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Prevalence of Asymptomatic HIV-associated Neurocognitive Disorder in a Tertiary Care Hospital in South India: A Single Centered Observational Study

Güney Hindistan'daki Üçüncü Basamak Bir Hastanede Asemptomatik HIV ile İlişkili Nörobilişsel Bozukluğun Yaygınlığı: Tek Merkezli Gözlemsel Bir Çalışma

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Abstract

Introduction: Asymptomatic HIV-associated neurocognitive disorder (HAND) is associated with increased morbidity, and it often goes undetected in outpatient clinics due to the lack of awareness and time constraints for a detailed assessment in such cases. We assessed the prevalence of HAND by using Montreal Cognitive Assessment (MoCA) test and evaluated the association between the severity of HIV using CD4 count and cognitive impairment.

Materials and Methods: This cross-sectional study enrolled 103 patients (age: 20-80 years) living with HIV who were sampled through convenient sampling technique. Demographic details such as the age, sex, and education, and the current CD4 count were recorded and the patients were accordingly assigned to the following groups: A (>500 cells/µl), B (200-499 cells/µl), and C (<200 cells/µl) with reference to the Center for Disease Control and Prevention guidelines for the distribution of $CD4^+$T cells in HIV. Cognitive impairment in patients was screened using MoCA with a cut-off score of <26. Data was defined using descriptive statistics, between-group comparison was performed using ANOVA and chi-square tests, and the association between the MoCA score and CD4 count was assessed by using Spearman's correlation coefficient. P<05 was considered to indicate statistical significance.

Results: HIV-associated neurocognitive disorder was prevalent among 73.8% of the sample population, where 8.7% had severe, 18.4% had moderate, and 46.6% had mild impairment. Based on the CD4 count, 10.6% were categorized into group A, 39.8% into group B, and 49.5% into group C. The association of the MoCA score with CD4 count was found to be moderately positive and statistically significant (r^2=0.644, p=0.000).

Conclusion: A high prevalence of HAND, specifically an asymptomatic form, was observed among patients living with HIV. The MoCA score was significantly associated with CD4 count, albeit moderately positive.

Keywords: HIV, neurocognitive disorders, Montreal Cognitive Assessment, prevalence, asymptomatic

Öz

Giriş: Asemptomatik HIV ile ilişkili nörobilişsel bozukluk (AHİNBB) artmış morbidite ile ilişkilidir. Farkındalık eksikliği ve ayrıntılı bir değerlendirme için zaman olmaması nedeniyle polikliniklerde tespit edilememektedir. Bu çalışmada, AHİNBB prevalansını Montreal Bilişsel Değerlendirme (MoCA) testi kullanarak değerlendirmek ve CD4 sayısına göre HIV şiddeti ile bilişsel bozukluk arasındaki ilişkiyi araştırmak amaçlanmıştır.

Gereç ve Yöntem: Yaşları 20-80 arasında değişen, uygun örnekleme tekniği kullanılarak seçilen HIV ile yaşayan 103 hasta üzerinde yapılan kesitsel bir çalışmadır. Yaş, cinsiyet ve eğitim gibi demografik özellikler ve mevcut CD4 sayısı kaydedildi ve hastalar CD4 sayılarına göre, Hastalık Kontrol ve

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Önleme Merkezi yönergelerine dayanarak, A (>500 hücre/µl), B (200-499 hücre/µl) ve C (<200 hücre/µl) olmak üzere gruplara ayrıldı. Hastalara bilişsel bozukluk tanısı koyarken MoCA kesme puanı <26 baz alındı. Veriler tanımlayıcı istatistikler kullanılarak tanımlandı, gruplar arası karşılaştırma ANOVA ve ki-kare testleri kullanılarak yapıldı ve MoCA skoru ile CD4 sayısı arasındaki ilişki Spearman'ın korelasyon katsayısı kullanılarak değerlendirildi. P değeri <0,05 anlamlı kabul edildi.

Bulgular: Asemptomatik HIV ile ilişkili nörobilişsel bozukluk örneklem popülasyonunun %73,8'inde saptandı. Bu hastaların %8,7'sinde ciddi, %18,4'ünde orta, %46,6'sında hafif bozulma tespit edildi. CD4 sayısına göre hastaların %10,6'sı grup A, %39,8'i grup B ve %49,5'i grup C içinde sınıflandırıldı. Montreal Bilişsel Değerlendirme skorunun CD4 sayısı ile ilişkisi orta derecede pozitif ve istatistiksel olarak anlamlı bulundu (r^2=0,644, p=0,000).

Sonuç: Asemptomatik HIV ile ilişkili nörobilişsel bozukluğun HIV ile yaşayan hastalarda yüksek bir prevalansa sahip olduğu gözlendi. Montreal Bilişsel Değerlendirme skoru CD4 sayısı ile anlamlı olarak, orta derecede ve pozitif yönde ilişkiliydi.

Anahtar Kelimeler: HIV, nörobilişsel bozukluklar, Montreal Bilişsel Değerlendirme, yaygınlık, asemptomatik

Introduction

HIV/AIDS is a global threat, with a prevalence of 37.7 million people and an estimated 0.7% adults aged 15-49 years presently live with HIV worldwide. In India alone, 2.3 million people live with HIV, and 64% of them had received anti-retroviral therapy (ART) by 2020[1].

HIV infection can also lead to cerebral manifestations in the form of cognitive, behavioral, motor, and autonomous dysfunctions. These neurological manifestations can be attributed to opportunistic infections due to immune deficiency in HIV patients[2,3]. Before the introduction of combined ART (cART), high viral loads and the resulting inflammation affected the brain, resulting in AIDS dementia[4]. HIV-associated neurocognitive disorder (HAND) is an umbrella term that refers to a range of neurocognitive dysfunction associated with HIV infection[5]. Based on its severity, HAND was classified into asymptomatic neurocognitive impairment, mild neurocognitive disorder (MND), and HIV-associated dementia, with a global prevalence of 23.5%, 13.3%, and 5.0%, respectively[4,6]. Based on the central nervous system (CNS) HIV Antiretroviral Therapy Effects Research (CHARTER) study, the prevalence of asymptomatic or mild HAND in adults was found to be approximately 50% despite being on cART[7]. Hence, early diagnosis of HAND is essential to prevent the worsening of symptoms and may reduce the associated morbidity. Symptomatic or mild HAND often goes undiagnosed in a busy outpatient clinic manned by physicians/infectious diseases specialists who lack expertise in the cognitive domain of their patients. This study was conducted to assess the prevalence of HAND using a simple and validated tool that can be used by physicians in an outpatient clinic.

HIV infection can cause immune system dysfunction by infecting and destroying $CD4^+$T cells, eventually leading to immune deficiency[8]. CD4 count is performed to identify the clinical status of HIV patients[9,10]. A meta-analysis reported increased presence of HAND in patients with a low nadir CD4 count[6]. Hence, we studied the association between HAND and CD4 count in this study.

Materials and Methods

This was a cross-sectional observational study, approved by PSG Institute of Medical Sciences and Research Institutional Human Ethics Committee (project no. 16/031, date: 21.01.2016), and conducted in a tertiary care teaching hospital in South India. The study included patients living with HIV, aged 20-80 years, who attended the general medicine outpatient department from April to September 2019. The patients were sampled through convenient sampling technique and enrolled after obtaining their written informed consent. Patients with CNS opportunistic infections, stroke, or history of any other neurological, psychiatric illnesses or addiction to alcohol, tobacco or other recreational drugs were excluded from the study.

The sample size was calculated as described previously by Chan et al.[11], using the following formula:

$$n = \frac{Z_{1-\frac{\alpha}{2}}^2 * P(1-P)}{d^2}$$

Where, **n** is the sample size required, **P** is the proportion, is the standard normal variate corresponding to level of confidence, d is the error term.

Based on the study of Chan et al.[11], the prevalence of HAND in South Asia was determined to be 22.7%, with a 95% confidence level and a relative error of 25% of prevalence, and the sample size was calculated as follows:

$$n = \frac{(1.96)^2 * 0.227(1-0.227)}{(0.06)^2}$$

n=95.53

By assuming inadequate samples as 7.5%, the final sample size will be 103 cases.

Demographic details such as age, sex, and education, as well as the clinical data including the latest CD4 count and the current therapy were recorded. Based on the Center for Disease Control and Prevention guidelines for the distribution of $CD4^+$T cells in HIV, the patients were categorized into the following three

groups: A (>500 cells/µl), B (200-499 cells/µl), and C (< 200 cells/µl)[12].

Cognitive impairment in patients was screened by using the Montreal Cognitive Assessment (MoCA), whereby the patients were subjects to different tasks to evaluate their short-term and delayed memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to space and time. The score range for the assessment was 0-30, with higher scores indicating better cognition. Patients scoring ≥26 were categorized as normal, 18-25 as with "mild cognitive impairment", 11-17 as with "moderate cognitive impairment," and ≤10 as with "severe cognitive impairment"[13,14].

Statistical analysis

Data was analyzed using Statistical Package for the Social Sciences version 19.0. The data was defined using descriptive statistics. Between-group comparisons of continuous variables were performed by one-way analysis of variance (ANOVA) with post-hoc (Bonferroni) analysis. The categorical variables were compared using Chi-square test. The association between the MoCA scores and CD4 count was initially verified using Pearson's correlation coefficient (r^2) and expressed in graphical representation (Scatter plot diagram). Logistic regression analyses were performed to evaluate the confounding effects of variables such as the age, sex, and education level on the association. The adjusted odds ratio (OR) and 95% confidence interval (CI) was used to express the risk levels for each category of severity of cognitive impairment with a change in the CD4 count. P<0.05 was considered to indicate statistical significance. A receiver operating curve (ROC) was generated to evaluate the sensitivity of CD4 count for the detection of cognitive impairment in all patients.

Results

Among the HIV patients who visited the outpatient department between April and September 2019, 103 consented to participate in the study; they had a mean age of 44.35±11.8 years and the majority of them were males (60.2%, n=62) and 27.18% of the participants had consumed alcohol. A majority of the participants did not suffer from any kind of comorbidity (69.90%), but the most common comorbidity among those who reported it was type 2 diabetes mellitus (24.17%). Most of the patients were on TDF/3TC/EFV (tenofovir disoproxil fumarate/lamivudine/efavirenz) treatment regimen. Among the 103 patients, most of them were graduates (64.1%, n=66) and the remaining had school-level education (35%, n=36), except that one was uneducated and could not read/write/speak in English (1.0%). The Tamil validated version of MoCA was administered to this patient[15]. The mean MoCA score across the study population was 21.35±5.78, where 8.7% had severe, 18.4% had moderate, and 46.6% had mild impairment. The mean CD4 count was 256.4±204.8 cells/µl, and the majority (58.3%, n=60) of them had a count of <250 cells/µl (Table 1).

Based on the CD4 count, 10.6% were categorized in group A (n=11), 39.8% in group B (n=41) and 49.5% in group C (n=51). On analyzing the difference in severity among the different age, sex, education levels, CD4 count, and MoCA scores across the groups, significant difference in age (p=0.0001), CD4 count (p=0.0001), and MoCA scores (p=0.0001) were observed (Table 2). On post-hoc analyses using Bonferroni multiple-comparison test, the difference in age between groups A and B, as well as between A and C were not found to be significant. The difference in the MoCA scores between groups A and B were also not significant (Table 2).

Using Spearman's Rho correlation coefficient, a statistically significant moderately positive association was detected between the MoCA score and CD4 count (r^2=0.644, p=.000). Using one-way ANOVA analysis, the mean age was found to be significantly different across MoCA severity (p=0.003) and the median CD4 count (p=0.000) (Table 3).

Table 1. Characteristics of the study population

Variables		n=103 (%)
Age (mean±SD in years)		44.35±11.8
Gender	Male	62 (60.2%)
	Female	41 (39.8%)
Education	Illiterate	1 (1.0%)
	School education	36 (35%)
	Graduate	66 (64.1%)
	Higher education	0 (0.0%)
Comorbidities	Type 2 diabetes mellitus	25 (24.27%)
	Subclinical hypothyroidism	15 (14.56%)
	Coronary artery disease	4 (3.88%)
	None	72 (69.90%)
Alcohol consumption		28 (27.18%)
Mean nadir CD4 count		185.20
MoCA score (mean±SD)		21.35±5.78
MoCA score >26 (no impairment)		27 (26.2%)
MoCA score ≤25 (impairment-all severity)		76 (73.8%)
MoCA score 19-25 (mild impairment)		48 (46.6%)
MoCA score 11-18 (moderate impairment)		19 (18.4%)
MoCA score <11 (severe impairment)		9 (8.7%)
CD4 count	Mean±SD in cells/µl	256.4±204.8
	<250 cells/µl	60 (58.25%)
	≥250 cells/µl	43 (41.75%)

SD: Standard deviation, MoCA: Montreal Cognitive Assessment

Table 2. Comparison of the general characteristics and cognitive impairment between the study groups based on their CD4 count

Variables		Group A (n=11)	Group B (n=41)	Group C (n=51)	p value
Age		41.6±10.3	39.1±11.5	49.1±10.6	**0.0001***
Gender	Male	4 (36.4%)	15 (36.6%)	22 (43.1%)	0.791
	Female	7 (63.6%)	26 (63.4%)	29 (56.9%)	
Education	Illiterate	0 (0.0%)	1 (2.4%)	0 (0.0%)	0.163
	School	4 (36.4%)	9 (22.0%)	23 (45.1%)	
	Graduate	7 (63.6%)	31 (75.6%)	28 (54.9%)	
CD4 count		697.7±158.9	332.2±82.2	100.2±51.8	**0.0001***
MoCA score		25±4	24.4±3.2	18.06±5.8	**0.0001***

*Indicates significance at p<0.05.
Group A- CD4 >500 cells/µl.
Group B- CD4 200-500 cells/µl.
Group C- CD4 <200 cells/µl.
MoCA: Montreal Cognitive Assessment

Table 3. Association of MoCA severity with the age and mean CD4 count

MoCA score	Variable	Min	Max	Mean (SD)	Median (IQR)	p value
Severe impairment	Age	38	64	52.3 (8.1)	53 (47-57)	**0.003†**
	CD4 value	26	132	71.3 (37.3)	68 (41-96)	**0.000‡**
Moderate impairment	Age	21	68	49.3 (12.4)	52 (41-61)	
	CD4 value	34	562	140.2 (117.9)	116 (68-168)	
Mild impairment	Age	22	77	44.7 (13.5)	43 (32-56)	
	CD4 value	3	1020	234.6 (190.5)	199 (125-290)	
Impairment	Age	29	52	41.8 (9.4)	42 (35-51)	
	CD4 value	22	806	255.6 (231.5)	165 (105-345)	
No impairment	Age	24	54	38.7 (8)	41 (32-45)	
	CD4 value	71	922	430.9 (174)	413 (332-470)	
Overall	Age	77	21	44.3 (11.9)	43 (35-53)	
	CD4 value	1020	3	256.4 (204.8)	202 (96-365)	

†One-way ANOVA performed for significant mean age among the MoCA score severity.
‡Non-parametric test-Kruskal-Wallis was performed for significant median CD4 count among MoCA score severity.
MoCA: Montreal Cognitive Assessment, SD: Standard deviation, Min: Minimum, Max: Maximum, IQR: Interquartile range

Furthermore, using univariate logistic regression analysis, the age and CD4 count was found to significantly affect the severity of MoCA scores. Unadjusted OR revealed that the odds of abnormal scores was 1.06-times higher, with every 1 unit/year increase in age. Similarly, in patients with a CD4 count <250 had increased odds for cognitive impairment compared to those with a CD4 count of ≥250 (OR: 40.28; 95% CI: 10.63-266.09). Moreover, on multiple logistic regression analysis, the adjusted OR for abnormal scores was 34.47 (95% CI: 9.94-229.61) for patients with a CD4 count of <250 compared to those with a CD4 count of ≥250 (Table 4). Finally, an ROC curve revealed the optimum cut-off value of CD4 count at the maximum specificity and sensitivity for identifying cognitive impairment using MoCA scores of 309 (area under the curve=0.87; 95% CI: 0.78-095) (Figure 1).

Discussion

HIV-associated neurocognitive disorder persists globally even in the cART era. Although severe forms of HAND such as HIV-associated dementia are rare among HIV-infected population, milder forms of this disease, such as NCI, have been increasingly prevalent[6]. The detection of asymptomatic or mild NCI has been difficult in busy clinical settings, owing to the lack of specific or sensitive biomarkers[3], thereby necessitating the importance of conducting simple tests and tools that can be easily incorporated in the routine check-ups of HIV patients.

Most of the patients included in the present study were on an Efavirenz-based regimen. It is associated with neurocognitive issues, but it was accounted for as participants with neuropsy-related symptoms were excluded from the study. In addition,

Table 4. Factors affecting the severity of cognitive impairment based on the MoCA scale

Factor	Sub-category	MoCA scale		OR [95% CI]	p value
		Abnormal	Normal		
Age (in years)	Intercept			0.21 [0.03, 1.24]	0.0911
	Mean±SD	46.36±12.43	38.7±7.96	1.06 [1.02, 1.11]	**0.0054***
Gender	Intercept			3.10 [1.58, 6.66]	0.0019
	Male	45 (72.58%)	17 (27.42%)	0.85 [0.34, 2.09]	0.7323
	Female	31 (75.61%)	10 (24.39%)		
CD4 count	Intercept			0.72 [0.39, 1.31]	0.288
	<250	58 (96.67%)	2 (3.33%)	40.28 [10.63, 266.09]	**<0.0001***
	≥250	18 (41.86%)	25 (58.14%)		
Multivariate model					
Factor	**Sub-category**			**AOR [95% CI]**	**p value**
Age (in years)	Intercept			0.15 [0.01, 1.35]	0.101
				1.04 [0.99, 1.10]	0.928
Gender	Male			0.95 [0.29, 3.09]	0.127
	Female			Reference	
CD4 count	<250			34.47 [9.94, 229.61]	**<0.0001***
	≥250			Reference	

"Normal" in MOCA scale considered as a reference.
*Indicates significance at p<0.05.
OR: Odds ratio, AOR: Adjusted OR, CI: Confidence interval, MoCA: Montreal Cognitive Assessment

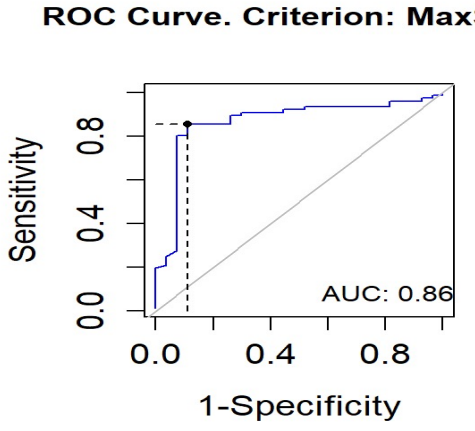

Figure 1. Receiver operating curve for the optimal CD4 cut-off value for determining HAND

HAND: HIV-associated neurocognitive disorder

23 patients on raltegravir-based regimen were included in the study.

The application of a comprehensive neuropsychological battery of tests has been reported as the gold standard to determine severe cognitive impairment in HIV patients. Tests such as HIV dementia scale (HDS), International HIV Dementia scale (IHDS), CogState computerized battery, and Mini-mental state examination (MMSE) have been applied to extensively determine HAND. Although considered as the gold standards, these tests, especially HDS and IHDS, have been deemed useful to efficiently detect severe NCI or dementia, but not the other milder forms[16,17]. The present study employed the MoCA, which is widely applied in several countries to effectively detect HAND with a higher sensitivity[18]. General cognitive dysfunction that amounts to milder forms of HAND can be determined using MoCA[19].

Using <26 as the cut-off score for MoCA, the present study found that HAND was prevalent in 73.8% of the study sample composed of HIV patients from South India. Among them, the majority had mild impairment (46.6%), followed by moderate (18.4%) and severe (8.7%) impairments. Another study conducted in Uttar Pradesh, India, reported a 52.5% prevalence of HAND among people with HIV, where the majority of the patients were diagnosed with asymptomatic NCI (47.5%) and the remaining had MND (5%), using a MoCA cut-off score of <26[20]. Past studies conducted in Central India reported a prevalence of 16.66%, and another in Uttar Pradesh, India of 21%[21,22], which were both lower than that observed in the present study. These studies[21,22], however, employed MMSE and IHDS to screen the patients for HAND, which are reportedly not efficient in identifying the mild forms of HAND. Another study conducted in South India, reported a lower prevalence of 33%, which was re-assessed by using the International Neuropsychological Test Battery translated to the native language[23]. The difference in the prevalence observed here can be attributed to the scales employed, which consisted of long-test batteries.

While MoCA is an efficient tool to assess mild cognitive impairment, the use of appropriate cut-off scores is necessary to negate false positives, and a cut-off score <26 has been suggested for the optimal identification of HAND[19]. A Malaysian study reported the overestimation of cognitive impairment in both HIV+ and HIV- sample when the cut-off score was ≤26. However, on correcting the demographic factors, they obtained lower MoCA scores[24]. Other studies have reported insufficiency of MoCA alone to diagnose HAND, indicating the need for other tools to confirm the diagnosis[19,25].

Along with the prevalence of HAND using MoCA scores, the current study revealed a statistically significant and moderately positive association of severity of HAND with the CD4 count, in that a lower count of CD <250 cells increased the odds of HAND by approximately 40.28-times based on the MoCA scores. Similar study conducted in Shimla, India, using the IHDS scale, reported severe HAND among patients with a CD4 count of <150/mm^3[26]. A recent meta-analysis reported HAND to be low among patients with a high nadir CD4 count and *vice-versa*[6]. The present study finding was consistent with that of the CHARTER study, which reported a higher rate of cognitive impairment with a lower nadir CD4 count[7]. A study conducted in Central India using MMSE for HAND reported a significantly lower mean scores in patients with a CD4 count of <500 when compared to the higher CD4 counts[22]. The AUC in the present study using MoCA scores was 0.87, which was closer to that of the scales such as IHDS, (0.73), frontal assessment battery (0.81), as reported in a study that compared the old and new scales for screening HAND[27]. Despite the differences in the scales used to evaluate HAND, lower levels of CD4 count have been consistently reported to be associated with HAND, although the association of CD4 with the severity of HAND warrants further exploration.

In this study, the study participants were screened for secondary causes of cognitive impairment in HIV, such as the use of drugs, opportunistic infections, and diagnosis of depression, and eliminating these factors provided robust evidence of cognitive impairment primarily related to HIV. More than a quarter of all included participants consumed alcohol, but none reported the use of any other recreational drugs. None of the included participants suffered from any type of opportunistic or endemic CNS infection. This study reflected a real-time scenario in an outpatient clinic, where the unsuspected and undiagnosed HAND was detected using a simple tool such as MoCA. This study highlights the necessity to screen for HAND owing to its high prevalence, especially in the asymptomatic category. Utilizing MoCA for the initial screening of HAND followed by detailed neuropsychiatric evaluation for the confirmation of HAND could help in the early identification and intervention.

Study Limitations

The major limitations of using neuropsychological tests such as MoCA is that deficits in the executive functions are not specific to cerebrovascular diseases as well as the bias noted in individuals with certain levels of education or cultural backgrounds affecting the accuracy of the assessment[28]. The present study also included the use of efavirenz, which has been shown to lower neurocognitive functioning and have side effects such as confusion, dizziness, and impaired confusion, which may have affected the present results[29]. The present study did not perform detailed evaluation on the sample, rendering the diagnosis of HAND provisional and less accurate for inferential statistics such as predictive analysis. The sensitivity and specificity of the cut-off score of MoCA employed for the diagnosis of HAND within this cohort was, thus, not assessed. The patients undergoing different ART were not evaluated for the difference in severity.

Conclusion

In conclusion, a high prevalence of HAND was observed among seropositive patients that could have otherwise remained undiagnosed and untreated. Future studies are thus warranted to validate the present findings in a larger sample size from an Indian context and perform predictive analysis after detailed neuropsychiatric evaluation.

Ethics

Ethics Committee Approval: The study was approved by the PSG Institute of Medical Sciences and Research Institutional Human Ethics Committee (project no. 16/031, date: 21.01.2016).

Informed Consent: The patients were sampled through convenient sampling technique and enrolled after obtaining their written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.P.C.J.D., A.N., Concept: Y.C., A.N., P.V., M.A., Design: N.S., Y.C., C.P.C.J.D., P.V., M.A., Data Collection or Processing: N.S., Y.C., P.V., B.K., Analysis or Interpretation: N.S., Y.C., C.P.C.J.D., B.K., Literature Search: N.S., Y.C., A.N., P.V., B.K., M.A., Writing: Y.C., C.P.C.J.D., A.N., B.K., M.A.

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