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Comparing smell identification ability among different motor subtypes of Parkinson's disease using the Vietnamese Smell Identification Test and the Brief Smell Identification Test

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ABSTRACT

Introduction: Olfactory dysfunction is one of the most common non-motor symptoms of Parkinson's disease (PD). The association between smell identification ability and motor subtypes of PD is not uniform in previous studies. This study aimed to compare the odor identification ability among different motor subtypes of PD in Vietnamese participants.

Methods: Patients who were diagnosed with PD according to the International Parkinson's Disease and Movement Disorder Society 2015 Diagnostic Criteria and had normal cognitive function were recruited. Participants were divided into akinetic-rigid (AR), tremor-dominant (TD), and mixed (MX) motor subgroups using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score. Olfactory identification ability was evaluated using the Vietnamese Smell Identification Test (VSIT) and the Brief Smell Identification Test (BSIT). Cognitive status was assessed using the Mini-Mental State Examination (MMSE). Age, age at PD onset, disease duration, smell identification ability, and cognitive function were compared among the three PD motor subtypes.

Results: The AR subgroup was the most common motor subtype (n = 164, 75.2 %), followed by TD (n = 39, 17.9 %), and MX (n = 15, 6.9 %) subtypes. Age, age at PD onset, sex, disease duration, and MMSE score were not significantly different between the three motor subgroups (all $p > 0.05$). The median (IQR) VSIT scores of AR, TD, and MX subgroups were 5.00 [4.00;7.00], 5.00 [3.50;7.00], and 5.00 [3.00;6.00], respectively. The median (IQR) BSIT scores of AR, TD, and MX subgroups were 6.00 [4.00;7.00], 5.00 [4.00;7.00], and 5.00 [4.50;7.00], respectively. The VSIT and the BSIT scores were not significantly different among the three motor subtypes (all $p > 0.05$).

Conclusion: Smell identification ability assessed in both the VSIT and BSIT did not differ across the three motor subtypes of PD.

1. Introduction

Parkinson's disease (PD), one of the most common neurodegenerative diseases, is characterized by classic motor symptoms and a wide range of non-motor symptoms. Olfactory dysfunction is a common non-motor symptom, with a prevalence of up to 90 % [1]. Hyposmia is an early non-motor sign that can occur many years before the onset of motor symptoms [2]. Most studies have not found an association between hyposmia and the severity of motor symptoms in PD as evaluated by the UPDRS scale [3–7] and the Hoehn & Yahr stage [4,5,8–10]. Olfactory function was also not significantly related to clinical index, including tremor, rigidity, bradykinesia, and gait disorders [11]. A systematic review of the relationship between olfactory function and disease progression has not been able to demonstrate a significant correlation. This could be accounted for by the heterogenous in the clinical evaluation of disease progression (disease durations, UPDRS scale, the Hoehn & Yahr stage, clinical subtypes, L-dopa equivalent daily dose, Mini-Mental State Examination, Montreal Cognitive Assessment),

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clinical scales for hyposmia and also the ceiling effect of the smell identification scales between studies [12]. However, a recent study examining the longitudinal MRI in PD patients has demonstrated the correlation between anosmia with the University of Pennsylvania Smell Identification Test (UPSIT) score ≤18 and brain atrophy [13]. There could be a correlation between olfactory function and disease progression that is not apparent on current clinical scales.

PD patients can be classified into three subgroups based on the most prominent motor symptoms: akinetic-rigid (AR), tremor-dominant (TD), and mixed (MX) subtypes [14–16]. Previous studies suggested that motor subtypes may have differences in clinical course and prognosis [14,17]. A few studies have found a significant association between motor subtypes and smell identification ability [18,19], whereas others reported no relationship [15,20].

Our previous study showed that the smell identification ability in Vietnamese patients with PD was impaired based on the Vietnamese Smell Identification Test (VSIT) as well as the Brief Smell Identification Test (BSIT) [21]. However, we did not assess the relationship between odor identification ability and motor phenotypes in PD. Also, to our knowledge, no studies have investigated the difference in BSIT between PD motor subgroups in the Southeast Asian population. This study was therefore conducted to compare the odor identification ability among patients with different motor subtypes of PD using the VSIT and the BSIT.

2. Materials and Methods

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

2.1. Participants

Patients diagnosed with PD according to the International Parkinson's Disease and Movement Disorder Society 2015 Diagnostic Criteria with normal cognitive function were recruited. The cognitive status was assessed using the Mini Mental State Examination (MMSE). We excluded patients with (1) MMSE less than 25, (2) infections in the upper respiratory tract two weeks before odor identification testing, (3) history of nasal surgery, nasal or head trauma, (4) pregnancy, (5) any medication affecting odor testing, (6) previous history of COVID and hyposmia, and (6) a history of functional neurosurgery for PD.

All participants provided written informed consent. The protocol was approved by the University Medical Center HCMC Ethics Committee, 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". We have reanalyzed the data of the published study and conducted subgroup analysis to investigate smell identification ability among different motor subtypes of PD. Our previous paper, which showed a difference in olfactory functions between the Parkinson's disease group and the control group using VSIT and BSIT. The same inclusion and exclusion criteria are applied for this study [21].

2.2. Clinical profiling

Information on socio-demographics, including age, gender, smoking history and disease-related characteristics, including age at PD onset, disease duration, and medication use were collected. Participants' cognition was assessed using MMSE. All PD patients were also evaluated using Hoehn & Yahr staging and the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) by neurologists specializing in movement disorders. All assessments were performed under ongoing treatment in the "ON" state of medication. The levodopa equivalent daily dose (LEDD) was calculated based on the systemic review published in 2023 [22].

Patients were divided into akinetic-rigid (AR), tremor-dominant (TD), and mixed (MX) motor subgroups using the MDS-UPDRS scores in a manner suggested by Christopher Adams and colleagues [16] in 2023. According to the VSIT score, the patients were classified into hyposmic (VSIT score of ≤7) and normosmic (VSIT score of ≥8) groups [21].

The olfactory identification ability of participants was evaluated using the VSIT [23] and the BSIT [24]. The VSIT was developed in 4 phases: determine the most familiar odors to the Vietnamese population, select the most identifiable odors, evaluate the combination of odors validity using the normosmic participants and hyposmic patients, and evaluate the test–retest reliability. The VSIT test then consists of 12 odors (Lemon, fish sauce, garlic, banana, coffee, orange, fish, mango, soy sauce, guava, watermelon, and apple) chosen from the most common and recognized odors by Vietnamese people. The odor was presented by tearing the sachets and revealing the cotton buds, which were dipped into a diluted odorous solution, to the participants. The cotton buds were placed in front of the nostril at about 2 cm for 2–3 s. Also, the presentation of subsequent odors must be after more than 20 s. The patients received one point in the total VSIT score with each correct odor identification. The VSIT has been developed and validated for the Vietnamese population [23]. The BSIT was also administered to the participants according to the manufacturer's instructions. The BSIT was supplied by the Sensonics Company.

2.3. Statistical analysis

We used the Kolmogorov-Smirnov test and the Q-Q plot to determine the normality. The ANOVA or Kruskal-Wallis H test was used to compare age, age at PD onset, VSIT scores, BSIT scores, MDS-UPDRS scores, and cognitive function among three PD motor subtypes. The Chi-Square or Fisher exact test was used for categorical variables such as smoking history, sex, and correct identification of each smell. Dunn's Test of multiple comparisons was used for post-hoc analysis. The effect size was calculated using eta squared based on the H-statistic for Kruskall Wallis test, cohen ω for Chi-Square and Fisher exact test. P values < 0.05 were considered significant. The data analysis was conducted using IBM SPSS Statistics for Windows, Version 20.0 software (Armonk, NY: IBM Corp. Released 2011).

3. Results

Two hundred and eighteen participants were enrolled: 164 PD patients with the AR subtype, 39 with the TD subtype, and 15 with the MX subtype.

3.1. Characteristics of clinical subtypes

The global demographic and clinical characteristics of patients with the AR, TD, and MX subtypes are summarized in Table 1.

The median (IQR) age was 61.0 [52.0;66.0] in PD patients with the AR subtype, 62.0 [55.5;67.0] in those with the TD subtype, and 64.0 [53.5;67.5] in the MX subtype. Median (IQR) of the age at PD onset in the AR, TD, and MX subtypes were 57.0 [47.0;63.0], 58.0 [50.0;63.0], and 57.0 [50.5;63.0], respectively. No significant differences were found for smoking history, sex, age, age at PD onset, and disease duration between all groups (all $p > 0.05$). No significant differences were observed between the three subtypes for Hoehn & Yahr stage, MDS-UPDRS I, MDS-UPDRS I, MDS-UPDRS II, MDS-UPDRS III, MDS-UPDRS total, and MMSE (all $p > 0.05$). Significant differences were found for LEDD, and MDS-UPDRS IV between these three groups ($p = 0.026$ and $p = 0.006$, respectively). Post hoc analysis using Dunn's Test of Multiple Comparisons revealed significant differences between the AR subtype and TD subtype in MDS-UPDRS IV (p adjusted = 0.006), while there was no significant difference in LEDD between these two groups.

Table 1
The demographic and clinical characteristics of PD patients with the akinetic-rigid (AR), tremor-dominant (TD), and mixed (MX) subtypes (N = 218).

Motor subtype	AR subtype N = 164	TD subtype N = 39	MX subtype N = 15	P	Effect size
Smoking history (N, %)	27, 16.46 %	9, 23.07 %	2, 13.33 %	0.629[a]	0.072[e]
Sex (N, % female)	88, 53.66 %	20, 51.28 %	9, 60.00 %	0.847[b]	0.039[e]
Age (median, IQR)	61.0 [52.0;66.0]	62.0 [55.5;67.0]	64.0 [53.5;67.5]	0.823[c]	−0.036[d]
Age at PD onset (median, IQR)	57.0 [47.0;63.0]	58.0 [50.0;63.0]	57.0 [50.5;63.0]	0.848[c]	0.023[d]
PD duration (median, IQR)	3.00 [2.00;6.00]	3.00 [2.00;6.00]	3.00 [2.00;6.00]	0.969[c]	−0.049[d]
Hoehn & Yahr 1	4 (2.44 %)	3 (7.69 %)	0 (0.00 %)	0.712[a]	0.135[e]
Hoehn & Yahr 2	126 (76.8 %)	29 (74.4 %)	12 (80.0 %)		
Hoehn & Yahr 3	32 (19.5 %)	7 (17.9 %)	3 (20.0 %)		
Hoehn & Yahr 4	2 (1.22 %)	0 (0.00 %)	0 (0.00 %)		
MDS-UPDRS I (median, IQR)	7.00 [3.00;9.00]	5.00 [2.00;7.00]	5.00 [3.00;9.00]	0.081[c]	0.093[d]
MDS-UPDRS II (median, IQR)	8.50 [5.00;11.2]	7.00 [3.50;11.0]	9.00 [6.00;11.5]	0.451[c]	−0.043[d]
MDS-UPDRS III (median, IQR)	36.0 [30.0;43.2]	34.0 [31.0;42.5]	43.0 [34.5;47.5]	0.182[c]	0.075[d]
MDS-UPDRS IV (median, IQR)	0.00 [0.00;4.00]	0.00 [0.00;0.00]	0.00 [0.00;1.00]	**0.006**[c]	−0.014[d]
Total MDS-UPDRS (median, IQR)	55.0 [41.0;64.2]	52.0 [36.5;59.0]	56.0 [50.5;65.5]	0.364[c]	0.057[d]
LEDD (median, IQR)	525 [375;750]	375 [312;600]	375 [281;569]	**0.026**[c]	−0.057[d]
MMSE (median, IQR)	28.0 [26.0;29.0]	28.0 [26.5;29.0]	26.0 [26.0;27.0]	0.06[c]	0.019[d]

[a] Fisher exact test
[b] Chi-square test
[c] Kruskal Wallis.
[d] eta squared based on the H-statistic
[e] Cohen ω.

3.2. Olfactory function

Based on the VSIT, the frequency of hyposmia in AR, TD, and MX subgroups were 84.15 %, 84.62 %, and 86.67 %, respectively. No significant differences were observed in the frequency of hyposmia between the three motor subtypes (p = 0.967).

The median (IQR) of VSIT scores were 5.00 [4.00;7.00], 5.00 [3.50;7.00], and 5.00 [3.00;6.00] in the AR, TD, and MX subtypes, respectively (Fig. 1). The Kruskall-Wallis test did not show a significant difference in VSIT scores among the three groups (p = 0.788).

The median (IQR) of BSIT scores were 6.00 [4.00;7.00], 5.00 [4.00;7.00], and 5.00 [4.50;7.00] in the AR, TD, and MX subtypes, respectively (Fig. 2). The Kruskall-Wallis test did not show a significant difference in BSIT scores among the three groups (p = 0.963).

No significant differences were found in the percentage of correct identification of each smell included in the VSIT between different clinical phenotypes of PD (all p > 0.05) (Fig. 3). Similarly, no significant differences were found in the percentage of correct identification of each smell included in the BSIT between different clinical phenotypes of PD (all p > 0.05) (Fig. 4).

3.3. Comparing motor subtypes between normosmia and hyposmia

The percentages of each motor subtype did not significantly differ between hyposmic and normosmic PD patients (p = 1.0) (Table 2).

4. Discussion

PD is a heterogeneous disorder in both clinical manifestation, pathogenesis, and long-term prognosis [17,25,26]. Multiple studies have been conducted to explore the difference in non-motor features between motor subtypes. In this cross-sectional study, VSIT scores and BSIT scores of TD, AR, and MX subtypes were compared. Our study did not show a significant difference in odor identification ability among these motor subtypes. Additionally, our study found that the percentage of correct identification of each odor included in the BSIT and the VSIT was not significantly different among the three motor phenotypes.

Regarding motor subtypes in PD, several different categorizations have been described in previous studies. Most studies split patients into either tremor-dominant or non-tremor dominant [AR or postural instability/gait difficulty (PIGD)], and intermediate or mixed phenotypes [16,17,27]. Scores of the UPDRS [17] and the MDS-UPDRS [16] were used to classify the different motor subtypes. In line with our results, some studies found that the AR subtype was more common than the TD and MX subtypes [18,20].

Regarding characteristics of three subtypes (TD, AR, and MX), our study showed that there was no difference in age, age at PD onset, sex, disease duration, Hoehn & Yahr, MDS-UPDRS part I, II, III, and MMSE among subtypes. Paolo Solla and colleague [20] also reported no significant differences were observed between the TD and AR subtypes for age, age at PD onset, PD duration, Hoehn & Yahr, UPDRS scores, and MoCA. Similar to our study, Paolo Solla and colleagues [20] did not find a difference in the LEDD of patients with the AR type and patients with the TD type. In another study, Hoehn & Yahr stage was significantly higher in the AR type than in the MX type or TD type, while UPDRS scores in the AR type were higher than in the TD type [18]. Our study revealed that MDS-UPDRS part IV was significantly higher in the AR type than in the TD type. In line with our results, some studies also demonstrated that patients with the AR type had higher frequency of motor fluctuation and dyskinesias than patients with the TD type [28,29]. This result may be related to differences in pathophysiological mechanisms of clinical motor subtypes [30,31].

A number of previous studies have identified a relationship between odor identification and PD subtype. Iijima and colleagues divided PD patients into TD, AR, and MX subgroups based on the UPDRS [18]. In this study, the Odor Stick Identification Test for Japanese (OSIT-J) was used to evaluate the smell identification ability of patients with PD. They showed that the mean odor identification score was significantly lower in the AR type than in the TD type, while OSIT-J scores did not significantly differ between AR and MX types or between TD type and MX types [18]. Stern and colleagues classified patients with PD into TD and PIGD-predominant subgroups [19]. This study found that the UPSIT scores were lower in the PIGD-predominant than in the tremor-predominant PD patients [19]. Another study, using the Iran-Smell Identification Test (Iran-SIT), showed that the Iran-SIT scores were higher in the TD subgroup than in the PIGD subgroup [32]. These three studies revealed that patients with TD had significantly better smell identification ability than patients with AR type [18] or PIGD-predominant type [19,32].

Contrary to the studies mentioned above, Nicola Tambasco and colleagues [15] found that scores on the Italian Olfactory Identification Test (IOIT) did not significantly differ among three motor phenotypes (TD, AR, and MX). In another study, Paolo Solla and colleagues [20] classified PD patients into AR and TD types and evaluated olfactory

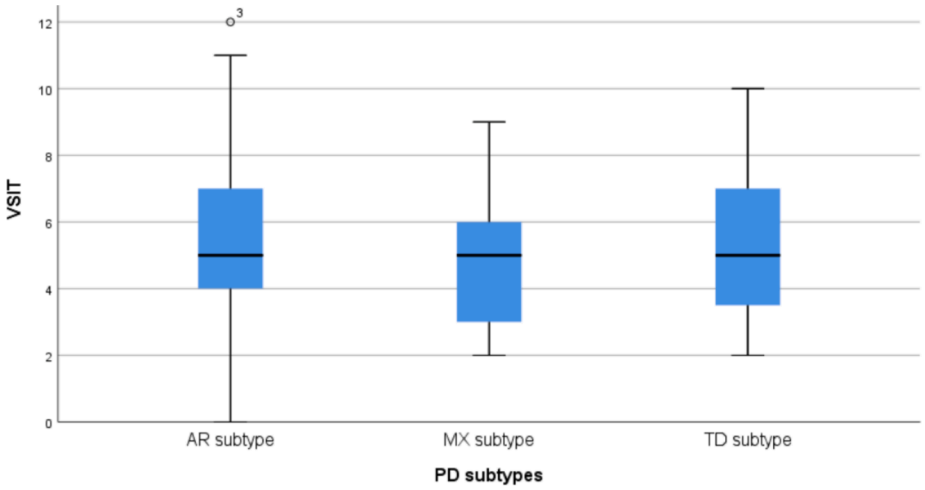

Fig. 1. Box plot shows VSIT scores across different clinical phenotypes of PD.

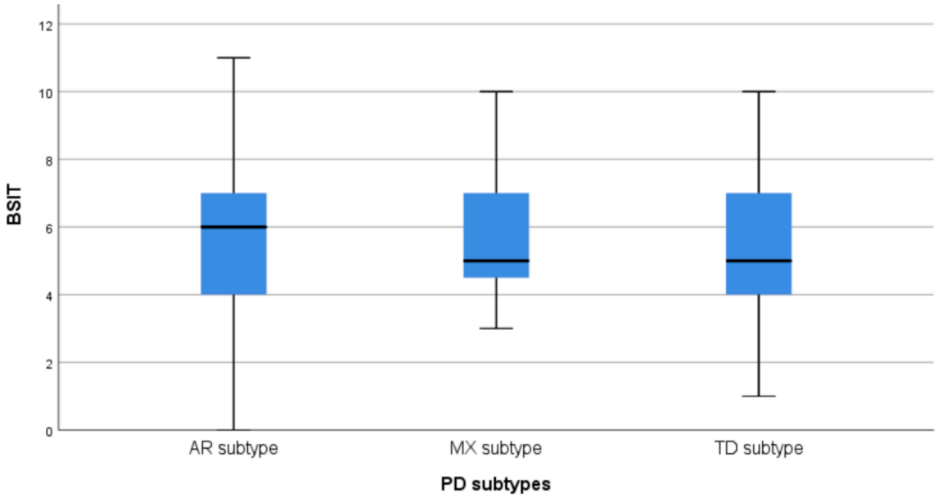

Fig. 2. Box plot shows BSIT scores across different clinical phenotypes of PD.

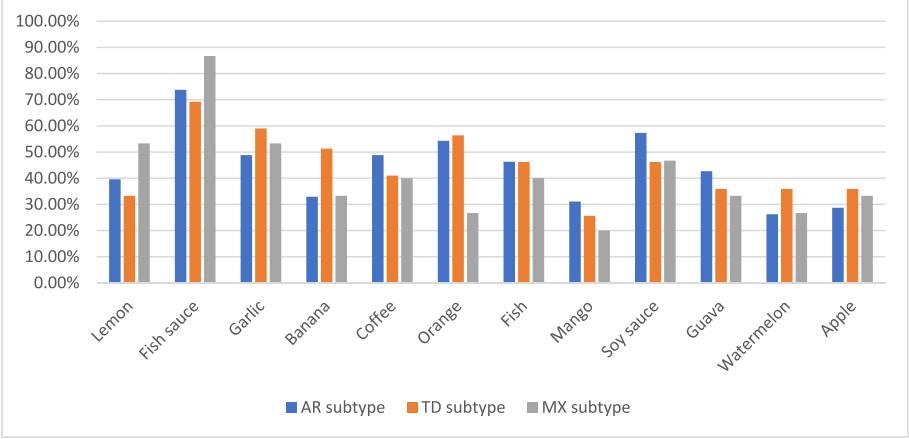

Fig. 3. Barplot of the percentage of VSIT odors correct identification between different clinical phenotypes of PD.

function with the Sniffin' Sticks Test. They reported no difference in odor identification scores between AR and TD subgroups, although odor threshold was significantly lower in the ARD than in the TD subtype [20].

As the aforementioned examples illustrate, findings related to the relationship between smell identification ability and motor subtypes in PD are not uniform in the literature. These inconsistent results might be related to several factors. Firstly, the tests used to evaluate olfactory

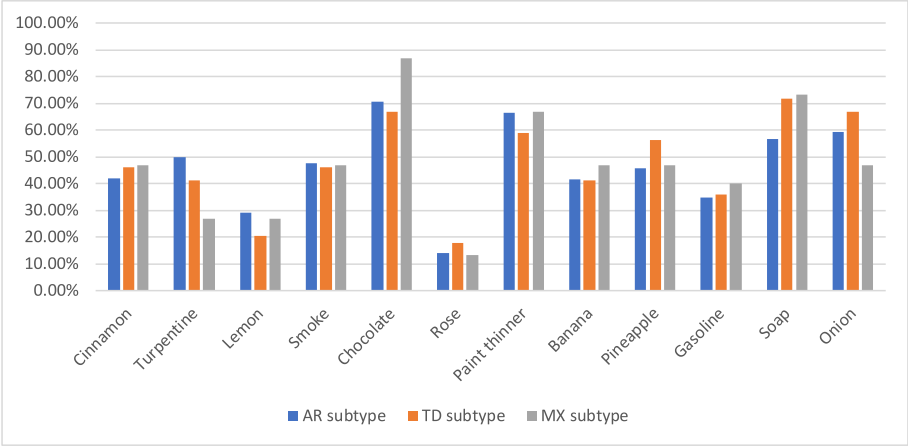

Fig. 4. Barplot of the percentage of BSIT odors correct identification between different clinical phenotypes of PD.

Table 2
Comparing motor subtypes between normosmic PD group and hyposmic PD group (N = 218).

Characteristic	Normosmia N = 34	Hyposmia N = 184	P	Effect size
Motor Subtypes (N, %)				
AR	26 (76.5 %)	138 (75.0 %)	1.0[a]	0.018
TD	6 (17.6 %)	33 (17.9 %)		
MX	2 (5.9 %)	13 (7.1 %)		

AR: akinetic-rigid, TD: tremor-dominant, MX: mixed.
[a] Fisher exact test

function in previous studies were different. Secondly, the use of various motor subtype classifications also influenced the results.

The present study also found no differences in motor subtypes between hyposmic PD patients and normosmic PD patients. This finding is in agreement with that of Runcheng He and colleagues [33], who showed no difference in motor subtypes (TD, PGID, and intermediate types) between the hyposmic group and the normosic group on the UPSIT.

One strength of our study was that two different smell identification tests were used to evaluate the olfactory function. The limitation was that the sample sizes in the TD and MX groups were relatively small.

5. Conclusion

In the present study, smell identification ability and the frequency of hyposmia did not differ among patients with different motor subtypes of PD. Additionally, there was no difference in motor subtypes between the hyposmic PD group and the normosmic PD group.

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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