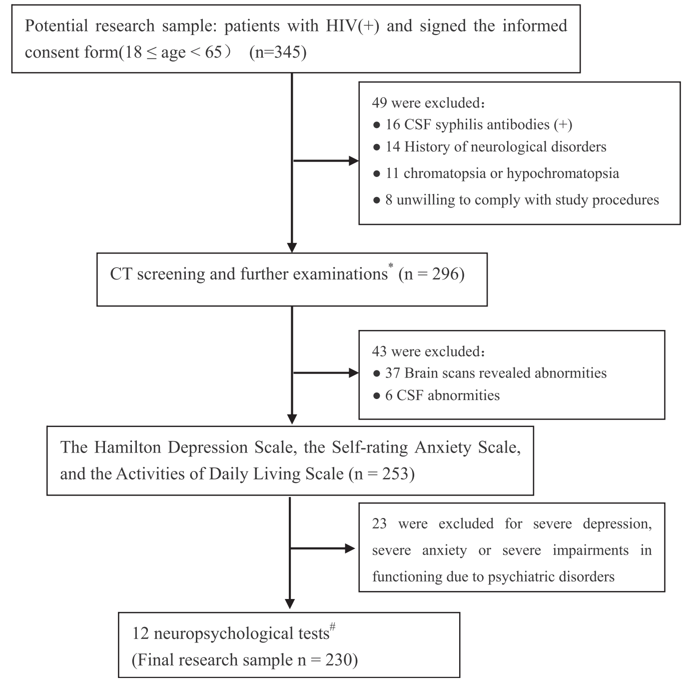

Figure 1. Flow chart of screening process
*Additional MRI (n = 88) and CSF (n = 79) examinations, who was suspected to need them.
#12 neuropsychological tests: The Digit Span Test and Trail Making Part A, Attachment; Immediate Visual and Visual Delayed Memory; Vocabulary and Concept Fluency; Digital Symbols, Wood Puzzles, and Total Arithmetic Scores; and the Stroop Test and the Wisconsin Classification Test.

two to three hours and were conducted by trained technicians in the participants' first language. All subjects received CT screening in the first round, and further testing, including cranial magnetic resonance imaging (MRI) (n = 88), CSF, was administered to any patient who was suspected to suffer from cognitive dysfunction (n = 79). However, due to the limitations of their medical conditions, not all patients evidenced cognitive dysfunction via MRI and CSF examinations. Before administering the tests, we administered the Hamilton Depression Scale, the Self-rating Anxiety Scale, and the Activities of Daily Living Scale to eliminate participants with severe depression, severe anxiety, and severe impairments in functioning due to psychiatric disorders, substance abuse, or significant neurological disorders.

After participants were diagnosed and classified into one of four HAND categories, the possibility of cognitive dysfunction or other brain diseases was ruled out for all of them through a CT examination, in accordance with the updated criteria established through recent research by Antinori et al.[10] In other words, none of the participants showed any sign of asymptomatic neuropsychological impairment (ANI) or mild neurocognitive disorder (MND). All participants who met the study criteria and who agreed to participate provided their written informed consent before they were screened with the IHDS/MMSE and the neuropsychological test battery. Approval to conduct the study was obtained from the Research Ethics Committee of Guangxi Medical University and the relevant clinical authorities.

2.2. Neuropsychological test battery

A neuropsychological test battery was administered to all participants to assess specific domains of neurocognitive functioning(n = 230). The battery consisted of 12 neuropsychological tests covering the Digit Span Test and Trail Making Part A, Attachment;

Immediate Visual and Visual Delayed Memory; Vocabulary and Concept Fluency; Digital Symbols, Wood Puzzles, and Total Arithmetic Scores; and the Stroop Test and the Wisconsin Classification Test. Control data for neuropsychological testing were obtained from 99 HIV-negative participants who were the patients' healthy family members or accompanying persons who tested negative on HIV antibody tests within three months of the study. The control and patient groups did not differ in four areas: age, sex, years of education, and income.

To determine neurocognitive disorder status, we used the above-mentioned neuropsychological test battery and an evaluation of functional assessment the Patient's Assessment of Own Functioning Inventory (PAOFI) and the Quality of Life and Enjoyment Satisfaction Questionnaire (QLESQ). Participants were classified into one of four HAND categories. Individuals who scored more than two standard deviations (SDs) below the mean on at least two domains of function and were noted to have significant functional impairment on self-reports were classified as having HAD. Those who displayed impairment between one and two SDs below the mean were classified as having either MND or ANI, depending on the presence or absence of functional impairment. The remaining participants were classified as non-impaired. The final classification was conducted by two HIV neuropsychiatrists and a neurologist.

2.3. Statistical analysis methods

Data were analyzed using SPSS 17.0. Homogeneity of variance data was described in terms of the mean and standard deviation, which were obtained through analyses of variance and covariance, as well as a comparison of the means. Heterogeneity of variance data was described in terms of the median and interquartile ranges using the rank-sum test. Correlation analyses were performed along with co-correlation analysis.

3. Results

3.1. HIV-related neurocognitive disorder detection rate

This study recruited 329 participants: 99 controls and 230 HIV/AIDS patients. According to the diagnostic criteria of the American Academy of Neurology, a neurologist or a psychological consultant with AIDS nervous system symptom expertise found that 144 (62.60%) HIV-positive patients were without cognitive impairment (UN), and 86 (37.39%) were diagnosed with HAND, including 42 cases of ANI (18.27%), 25 cases of MND (10.87%), and 19 cases of HIV-related dementia (8.26%).

3.2. Test-retest reliability of the IHDS and its items

Test-retest reliability was evaluated using correlation results from Pearson correlation tests performed twice with the same patients within a one-week interval. Surveying errors caused by variations in time or occasion on the two tests indicated testing needed to be implemented within the span of a week. The results are detailed in Table 1. The IHDS and all of its items had good test-retest correlations. Coefficients were greater than 0.75, and correlation hypothesis test P values were less than 0.01. The IHDS total score retest results were the most stable. This correlation coefficient (0.955) was the highest, which suggested greater stability.

The last item on the scale assessed memory recall, whereby patients were asked to recall four words. For words that were not recalled, patients were given prompts containing semantic clues, such as animal (for "dog"), piece of clothing (for "hat"), vegetable (for "bean"), and color (for "red"). They were given 1 point for each

Table 1
Test-Retest Reliability of the IHDS and Its Items

Statistical measure	IHDS	Item 1	Item 2	Item 3
Pearson's correlation coefficient	0.955	0.947	0.910	0.783
P value	0.000	0.000	0.000	0.000

word spontaneously recalled and 0.5 points for each correct answer after prompting. The test-retest reliability of this item was the least stable of all the items on the IHDS, as it had the lowest correlation coefficient (0.783).

3.3. Homogeneity reliability of the IHDS

Cronbach's α coefficient was used to rate the scale's internal consistency. The scale's reliability coefficient was 0.580, indicating that there was unsatisfactory homogeneity bias. Additionally, observations regarding the statistical impact of each item and changes in the mean total score and variance were made via Spearman's correlation coefficient sensitivity analyses for each entry when the item was removed. As shown in Table 2, when Questions 1, 2, and 3 were removed, Cronbach's α coefficients were 0.348, 0.273, and 0.656, respectively.

3.4. Analysis of the validity of the IHDS

The scale's total score, as well as the three individual items, was compared using the F-test in the normal control (HIV-), HIV-positive without cognitive impairment (UN), HIV-associated ANI, HIV-associated MND, and HIV-associated dementia (HAD) groups. The total score of the IHDS and each of its items ($P < 0.05$) were significantly different, suggesting the scale was able to differentiate among the different types of HIV dementia. However, comparisons within each group showed that the IHDS did not distinguish well between varying degrees of severity of HIV-associated dementia. Table 3 displays the concrete test results.

3.5. Diagnostic efficiency evaluations of the MMSE and IHDS

The receiver operating characteristic (ROC) curves for the IHDS and MMSE were drawn from clinical findings, as well as from data from a battery of neuropsychological tests, the gold standard for HAD evaluations (see Figure 2). The areas under the curves were 0.687 and 0.772 when the MMSE and IHDS were used to diagnose the HAD and normal groups. The results suggested that the IHDS possessed stronger diagnostic capabilities than did the MMSE.

Our study also identified the scale's sensitivity and specificity and the Youden index demarcation point within the scope. Table 4 reveals the maximum Youden indexes that were selected as optimal cut-off points for distinguishing the HAD and normal groups using both scales. The highest Youden index of the IHDS was 0.450, with a corresponding cut-off point of 7.25. The sensitivity and specificity were 0.737 and 0.713, respectively. The highest Youden index of the MMSE was 0.358, and its corresponding cut-off point was 24.5. The sensitivity and specificity were 0.474 and 0.884, respectively. In the analysis of the HIV-positive group that included the selection of cut-off points, one decimal was kept, so that the diagnostic cut-off value of the IHDS for the normal group was estimated to be greater than 7.3.

3.6. IHDS scores of AIDS patients with different characteristics

IHDS scores of AIDS patients with different characteristics are shown in Table 4. There was a significant difference between patients who were aged 60 years or above and those below age 60. In addition, there were significant differences between Zhuang

Table 2
Analysis of the Sensitivity of the IHDS and Its Items

Item	Scale mean after this item was removed	Scale variance after this item was removed	Total correlation coefficient of correcting entries	Multiple regression coefficient squared	Cronbach's α coefficients after this item was removed
IHDS FT subscore	5.69	2.028	0.474	0.255	0.348
IHDS hand sequence subscore	5.83	1.366	0.516	0.281	0.273
IHDS 4-word recall	4.46	3.088	0.246	0.065	0.656

Table 3
Comparison of IHDS Total Scores and Individual Item Scores by Participant Group

Item	HIV(n = 99)	UN (n = 144)	ANI (n = 42)	MND (n = 25)	HAD (n = 19)	P value	Comparison between groups*
IHDS score	10.02 ± 1.08	8.22 ± 1.93	8.06 ± 1.94	7.62 ± 1.88	6.53 ± 2.23	0.000	1>2 = 3 = 4>5
IHDS FT subscore	3.24 ± 0.48	2.44 ± 0.88	2.12 ± 0.80	2.04 ± 1.02	2.05 ± 0.85	0.000	1>2>3 = 4 = 5
IHDS hand sequence subscore	3.31 ± 0.55	2.19 ± 1.11	2.38 ± 1.15	2.00 ± 1.16	1.63 ± 1.17	0.000	1>2 = 3 = 4>5
IHDS 4-word recall	3.58 ± 0.50	3.61 ± 0.51	3.54 ± 0.56	3.58 ± 0.66	2.84 ± 1.03	0.000	1 = 2 = 3 = 4>5

* 1 for HIV-, 2 for UN, 3 for ANI, 4 for MND, 5 for HAD.

minorities and Han Chinese (t = 2.386, P = 0.018), and between patients who graduated from junior high school and those who did not (t = -5.754, P = 0.000). However, there were no significant differences between the genders or between patients who smoked and drank alcohol excessively and those who did not (P > 0.05).

4. Discussion

The IHDS is a convenient and effective screening tool for HAND as it has the following characteristics: (1) It was especially developed for subcortical dementia, including HIV/AIDS-related dementia. This considers not only psychomotor and executive ability, but also information processing and language ability; (2) The IHDS, which consists of three main entries assessing four aspects, including memory registration, motor speed, psychomotor speed, and memory recall, is simple and easy enough for non-professionals to implement; (3) As its content basically avoids language and cultural differences, the IHDS can be used worldwide; and (4) The sensitivity and specificity of the IHDS are relatively higher than are those of other HAND measures. Previous studies reporting on the screening performance of the IHDS have noted that its scientific and rational design make it easy to understand and operate. Due to its relative ease of use, it can be applied in Europe and some African regions where English is not the first language. The findings of our study confirm that the scale is an economical, efficient, and well-performing screening tool suitable for use in China.

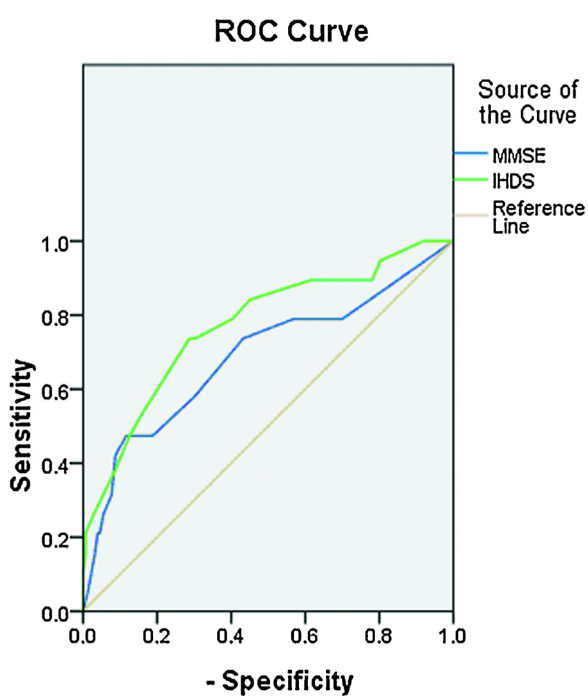

Figure 2. ROC curves of MMSE and IHDS scores.

Generally, scale reliability is considered good when the reliability index is greater than 0.7. The entire scale's test-retest reliability was an optimal 0.949 in this study. The test-retest reliability of items 1, 2, and 3 were 0.940, 0.894, and 0.743, respectively. The test-retest reliability of the entire scale was optimal, but the third item demonstrated less stability than the first two. While the test-retest reliability of each item was better than the scale's homogeneous reliability of 0.580, the third item's test-retest reliability was relatively low.

There are several possible reasons for this low index. First is the reliability coefficients of the scale are related to the number of items it contains; the greater the number of items, the larger the reliability coefficients. Because the IHDS had only three items, its reliability coefficient was low. Second, items included in the analyses of the scale's sensitivity may have also had an impact on reliability coefficients. In this study, we found that if we removed the first and second entries, the homogeneity reliability coefficient was reduced, but when we deleted the third entry from the scale, the scale's homogeneity reliability coefficient rose markedly, from 0.580 up to 0.656. This suggests that the third item may be an important factor that needs to be explored in greater depth.

The results of the discriminant validity analysis revealed significant differences among all the study participant groups, which indicates that the scale's discriminant validity is acceptable. Although the IHDS and MMSE can both be used to screen for HAND across different languages, cultures, and education levels, the IHDS demonstrates better screening capacity compared to the MMSE in our study. Possible explanations for this finding may lie in the fact that the IHDS was especially designed to screen for HIV/AIDS cortical dementia. Second, the IHDS considers not only psychomotor and executive functioning but also subjects' learning and information processing capabilities. The IHDS also contains less content, screening subjects through only 3 items/entries on "memory registration," "psychomotor speed," and "memory recall." In contrast, the MMSE consists of 30 entries, and its contents are more difficult to administer, normally taking about 20–30 minutes to complete.

Finally, as far as our study population is concerned, the IHDS shows a higher degree of sensitivity, specificity, and accuracy in screening for HAND than does the MMSE. Studies on similar populations have indicated that the IHDS has better sensitivity and specificity than the MMSE. Power et al.[1] used the IHDS and MMSE to screen for HIV dementia in the same group of participants in order to compare the effectiveness of both tools. The results showed that the accuracy of the IHDS was superior to that of the other scale (84%, compared to 72%). Ganasen et al.[11] found that the sensitivity and specificity of the IHDS were both 80% in South Africa. Mishra's research indicated that the IHDS, with a sensitivity and specificity of 76.90% and 65% respectively, could be used to effectively screen for HAND in India. The results of the present study show that the IHDS's area under the curve is 0.772, while the MMSE's is 0.687.

Our research team performed a meta-analysis of the IHDS in 2012 and found that the summary ROC (SROC) curve drawn from HAND data demonstrates a sensitivity of 0.90 [95% confidence interval (CI), 0.88–0.91] and overall specificity of 0.96 (95% CI, 0.95–0.97) for the IHDS. The scale's Q*-value is 0.9195, and its diagnostic odds ratio (DOR) is 162.28 (95% CI, 91.82–286.81).[12] A comparison of the ROC curves of both scales in the present study also prompted the conclusion that the IHDS is more effective in screening for HAND than is the MMSE. At the IHDS's optimal cut-off, the sensitivity and specificity of the scale are 73.7% and 69.7%, respectively, whereas the MMSE's are 47.4% and 88.4%.

Currently, the international community recommends a diagnostic cut-off of $\leq$10 points on the IHDS. However, this does not include the influence of educational level, age, ethnicity, and other sociocultural factors in its definition. Cultural differences in terms of educational attainment that exist in different geographical areas may affect the IHDS's diagnostic cut-offs. Several studies performed in underdeveloped regions demonstrated that HIV-positive individuals who scored lower on the IHDS also had lower educational levels, indicating that IHDS scores may be related to the degree of educational attainment. If the cut-off score of $\leq$10 points is applied to HAND diagnoses in underdeveloped regions, false positives may increase. The emergence of false positives will elevate the rate of misdiagnosis and waste limited health resources.

Table 4 depicts the significantly different IHDS scores we observed among individuals with different levels of educational attainment (t = -5.754, P = 0.00). Drenna[13] also found that educational level influenced diagnostic results in India. In addition, the IHDS has been known to not be as sensitive in screening for HAND in populations with middle or high educational levels. If these individuals were assessed with the IHDS on a cutoff of $\leq$10 points, the diagnoses may lead to more false negatives. Thus, different IHDS diagnostic cut-offs should be developed for regions with different cultural and educational backgrounds. The Guangxi Zhuang minority autonomous region, located in a remote mountainous area where poverty is widespread, is known to be socio-economically underdeveloped, as well as having poor natural environmental conditions and limited educational and sociocultural attainment. In the Guangxi Zhuang minority autonomous region, which is ranked second in China in incidence of AIDS, few individuals infected with HIV receive much in the way of schooling.

Our study collected data on 230 cases of HIV-seropositive individuals, of whom only 49 had a high school or higher level of education, accounting for approximately 21.30% of all cases. As a result, the diagnostic cut-off ($\leq$7.25) was ascertained to be lower than the internationally recommended standard of $\leq$10 points. In other words, our study demonstrates the need for exploring not one but a range of diagnostic cut-offs for the IHDS, which suggests that different diagnostic values should be recommended for various populations or groups of individuals with different educational and sociocultural backgrounds. However, which level of educational attainment corresponds with which diagnostic cut-off remains to be determined.

Table 4
IHDS Scores for AIDS patients with different characteristics

Characteristics	Score	t value	P value
Age			
<60 years	8.13 ± 2.05	3.96	0.000
≥60 years	7.05 ± 1.32		
Gender			
Male	7.86 ± 1.96	-1.350	0.178
Female	8.23 ± 2.05		
Ethnicity			
Han Chinese	8.15 ± 2.01	2.386	0.018
Zhuang minorities	7.45 ± 1.86		
Education			
Did not graduate from junior high school	7.33 ± 1.91	-5.754	0.000
Did graduate from junior high school	8.76 ± 1.83		
Smoking			
Smoker	7.75 ± 2.14	0.978	0.329
Non-smoker	8.05 ± 1.95		
Drinking			
drinker	8.02 ± 2.08	0.151	0.880
Non-drinker	7.97 ± 1.98		

5. Conclusion

In the present study, a full neuropsychological evaluation of the gold standard was conducted to identify the incidence/prevalence of HAND in a region of Southern China where residents had limited formal schooling. Additionally, we sought to locate the optimal cut-off value on the scale using ROC curves. Given our Youden index, cut-off point, and sensitivity and specificity values, our results verify the scale's efficacy and feasibility for screening for HAND in underdeveloped regions of China with less educated populations.

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Conflict of interest: The authors declare that they have no conflicts of interest.

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