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Utility of Using the Montreal Cognitive Assessment (MoCA) as a Screening Tool for HIV-Associated Neurocognitive Disorders (HAND) In Multi-Ethnic Malaysia

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Abstract

This study determines the optimal cut-off scores for the Montreal Cognitive Assessment (MoCA) to detect HIV-associated neurocognitive disorders (HAND) in a multi-ethnic Malaysian HIV-positive cohort by developing demographically corrected normative standards among 283 HIV-negative community-based controls with overlapping demographic characteristics. The norms (corrected for age, sex, education, ethnicity) were applied to 342 HIV-positive virally suppressed individuals on cART. Impairment rates were classified using the Global Deficit Score (GDS .5) method. The MoCA was also scored according to the recommended cut-off of 26, and functional decline was applied to both impairment definitions to classify HAND per the Frascati criteria. The 26 cut-off considerably overestimated cognitive impairment in both samples (59.4% HIV-negative; 69.3% HIV-positive). In contrast, corrected scores yielded impairment rates consistent with what has been reported internationally in virally suppressed cohorts (23.4% with 83.3% mild

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Compliance with Ethical Standards

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the University of Malaya and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent It was obtained from all individual participants included in the study.

Conflict of interest All authors declare no conflict of interest.

impairment, 16.7% moderate impairment). A supplemental file allowing the computation of corrected MoCA scores and impairment status is included.

Keywords

Hand; HIV; MoCA; Normative values; Malaysia

Introduction

HIV-associated neurocognitive disorders (HAND) continues to affect up to half of all people living with HIV (PLWH) [1]. Although HIV-associated dementia (HAD), the most severe form of HAND, has decreased markedly in the era of combination antiretroviral therapy (cART), milder forms of neurocognitive impairment continue to persist and adversely impact quality of life, reduce daily functioning, employment and adherence to ART, and increase mortality [2–5].

HAND is typically classified into three categories based on the “Frascati criteria”, which account for disease severity and impact on daily functioning [6]. Optimal diagnostic methods for HAND call for a comprehensive neuropsychological assessment, or the use of screening tools when such assessments are unavailable [6]. Screening tools can assist in quantifying the burden of HAND and help manage neurocognitive impairment in PLWH, especially in resource-constrained settings. However, the Frascati criteria do not provide guidance in how to practically assess the validity of screenings, especially in culturally diverse settings. Two independent systematic reviews of HAND screening instruments in the cART era revealed that not all tools are sensitive to HIV-related cognitive impairment and/or to milder forms of HAND [asymptomatic neurocognitive impairment (ANI)/mild neurocognitive impairment (MND)] [7]. Furthermore, most screening tools have been developed and validated in North America with recommended impairment cut-offs that are dependent on the demographic characteristics of these samples. While impairment cut-offs offer a simple strategy for detecting HAND in busy HIV clinics, they remain as problematic as any cognitive test, including screening tools, because they embed normal demographic effects on performance [8]. When these demographics effects are not corrected for, the detection of impairment in clinical samples are inaccurate [7].

The Montreal Cognitive Assessment (MoCA) has been previously used to detect neurocognitive impairment in the context of HIV infection. When compared to other screening tools, the MoCA is advantageous in that it is relatively comprehensive as it assesses short-term memory recall, visuospatial ability, executive functioning, attention, concentration and working memory, language, and orientation to time and place [9]. A cut-off score of 26 is recommended to detect a mild degree of cognitive deficit [9] and it has been used in PLWH populations [10, 11] with relative success. Although the MoCA was originally developed and standardized in Canada, it is easily adaptable to other languages and cultural settings. Studies in both HIV-positive and HIV-negative populations from Portugal, South Africa and India, however, have shown that age and particularly education influence normative values on the total MoCA score [12–14].

There is a relative paucity of studies examining the ability of screening tools to detect HAND in Asia, where the HIV epidemic burden is only second to that of Sub-Saharan Africa [15]. To the best of our knowledge there has been only one such study conducted in this region—in Singapore where the standard of living is higher than in Malaysia. In the study, the authors used the MoCA, the International HIV Dementia Scale (HDS) and a standard assessment of IADL to categorize HAND. They reported a 22.7% prevalence of HAND, of which 70% were ANI, 23.3% had MND, and 6.7% had HAD [16]. Study investigators used the standard MoCA cut-off 26 to classify impairment, and justified their choice by stating that this cut-off had been validated in an elderly community-based group in an unpublished report. However, when this report was later published it was reported that a large effect of education interfered with the ability to detect mild cognitive impairment in this community-based sample [17]. Therefore, it is unclear what the 22.7% rate of HAND means without normative scores that have been corrected for educational variations in this Singaporean sample. Another multi-site study in the Asia-Pacific region [16] yielded broad regional estimates of neurocognitive impairment based on brief sets of neuropsychological tests but with inadequate cultural adequacy and no norms. Because of the lack of norms, the authors concentrated only on severe impairment and found that 11.7% of patients had severe HIV-related impairment.

Malaysia is a culturally and ethnically diverse country composed of Malay (50%), Chinese (23%), Indian (7%) and indigenous (12%) populations. The prevalence of HIV in Malaysia is 0.4% among the general population, with 91,848 people living with HIV [18]. Similar to other countries, HIV/AIDS in Malaysia is concentrated among key populations of MSM (8.9%), transgender women (5.6%), people who inject drugs (16.3%), and sex workers (7.3%) [19]. A large study to assess the prevalence of HAND in Malaysia has yet to be reported.

Compared to North American cohorts where the MoCA was developed, the Malaysian HIV population is typically younger, includes people with a wider range of educational achievement, and includes an ethnic diversity where persons of Chinese background tend to have more socioeconomic opportunities than their Malay and Indian counterparts [20, 21]. Therefore, it is important to account for this complex demographic diversity when utilizing screening tools because such factors are known to affect normal cognitive performance and thus impact the accuracy of cognitive impairment detection in clinical samples. This strategy also facilitates equitable access of standard neuropsychological methods to diverse populations around the world rather than a select few in western countries.

The specific aims of this study are to first develop demographically corrected scores on the total MoCA score based on 283 HIV-negative participants with overlapping demographic characteristics when compared to the HIV-positive cohort and secondly to apply the demographically corrected scores to HIV-positive participants and then use the Global Deficit Score (GDS .5) method to estimate cognitive impairment rates [22]. Finally, the third aim of the study is to use the GDS impairment classifications and functional decline rates to apply the Frascati criteria in order to estimate the “screen” prevalence of HAND among a fairly representative sample of PLWH in urban Malaysia. To assess the sensitivity and specificity of the demographically corrected impairment rate in the HIV-negative and

HIV-positive samples, we will compare the rates of cognitive impairment using the recommended cut-off score (≥ 26) and the demographically-corrected score.

Methods

Study Design and Setting

This was a cross-sectional study completed between September 2014 and July 2016 at University of Malaya Medical Center (UMMC) in Kuala Lumpur, Malaysia.

Patient Population

The Malaysian HIV and Aging study was established to characterize the extent of geriatric health issues experienced by individuals undergoing routine HIV care through the HIV clinic at UMMC. The clinic provides ambulatory care to approximately 1100 patients in urban Klang Valley region in Kuala Lumpur, Malaysia. All registered patients were invited to participate in the study during their routine follow-up if they fulfilled the following criteria: age at least 25 years, stable on cART, virally suppressed (HIV RNA < 50 copies/mL for at least 12 months), not pregnant, and had no acute infectious illness at recruitment. HIV-negative participants of similar age range were recruited among accompanying friends of the HIV-positive participants, hospital staff volunteers, and among community-dwelling individuals who responded to study fliers distributed in the hospital catchment area. All HIV-negative participants consented to a rapid HIV screening test (Alere HIV Combo, Chiba, Japan) to rule out HIV sero-positivity prior to enrollment. All biomedical screening and neurocognitive assessments were completed at two consecutive clinic visits scheduled within 6 months. All participants provided informed consent, and the protocol was approved by the institutional review board at UMMC (MEC 20151-937).

Ultimately, a total of 342 HIV-positive and 283 HIV-negative participants were assessed. Among the HIV-positive participants, four had a history of drug use, and one had dementia that may have been due to HIV-related opportunistic infection. Because the MoCA has been successfully utilized in populations with dementia and substance abuse disorders, we decided to include them in the HIV-positive group [23, 24]. All HIV-negative participants had no history of drug use, dementia or reported psychiatric illnesses, and were used in creating demographically corrected values.

Study Measures

All participants were administered the MoCA and Lawton Instrumental Activities of Daily Living (IADL) in their preferred language (English, Mandarin or Malay) by trained study personnel. The MoCA takes approximately 10 min to complete, and has 8 subtests to evaluate short-term memory recall (3 points), visuospatial ability and executive functioning (5 points), attention (6 points), concentration and working memory (5 points), language (3 points), abstraction (2 points) and orientation to time and place (6 points). The subtests are summed to create a raw score ranging from 0 to 30.

The IADL evaluates independent living skills as a measure of disease function across 7 domains, with summary scores ranging from 0 to 7. Lower scores are indicative of lower

functional status, and was rated as follows: Total IADL score = 7 = “No IADL Decline”; Total IADL score = 2–6 = “Mild to Moderate Decline”; Total IADL score = 1 = “Severe IADL Decline”. The Lawton IADL was selected because it is widely used in NeuroAIDS studies, and the activities assessed correspond to the everyday life of most Malaysian people.

We also reviewed patient medical records for all HIV-positive participants in order to obtain HIV clinical care data including CD4 T cell count, viral load, and cART status.

Data Analysis

Sociodemographic factors, HIV risk and HIV care are summarized using the mean $\pm$ SD for continuous variables or number and proportion for categorical variables in Table 1.

Significant mean differences were evaluated using a t-test for independent samples and Chi squared test where appropriate.

Cognitive impairment based on MoCA raw scores were evaluated using the published cut-off score of 26, and using global deficit scores (GDS) 0.5 based on demographically corrected T-scores. In order to develop demographically corrected T-scores for the total MoCA score, the raw scores in the HIV-negative sample were converted into normally distributed scaled scores (mean = 10; SD = 3). Next, the effect of age (range 24–81 years), education (primary, secondary; tertiary), ethnicity (Malay, Chinese, Indian) and self-identified gender (male, female) was assessed on the total MoCA scaled score using a standard linear regression analysis. Age [estimate = -0.05 (95% CI -0.07 to -0.02); $\beta = -0.20$; $p < 0.001$], education [estimate = 0.130 (95% CI 0.73 – 1.90); $\beta = 0.27$; $p < 0.001$], ethnicity [estimate = 0.73 (95% CI 0.19 – 1.26); $\beta = 0.15$; $p < 0.001$] and sex [estimate = 0.82 (95% CI 0.15 – 1.50); $\beta = 0.13$; $p < 0.02$] all significantly impacted MoCA performance. Specifically, those of Chinese ethnicity and female participants performed better. First order interactions between demographic factors were tested, but none further explained the model variance. Therefore, the final regression formula to build the T-scores (mean = 50; SD = 10) were corrected for the main demographics, similar to the methods developed by Heaton et al. [25].

The demographically adjusted T-scores were converted into GDS. GDS grades the impairment performance in five categories of abnormalities and collapses normal performance into one category [25, 26]. In this analysis, a deficit score of 0 indicated no impairment (T-scores > 39), 1 indicated mild impairment (T-scores 39 – 34), 2 indicated mild to moderate impairment (T-scores 34 – 29), 3 indicated moderate impairment (T-scores 29 – 24), 4 indicated moderate to severe impairment (T-scores 24 – 19), and 5 indicated severe impairment (T-scores < 19). Deficit scores were averaged into a summary GDS, in which GDS 0.5 represents clinically significant cognitive impairment, and yields adequate sensitivity and specificity [26]. HAND classification was derived using GDS and functional impairment according to the Frascati criteria (Fig. 1a, b) [22]:

- *ANIGDS* MoCA 0.5 and IADL 7 (no IADL decline)
- *MNDGDS* MoCA 0.5 and IADL = 2–6 (mild to moderate IADL decline)
- *HADGDS* MoCA 1.5 and IADL 1 (severe IADL decline).

- *Unimpaired* GDS MoCA < 0.5 and IADL = 7 (no IADL decline or mild to moderate decline)

Results

Cohort Demographic and Clinical Characteristics

Descriptive statistics and sociodemographic factors are described in Table 1. There was no difference in age between the HIV-positive and HIV-negative groups; however, the HIV-positive group had significantly more males, ethnically Chinese, and less educated participants than the HIV-negative group ($p < 0.001$). Participants who are male (62.0%), Chinese (57.6%) and less educated (35.0%) were however well represented in the HIV-negative group meaning that normative reference for these subsets was also valid. The majority of HIV-positive participants had acquired HIV through sexual transmission (96.7%), and had a nadir CD4 T-cell count of min: 0, max: 734, interquartile range: 200.5 cells/ μ L. All HIV-positive participants were virally suppressed, with good immune recovery (current CD4 T-cell count min: 73, max: 1736, interquartile range: 345 cells/ μ L) and virologically suppressed (< 50 copies/mL). When examining functional decline, the majority of HIV-positive participants reported no physical impairment (83.7%).

Cognitive Impairment Rates in the HIV- and HIV+ Samples

When using the total MoCA impairment cut-off score of = 26, it was estimated that 220 (64.3%) of HIV-positive and 170 (59.4%) of HIV-negative individuals were classified as cognitively impaired (OR 1.23 (0.89, 1.71). When using total MoCA demographically corrected T-scores 78 (23.4%) HIV-positive and 40 (14.1%) HIV-negative individuals were classified as cognitively impaired (OR 1.72 (1.14, 2.60) (Fig. 2). After incorporating IADL scores and applying the Frascati criteria to the demographically corrected scores, we found that among the 78 impaired, 65 (83.3%) had ANI, 13 (16.7%) had MND; HAD was not detected in this population (Fig. 3). When using a cut-off score of = 26, impairment was detected in 235 participants, of which 196 (83.1%) were classified with ANI, 37 (15.7%) with MND 3 (1.3%) with HAD.

Discussion

To our knowledge, this is the first study in Malaysia to utilize demographically corrected MoCA scores to determine the prevalence of HAND. We chose to use total MoCA scores rather than any series of sub-scores because the MoCA was validated to be used as a summary score [9]. Moreover, screening sub-scores yield valuable clinical information, however, they are less amenable to developing normative standards because they are based on a restricted set of items.

The total MoCA cut-off score of = 26 dramatically overestimated the rates of low performance in the HIV-negative sample and impairment rate in the HIV-positive sample. In contrast, the demographically corrected rates were in agreement with international HAND prevalence rates in treated and virally suppressed HIV-positive populations [27–31]. Of note the rate of low performance in the HIV-negative sample was determined by design when

building the normative formula to have optimal sensitivity and specificity to at least mild level of cognitive impairment [32].

Probable reasons for the large overestimation of low performance in the HIV-negative sample and impairment rate in the HIV-positive sample relates to the effects of uncorrected demographic factors. When building normative standards, we found that all the considered demographic effects impacted the total MoCA score. Older age and lower education effects on reduced normal performance have already been amply reported on the total MoCA [12–14], however, the effect of ethnicity is new. This effect ought to be interpreted in the particular context of modern Malaysia where it is known that persons of Chinese descent tend to have higher socioeconomic status when compared to their Malay and Indian counterparts [33]. The effect of sex is less easily interpretable and relates perhaps to the fact that the included Chinese HIV-negative women performed particularly well compared to their HIV-negative Malay and Indian counterparts. These observable differences demonstrates that even screening tests can detect complex sociodemographic effects in line with what has been shown in cross-cultural studies using larger neuropsychological test batteries [34]. Care and scientific caution is therefore warranted when interpreting cognitive performance in ethnically diverse samples.

The majority of HAND cases in the cART era are mild, making it imperative to use HAND classification methods that are sensitive enough to detect less overt forms of neurocognitive deficits. Interestingly, the demographically corrected impairment rates generated only ANI and MND classifications when applying the Frascati criteria. The 26 cut-off detected a few cases with dementia showing that this method not only overestimates rates but also inaccurately quantifies severity. Functional decline was used to discriminate between the different categories of HAND and was self-reported using the Lawton IADL. While it is possible that functional ability may have been minimized in some cases due to a lack of insight [35], this scale was chosen because it is widely used, and had demonstrated good cross-cultural validity among Chinese, Malay and Indian communities in ethnically similar Singapore [36]. The fact that the majority of impaired cases were classified as ANI and MND is in line with findings from other virally suppressed cohorts [27–31]. None of the HIV-positive participants were classified as HAD, in contrast to most international cohorts where HAD is typically detected at 2–7% [37]. One potential explanation for this result is that the current cohort did not include demented patients due to an ascertainment bias. Another possible explanation for this observation is increased mortality among the HAD patients due to the later introduction of cART in Malaysia, when compared to most Western countries. A lack of sensitivity to detecting HAD is an unlikely explanation because we detected the milder forms of HAND (ANI, MND) in this population.

Although cut-off scores provide a means to quickly identify cognitive impairment when using screening tools, demographically corrected values enhance the utility of the MoCA in diverse populations. While the demographically corrected method yields a more accurate impairment estimate, it is a method that demands knowledge of quantitative neuropsychology and therefore may not be easily adaptable to busy HIV clinics in resource-constrained settings. To alleviate this problem, we provide a supplemental file with guidelines to perform the demographic corrections and output an impairment status. We

recommend that all care providers be thoroughly trained in using the MoCA prior to using these demographically-corrected values and consult the clinical recommendations to reduce any potential erroneous interpretation and unethical use of the MoCA scores. We also recommend using these formulas in populations who are demographically comparable to that of the current study sample. Moreover, we note that interpretation of cognitive and functional impairment should take place in the wider clinical context of the patient (see Cysique et al. for further recommendations on this point: [38]).

Although this study provides a means to screen for HAND in multi-ethnic Malaysia, several limitations must be noted. We have partly relied on the international literature to determine that our estimate of HAND prevalence was more accurate than the cut-off method. Nevertheless, to be certain, the current MoCA proposed method should be tested against a standard neuropsychological test battery and the gold standard clinical rating. Because of this, we were not able to evaluate the sensitivity, specificity or other indexes of criterion validity using the demographically corrected MoCA in this population. This warrants further investigation, and is an important area of interest as any screening test using the MoCA results will include some false negatives and false positives [7]. For this reason, we recommend that all users of the supplementary file to carefully read the guidelines and clinical recommendations, which emphasize the interpretation of the MoCA score in a wider clinical context. Moreover, the demographic correction eliminated the demographic effects in the HIV-negative sample (all effects $p > 0.95$). However, small effects persisted in the HIV-positive group for ethnicity, education and sex (the normal age effect was entirely corrected). The ethnicity and education effects were the same original direction as the HIV-negative sample and were much smaller. The sex effect however was in the opposite direction to that of the HIV-negative sample meaning that the HIV-positive females performed worse than the HIV-positive men. While it is possible that HIV-positive women in Malaysia are at higher risk of cognitive impairment, this may have been slightly driven by some highly performing women in the HIV-negative group. Alternatively, non-measured socioeconomic and other more complex demographics characteristics may be at play only in the HIV-positive group, particularly in the women (e.g., stigma, health care access) which may yield an additional impact on cognitive performance. Further study will be needed to clarify this issue. Finally, because non-HIV related neurological or psychiatric disorders were not explicitly excluded for, some level of residual confounding may still exist in this population.

Conclusion

The MoCA is a brief screening tool available in multiple languages, and with some training, is easy for clinicians to use as a measure for detecting mild cognitive impairment among HIV populations. It has greater sensitivity in detecting HIV-related cognitive impairment when compared to other measures such as the MMSE and HDS [39, 40]. Taking these advantages into consideration, the current study further improves the utility of the MoCA by developing demographically corrected impairment status in a large Malaysian HIV-positive cohort on cART. With some recognized limitations, this strategy could be applied to more accurately detect HAND in places where standard neuropsychological assessment are not routinely available and help document HAND prevalence internationally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

a Calculation of Global Deficit Scores Carey et al. [26]. **b** Frascati Criteria for HAND classification Antinori et al. [6]

Fig. 2.
Overall impairment rates using standard and adjusted MoCA scores

Fig. 3.
HAND classifications using standard and adjusted MoCA scores

Table 1

Demographics, laboratory and clinical characteristics of the study sample

Characteristic	HIV+ N = 342	HIV– N = 283	p value
Age (mean years $\pm$ SD)	44.7 $\pm$ 10.2	43.8 $\pm$ 13.2	0.33
Gender N (%)			< 0.001
Male	281 (82.2)	175 (61.8)	< 0.001
Ethnicity N (%)			0.001
Malay	64 (18.7)	83 (29.3)	0.002
Chinese	245 (71.6)	169 (59.7)	< 0.001
Indian	32 (9.4)	31 (11.0)	0.510
Highest level of education attained N (%)			< 0.001
Primary	50 (14.9)	17 (6.0)	< 0.001
Secondary	115 (34.3)	80 (28.3)	0.109
Tertiary	170 (50.7)	186 (65.7)	< 0.001
HIV-related characteristics		–	
HIV mode of transmission; N (%)			
Homosexual	141 (41.3)		
Heterosexual	189 (55.4)		
Injection drug user	4 (1.2)		
Other	7 (2.1)		
Nadir CD4 cells/ μ L median [25 th –75 th %]	111 [37–246]		
Nadir viral load log ₁₀ copies/mL (mean $\pm$ SD)	(5.09 $\pm$ 0.70)		
Current CD4 cells/ μ L median [25 th –75 th %]	561.5 [396–739]		
Undetectable Viral Load (< 50 copies/mL) N (%)	321 (93.9)		
Years of living with HIV (mean $\pm$ SD)	(7.81 $\pm$ 4.97)		
Years on cART (mean $\pm$ SD)	(6.3 $\pm$ 4.5)		
Daily functioning N (%)			0.180
No decline (IADL $\geq$ 7)	282 (83.7)	251 (88.7)	0.074
Mild to moderate decline (IADL 2–6)	52 (15.4)	32 (11.3)	0.136
Severe decline (IADL < 2)	3 (0.89)	0 (0)	0.108

cART combination antiretroviral therapy, *IADL* instrumental activities of daily living