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Diagnostic value of vietnamese smell identification test in Parkinson's disease

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ABSTRACT

Introduction: The Vietnamese Smell Identification Test (VSIT) has been validated in determining olfactory dysfunction in the Vietnamese population; however, its value in diagnosing Parkinson's disease (PD) has not been established.

Methods: This case-control study was conducted at University Medical Center HCMC, Ho Chi Minh City, Vietnam. The study sample included non-demented PD patients and healthy controls (HC) who were gender- and age-matched. All participants were evaluated for odor identification ability using the VSIT and the Brief Smell Identification Test (BSIT).

Results: A total of 218 HCs and 218 PD patients participated in the study. The median VSIT and BSIT scores were significantly different between PD and HC groups (VSIT, 5 (3) vs. 9 (2), $P < 0.0001$; BSIT, 6 (3) vs 8 (2), $P < 0.0001$). Using the cut-off of <8 for correct answers out of 12 odorants, the VSIT had higher sensitivity (84.4%) and specificity (86.2%) than those of the BSIT (sensitivity of 81.7% and specificity of 69.3%) for the diagnosis of PD. The area under the curve (AUC) value was greater for the VSIT than for the BSIT (0.909 vs 0.818). The smell identification scores were not significantly correlated with disease duration, disease severity, or LEDD (all $p > 0.05$).

Conclusion: The VSIT can be a valuable ancillary tool for supporting the diagnosis of PD in Vietnam. Olfactory dysfunction in PD was unrelated to the disease duration and severity. The VSIT can be applied to improve the accuracy of clinical PD diagnosis.

1. Introduction

A prominent non-motor symptom in patients with Parkinson's Disease (PD) is the loss of smell. From 70 to 96.7% of patients with PD have been shown in previous studies to experience olfactory dysfunction [1–3]. The importance of hyposmia as a cardinal symptom of PD is further hightlighted by its inclusion into the International Parkinson's Disease and Movement Disorder Society 2015 Diagnostic Criteria [4]. Yet, despite the overwhelming prevalence of this symptom, many patients with PD are unaware of their olfactory dysfunction until they receive formal olfactory dysfunction testing [5,6].

Many different smell identification tests are available to assess olfactory dysfunction for patients with PD. These tests include: the UPSIT (University of Pennsylvania Smell Identification Test), the BSIT (Brief Smell Identification Test), and the SIT (Sniffin' Sticks Test) [7–9]. These mainstay assessment methods were all developed in Western countries and have not been previously validated in a Vietnamese patient population [10]. Previous research has adopted a smell identification test specific to the Vietnamese patient population. The 12-item Vietnamese smell identification test (VSIT) was developed using odors that are familiar, well-recognized, and pleasant to Vietnamese patients [10].

Many studies showed that various smell identification tests could discriminate PD from healthy individuals [11,12]. Although the VSIT

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has been validated in determining olfactory dysfunction in the Vietnamese patient population, its value in diagnosing PD has not been assessed [10]. Therefore, this study aimed to investigate the diagnostic value of the VSIT in the PD population. In addition, the VSIT was also compared with the BSIT in discriminating patients with PD from healthy controls.

2. Materials and methods

This case-control study was conducted at the University Medical Center HCMC, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam.

2.1. Participants

The study patient population included 218 non-demented patients with PD and 218 healthy control (HC) volunteers who were matched by gender and age. The control subjects were recruited from healthy hospital staff members or patient caregivers without any neuropsychiatric disorder or olfactory dysfunction.

Patients with PD were recruited from the Parkinson's Disease and Movement Disorders Clinic at University Medical Center HCMC, Ho Chi Minh City, Vietnam. The PD diagnoses were made by neurologists who specialized in movement disorders according to the International Parkinson's Disease and Movement Disorder Society 2015 Diagnostic Criteria [4]. None of the patients had undergone functional neurosurgery for PD.

Exclusion criteria were established according to factors that have been shown to influence olfactory function. Exclusion criteria for both groups were as follows: (1) the presence of cognitive impairment (Mini Mental State Examination (MMSE) score of 24 or less, (2) upper respiratory tract infections within the two weeks prior to testing, (3) history of chronic nose/sinusoid diseases, diabetes mellitus, nasal surgery, nasal or head trauma, (4) pregnancy, (5) medication use that might affect olfactory function. Patients with a previous history of Covid and hyposmia were excluded from the study. Patients with a history of viral infection within 2 weeks prior to enrollment were also excluded. The exclusion criterion for the control group was a medical history or family history of neurologic and/or psychiatric disorders.

All participants provided written informed consent. The protocol was approved by the Ethics Committee of the University Medical Center HCMC, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (688/HĐĐĐ-DHYD). This study was registered with ClinicalTrials.gov, using the NCT number “NCT05837637”.

2.2. Outcome measures

Information on socio-demographics, including age, gender, level of education, place of residence, and smoking history of both groups and disease-related characteristics of the PD group were collected. Participants' cognition was assessed using the MMSE. Patients with PD were also evaluated for Hoehn and Yahr (H & Y) staging and the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). All assessments were performed under ongoing treatment in the “ON” state of medication. Levodopa equivalent daily dose (LEDD) was calculated as suggested by Stefanie and colleagues in 2023 [13]. All subjects underwent olfaction evaluation using the VSIT and the BSIT.

1. The MDS-UPDRS was used to assess motor and non-motor symptoms.
2. The MMSE was used to evaluate cognitive function. The maximum score for the MMSE is 30. A score of 24 or less indicates cognitive impairment.
3. The H & Y scale was used to evaluate the stage of PD.
4. The VSIT and BSIT were used to assess olfactory function.

Odorants of the VSIT were presented in cotton buds, including orange, banana, soy sauce, fish sauce, garlic, coffee, lemon, apple, guava, mango, fish, and watermelon. These cotton buds were packaged in sterile, non-volatile sachets. To perform the test, investigators tore the outer package and placed the bud of the cotton swab approximately 2 cm in front of the participants' nostrils for 2–3 s. The participants were requested to identify the smell by choosing the correct odor from four descriptors presented in multiple forced-choice designs. The score was based on the number of items correctly answered and ranged from 0 to 12. The score corresponds to the participant's olfactory function [10].

The Sensonics company supplied the BSIT, and the test was performed according to the manufacturer's instructions. The 12 odorants in the BSIT include cinnamon, turpentine, lemon, smoke, chocolate, rose, thinner, banana, pineapple, onion, gasoline, and soap. Odorants are microencapsulated on the paper, and odors are released when the subject uses a pencil to scratch the microcapsule coating. Odorants were placed 2 cm from both nostrils, and participants were asked to select the correct smell from four possible alternative answers for each odorant. Each correct answer was given one mark, so a total score ranged from 0 to 12 [9].

2.3. Statistical analysis

Data analysis was performed using SPSS 20.0 software (IBM Corp. Released 2011). For descriptive statistics, quantitative variables with normal distribution (based on the Kolmogorov–Smirnov test) were reported by means and standard deviations (SD). Median and interquartile range (IQR) were used to describe non-normally distributed continuous variables. The chi-square test was used for the pairwise comparison of frequencies of categorical variables, including level of education, place of residence, and smoking history. Age, MMSE, VSIT scores, and BSIT scores for the PD and control groups were compared using the Mann-Whitney U test. The Spearman rank correlation coefficients were used to explore correlations between VSIT scores or BSIT scores and disease-related factors, including age, age of onset, disease duration, LEDD, H & Y stage, and MDS-UPDRS part III. The correlation between smell identification scores and the H & Y stage was examined using the Kruskal-Wallis test.

A receiver operating characteristic (ROC) curve was used to evaluate the performance of the VSIT and the BSIT in detecting individuals with PD. The sensitivity and specificity of the VSIT and the BSIT were calculated at each cut-off point. The Youden Index was also calculated to choose the best cut-point. Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value for PD were also calculated for each item. Pearson's chi-squared test was used to compare the percentage of the HC group and PD patients who correctly identified each item of the VSIT. The area under the receiver operating characteristic curve (AUC) was calculated for each VSIT and BSIT item. The level of significance was set at <0.05.

3. Results

3.1. Demographic and clinical characteristics of participants

A total of 218 patients with PD and 218 HC volunteers were enrolled in the study. The median ages of the PD and HC groups were 61.5 (14) years and 60.0 (13) years, respectively. A majority of the participants were women (53.7%). The median disease duration of patients with PD was 3.0 (4) years. The median LEDD was 500.0 (362.5) mg. According to H&Y staging, 7 (3.2%) patients were in stage 1, 167 (76.6%) in stage 2, 42 (19.3%) in stage 3, and 2 (0.9%) in stage 4. The median MMSE scores for the PD and HC groups were 28 (3) and 30 (2), respectively.

There were no statistically significant differences between the PD and HC groups regarding sex, age, level of education, place of residence, or smoking history (all $P > 0.05$). The demographic and clinical information of the study subjects is presented in Table 1.

Table 1
Demographic and clinical characteristics of PD and HC groups.

Variables	PD group (*N* = 218) N %/Median (*IQR*)[a]	HC group (N = 218) N %/Median (IQR)	PD & HC groups *P* value
Sex			
Male	101 46.3%	101 46.3%	1[e]
Female	117 53.7%	117 53.7%	
Age (Year)	218 61.5 (14)	218 60.0 (13)	0.786[f]
Level of education			
Second school and	114 52.3%	127 58.3%	
lower	58 26.6%	44 20.2%	0.27[e]
High school	46 21.1%	47 21.5%	
Diploma and higher			
Smoking history			
Yes	38 17.4%	43 19.7%	0.54[e]
No	180 82.6%	175 80.3%	
Place of residence			
Urban	119 54.6%	118 54.1%	0.92[e]
Rural	99 45.4%	100 45.9%	
MMSE[b]	28 (3)	30 (2)	<0.0001[f];
Duration of illness (Year)	3 (4)	–	–
Hoehn & Yahrs stage		–	–
(ON)	7 3.2%		
1	167 76.6%		
2	42 19.3%		
3	02 0.9%		
4			
MDS-UPDRS[c] I (ON)	6 (6)	–	–
MDS-UPDRS[c] II (ON)	8 (6)	–	–
MDS-UPDRS[c] III (ON)	36 (14)	–	–
MDS-UPDRS[c] IV (ON)	0 (3)	–	–
MDS-UPDRS[c] total (ON)	52.5 (23)	–	–
LEDD[d] (mg/d)	500.0 (362.5)	–	–

[a] Inter-quartile range.
[b] Mini-Mental State Examination.
[c] Movement Disorder Society-Unified Parkinson's Disease Rating Scale.
[d] Levodopa equivalent daily dose.
[e] χ^2 test for categorical variables.
[f] Mann Whitney *U* test.

3.2. Comparison of odor identification ability between the PD and HC groups

The median score of the VSIT was significantly lower in PD patients than in controls (5.0 (3.0) & 9.0 (2.0), P < 0.001). The same was true for BSIT scores (P < 0.0001; patients: 6.0 (3.0); controls: 8.0 (2.0)).

3.3. Relationship between olfactory function and disease-related characteristics in patients with PD

As illustrated in Table 2, smell identification scores were not significantly correlated with disease duration, disease severity, or LEDD.

Table 2
Relationship between olfactory function and disease-related characteristics in patients with PD.

Characteristic	VSIT	BSIT
Duration	$r_s = 0.05$ ($p = 0.43$)	$r_s = 0.05$ ($p = 0.44$)
Hoehn & Yahr stage	p[a] = 0.69	p[a] = 0.64
MDS-UPDRS III	$r_s = -0.13$ ($p = 0.05$)	$r_s = -0,12$ ($p = 0.09$)
LEDD	$r_s = 0.04$ ($p = 0.56$)	$r_s = 0.01$ ($p = 0.88$)

r_s: Spearman's rank correlation coefficient.
[a] The Kruskal–Wallis test.

3.4. Receiver operating characteristic (ROC) curve analysis, sensitivity, and specificity of the odor identification tests for separating PD and HC groups

The areas under the ROC curve of VSIT scores and BSIT scores were 0.909 and 0.818, respectively (all P < 0.0001) for discriminating PD patients from the HC group (Fig. 1). The sensitivity, specificity, PPV, NPV, and Youden index for the two olfactory tests are presented in Table 3. The Youden indexes of the BSIT and the VSIT were both the highest at a cut-off value of 8 (< 8 indicates hyposmia). However, using a cut-off of 8, the VSIT discriminated between PD and HC groups with a sensitivity of 84.4% and a specificity of 86.2%, whereas the BSIT showed 81.7% sensitivity and 69.3% specificity.

3.5. Item analysis of the VSIT and the BSIT

Differences in odor identification ability between the PD and HC groups were found for all odors included in the VSIT and the BSIT except for smoke (Table 4). The percentage of HCs and PD patients who correctly identified smoke did not show significant differences (P = 0.5). The odorants of the VSIT that had the greatest sensitivity for detecting PD were watermelon (71.9%), mango (70.5%), and apple (69.6%) (Table 4), while items of the BSIT with sensitivity above 70.0% were rose (85.3%) and lemon (72.8%). Diagnostic measures for each item are described in Table 5. Items of the VSIT with a diagnostic accuracy above 70.0% were banana (71.5%), guava (70.6%), and mango (70.1%). There were 4 odors in the BSIT including smoke, chocolate, rose, and gasoline that were not ineffective in discriminating PD from HCs (all P > 0.05).

4. Discussion

Our study has demonstrated that smell identification tests can help differentiate PD patients from HCs in the Vietnamese population. Furthermore, the sensitivity and specificity of the VSIT were higher than the BSIT in the detection of Vietnamese PD patients. We also noticed that several specific odors could discriminate the PD group from the HCs group more effectively than others.

Detecting hyposmia is useful for identifying early stage PD and distinguishing PD with different disorders, such as essential tremor and

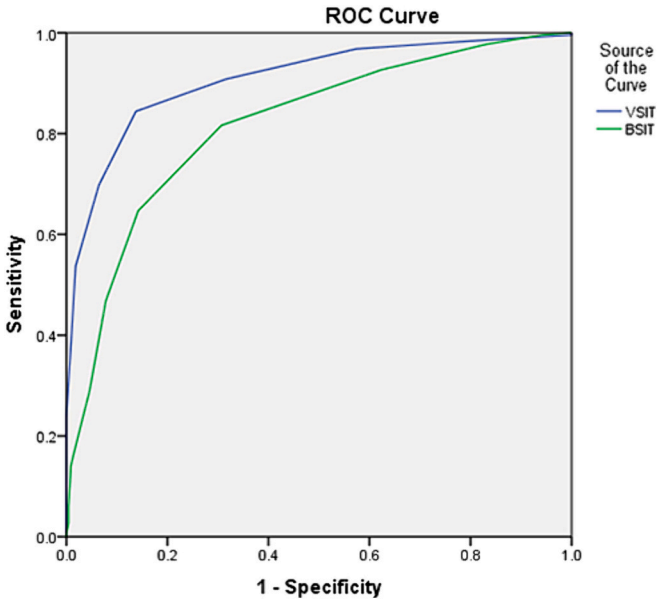

Fig. 1. The ROC curve of two olfactory tests for diagnosing PD. Area under the curve for the VSIT 0.909 (95% CI: 0.881-0.937), P < 0.0001. Area under the curve for the BSIT 0.818 (95% CI: 0.778-0.858), P < 0.0001

Table 3
The sensitivity, specificity, PPV, NPV, and Youden Index of the VSIT and the BSIT.

Cut-off	Sensitivity		Specificity		PPV		NPV		Youden Index	
	VSIT	BSIT	VSIT	BSIT	VSIT	BSIT	VSIT	BSIT	VSIT	BSIT
< 7	0.697	0.647	0.936	0.858	0.916	0.820	0.756	0.708	0.344	0.505
< 8	0.844	0.817	0.862	0.693	0.860	0.727	0.847	0.791	0.706	0.510
< 9	0.908	0.927	0.683	0.376	0.742	0.598	0.882	0.837	0.591	0.303
< 10	0.968	0.977	0.427	0.170	0.628	0.541	0.930	0.881	0.395	0.147

Table 4
Item analysis of the VSIT and the BSIT in patients with PD and HCs (chi-square test).

Olfactory Test	Item	Sensitivity	Specificity	PPV	NPV	P[a] value
VSIT	Lemon	0.606	0.633	0.623	0.616	< 0.0001
	Fish sauce	0.261	0.908	0.740	0.552	< 0.0001
	Garlic	0.491	0.835	0.748	0.621	< 0.0001
	Banana	0.638	0.798	0.760	0.688	< 0.0001
	Coffee	0.532	0.688	0.630	0.595	< 0.0001
	Orange	0.472	0.862	0.774	0.620	< 0.0001
	Fish	0.541	0.817	0.747	0.640	< 0.0001
	Mango	0.706	0.702	0.703	0.705	< 0.0001
	Soy Sauce	0.454	0.789	0.683	0.591	< 0.0001
	Guava	0.592	0.817	0.763	0.667	< 0.0001
	Watermelon	0.720	0.583	0.633	0.676	< 0.0001
	Apple	0.697	0.693	0.694	0.696	< 0.0001
BSIT	Cinnamon	0.569	0.770	0.713	0.640	< 0.0001
	Turpentine	0.535	0.638	0.595	0.579	< 0.0001
	Lemon	0.725	0.477	0.581	0.634	< 0.0001
	Smoke	0.528	0.468	0.498	0.498	0.50
	Chocolate	0.289	0.853	0.663	0.545	< 0.0001
	Rose	0.853	0.275	0.541	0.652	0.01
	Paint thinner	0.349	0.826	0.667	0.559	< 0.0001
	Banana	0.583	0.587	0.585	0.584	< 0.0001
	Pineapple	0.523	0.807	0.731	0.629	< 0.0001
	Gasoline	0.647	0.509	0.569	0.590	0.01
	Soap	0.394	0.922	0.835	0.604	< 0.0001
	Onion	0.404	0.894	0.793	0.600	< 0.0001

NPV: negative predictive value, PPV: positive predictive value.
[a] chi-squared tests were used to compare the percentage of HCs and PD patients who correctly identified each item.

Table 5
Diagnostic accuracy of items including in the VSIT and the BSIT.

Olfactory Test	Item	AUC for each item	P
VSIT	Lemon	0.619	<0.0001
	Fish Sauce	0.585	0.02
	Garlic	0.663	<0.0001
	Banana	0.716	<0.0001
	Coffee	0.610	<0.0001
	Orange	0.667	<0.0001
	Fish	0.679	<0.0001
	Mango	0.704	<0.0001
	Soy Sauce	0.622	<0.0001
	Guava	0.704	<0.0001
	Watermelon	0.651	<0.0001
	Apple	0.695	<0.0001
BSIT	Cinnamon	0.669	<0.0001
	Turpentine	0.586	0.01
	Lemon	0.601	<0.0001
	Smoke	0.498	0.93
	Chocolate	0.571	0.09
	Rose	0.564	0.17
	Pain thinner	0.587	0.02
	Banana	0.585	0.02
	Pineapple	0.665	<0.0001
	Gasoline	0.578	0.06
	Soap	0.658	<0.0001
	Onion	0.649	<0.0001

drug-induced parkinsonism [14,15]. Furthermore, olfactory dysfunction is also able to discriminate PD patients from healthy individuals [16]. Therefore, smell tests have been used as a supportive diagnostic tool for PD [4]. However, cross-cultural differences are an important issue in the application of smell identification tests. Although the BSIT has been found to be an effective instrument to detect hyposmia in PD in other countries [17,18], the VSIT and BSIT haven't been evaluated in the Vietnamese PD population. Our study results revealed that, in a Vietnamese population, both these tests could be useful to differentiate PD patients from HCs. Furthermore, the sensitivity and specificity of the VSIT were higher than those of the BSIT in the detection of Vietnamese PD patients. In our sample, with the cut-off score of <8, the VSIT had a diagnostic accuracy of 0.909, a sensitivity of 84.4%, and a specificity of 86.2% for distinguishing PD patients from HCs. However, using a similar cut-off score, the BSIT had a diagnostic accuracy of 0.818, a sensitivity of 81.7%, and a specificity of 69.3%. The main reason for the better results of the VSIT is that the odors included in the VSIT are more familiar to Vietnamese people [10]. Similar to our findings, one study carried out in Chinese and German populations of healthy subjects and PD patients by hands of a directly compared diagnostic value of the SIT-12 test and a China-SIT-12 test revealed that the original SIT-12 test discriminated between German PD patients and HCs with a specificity of 0.98, while that of Chinese population was 0.69. On the contrary, when using the China-SIT-12 test to evaluate olfactory function, the specificity was 0.69 for Germans and 0.97 for Chinese [19]. These data showed that smell identification tests must be developed or modified to adapt to the regional culture where they are intended for use.

For diagnosing PD in Vietnam, our study found that a score of 8 was the most appropriate cut-off value for both the VSIT and the BSIT, whereas the cut-off value of 9 with higher sensitivity can be used to screen potential patients with hyposmia. In line with our study, the cut-

off point at 8 was also suggested by the VSIT and the BSIT developers to identify hyposmia in the adult population [9,10]. Some previous studies in Spain, Germany, and China that evaluated olfactory function using the BSIT or SS-12 have reported that the same cut-off score can result in sensitivity and specificity values ranging from 0.60 to 0.85 and 0.83 to 0.98, respectively, for distinguishing PD from HC subjects [19–22]. Based on a meta-analysis, olfactory tests can identify PD from HC with a mean sensitivity of 83% and a mean specificity of 84% [12]. In summary, like other smell identification tests, the VSIT helps increase diagnostic value for PD.

In our study, there was no significant correlation between olfactory function with disease duration and severity of motor symptoms assessed with the H&Y scale. Most previous studies also reported similar results [1,23–26]. However, one prospective cohort study showed a mild progression of hyposmia when comparing baseline and five-year follow-up data [27]. Hyposmia is a slowly progressive non-motor symptom in PD, so it is understandable that our case-control study could not determine this correlation.

Regarding the diagnostic value of each odor in PD, some previous studies reported that several specific odors discriminated the PD group from the HC group more effectively than others [26,28,29]. Five of the 12 BSIT odors, including gasoline, banana, smoke, cinnamon, and pineapple, were demonstrated to be able to distinguish PD patients from controls with higher sensitivity and specificity than the entire BSIT test [26]. One study using the Snifin's Sticks found peppermint, anise, and coffee best to differentiate PD from healthy individuals [30]. When each smell from the UPSIT was analyzed, a study in America revealed that banana, licorice and dill pickle showed the most significant difference in odor identification between PD patients and controls [31]. In contrast, a British study found the most remarkable differences in the identification of pizza and wintergreen [28]. Another study in Germany found cinnamon to be ineffective for PD discrimination [32]. In our study, three odors of the VSIT with the highest accuracy for diagnosing PD were banana, mango, guava, and apple. When applying the BSIT in the Vietnamese population, we found that cinnamon pineapple, soap, and onion had the best discriminatory value between PD patients and HCs whereas correct identification frequencies of smoke were not significant differences between the two groups. Cultural differences in the relationship to specific odors can result in limited comparison between different studies. While some previous results suggested selective hyposmia in PD when comparing PD patients and HCs [28], another study showed that selective hyposmia of PD was not identified when compared with non-Parkinsonian hyposmic patients [33].

This study has limitations. The HC volunteers were defined based on history and clinical examination without any further diagnostic tests to exclude diseases with olfactory dysfunction. However, using imaging to rule out nose or sinusoid disease is costly. Furthermore, previous studies on validating smell identification tests in PD detection also used only history and clinical examination for the HCs group [8,9,18,20,29]. Next, although all recruited participants had MMSE scores greater than or equal to 25, there was a significant difference in MMSE scores between PD patients and HCs. Finally, this was only a case-control study. Therefore, a longitudinal prospective study is needed to confirm the value of this smell test in the future.

5. Conclusion

The VSIT can be a valuable ancillary tool for supporting the diagnosis of PD in Vietnam. Compared to the BSIT, the VSIT had a higher accuracy in discriminating Vietnamese PD patients from HC individuals. Our study also revealed that the olfactory dysfunction in PD was unrelated to the disease duration and severity. The VSIT can be applied to improve the accuracy of clinical PD diagnosis in Vietnam.

CRediT authorship contribution statement

Thuong Huyen Thi Dang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Tai Ngoc Tran:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Frank Xing:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Uyen Le Ngoc Ha:** Writing – review & editing, Visualization, Validation, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Khang Chung Ngoc Vo:** Writing – review & editing, Investigation. **Khang Vinh Nguyen:** Writing – review & editing, Formal analysis. **Hien Thi Le:** Writing – review & editing, Investigation. **Daniel Truong:** Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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