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**Original article**

# Prevalence of neuropsychiatric symptoms in patients with mild cognitive impairment at King Chulalongkorn Memorial Hospital

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***Background:*** Thailand has already become aging society since 2005. Previous studies showed that cognitive impairment is common in the elderly. Mild cognitive impairment (MCI) is a cognitive decline condition between the normal aging and dementia population. Moreover cognitive impairment condition is commonly found with neuropsychiatric symptoms (NPS). NPS are significantly related to poor disease prognosis and can cause serious care problems.

***Objective:*** To estimate the prevalence, severity and character of NPS in Thai patients with MCI.

***Methods:*** A cross-sectional descriptive study conducted in 100 patients, who were diagnosed with MCI by the international working group criteria. The main outcome was the prevalence of NPS in Thai patients with MCI. This study used the Neuropsychiatric Inventory Questionnaire (NPI-Q) for the main measurement.

***Results:*** The mean age was 71.3 years, 65.0% were females. The mean TMSE, MoCA scores and DAD-T percentage were 27.8, 21.7, and 96.6, respectively. The prevalence of at least one NPS was 65.0%. It was found that the most common NPS was irritability (33.0%), the second was sleep problems (31.0%), the third was anxiety (29.0%) whereas the lowest prevalence was hallucination (6.0%). The presence of NPS had a significant relationship with using the lipid-lowering drug and history of others noticed that the subject had memory/attention problems. The MCI patients with NPS had lower total DAD-T percent, MoCA and TMSE scores. A large part of the variance in DAD-T (43.0%), MoCA (27.0%) and TMSE (17.0%) was explained by mainly agitation and apathy.

***Conclusions:*** NPS are very common in Thai MCI patients. Therefore, the management of patients with MCI should always be assessed for NPS.

***Keywords:*** Mild cognitive impairment, dementia, neuropsychiatric symptoms, prevalence.

According to data from the National Statistical Office of Thailand (2014), Thailand has become an aging society since 2005, which means that 10.0% of its population is over 60 years of age. It is expected that by 2021, the proportion of Thailand's aging population will reach 20.0% making the country a complete aged society. [1]

From the Thai National Health Examination Survey in 2008 - 2009 by the National Health Examination Survey Office, Health System Research Institute, it was found that 12.3% of people aged over 60 years have dementia[2], which is a cognitive impairment condition, commonly found with 75.0% - 100.0% of NPS. [3] NPS are significantly related to poor disease prognosis and can cause serious care problems.

MCI is also a cognitive decline condition between the normal aging and dementia population. MCI patients have more cognitive decline than the elderly, who have the same level of education but are still able to take care of their daily life. The prevalence of MCI in people older than 65 years is 3.0 - 19.0%.[4] MCI patients also have NPS similar to dementia patients. Many studies found that the prevalence of NPS in MCI patients was 35.0 - 85.0%. [5 - 9] NPS also result in the suffering of caregivers. As a result, appropriate management of NPS is very important for improving the patient's well-being and caregiver's distress.[10, 11] Nowadays, the information about NPS in MCI patients is very limited in Thailand. Therefore, this study aimed to explore the prevalence and characteristics of NPS in Thai MCI patients.

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## Materials and methods

This cross-sectional descriptive study was conducted in patients at the Psychiatry Outpatients Department and Cognitive Fitness Center in King Chulalongkorn Memorial Hospital, Bangkok, Thailand between November 2017 and April 2018. This study has been approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (COA No. 648/2017). An informed consent was obtained from all subjects and caregivers. The primary outcome was the prevalence of NPS in Thai patients with MCI. The secondary outcome was the associations between the presence of NPS and cognitive tests.

Subjects were recruited in the study if they were 50 years of age or over, diagnosed with MCI by the international working group criteria [12] and reassessed by the TMSE and MoCA (must have a TMSE score of more than 23 and MoCA score less than 25), and had a caregiver. The caregiver could participate in this survey at the hospital or by phone (caregiver means the person who observes the habit and knows the personality of the subject. There is no need to provide care for cognitive disease), and had sufficient Thai written and verbal skills. Subjects were excluded if they had a history of abnormal neurodevelopment (intellectual disability and autistic spectrum disorder). The sample size = 100 was calculated from the formulation $n = z_1^2\text{-}_{\alpha/2}\ p(1\text{-}p)/d^2$, which had an acceptable error of (d) = 0.1 and prevalence of (*P*) = 0.75 based on the study of Panasathit. [9]

***Measures* for each subject consisted of three parts as follows:**

Demographic data included a self-report about personal information: gender, age, highest educational level, marital status, and doctor review medical information: physical disease, psychiatric disorder, history of substance use, history of family underlying disease, and relationship with the caregiver.

The Thai Mental State Examination (TMSE)[13, 14], a Thai version of the Mini Mental State Examination (MMSE), has six domains that comprise orientation, registration, attention, calculation, language and recall. The total score of the TMSE ranged from 0 to 30 points. The elimination point for the non-dementia Thai elderly population was over 23.

The Thai version of the Montreal Cognitive Assessment (MoCA) [15] has been translated and culturally modified for Thai patients. There are eight domains composed of visuospatial/executive, naming, memory, attention, language, abstraction, delay recall and orientation. The total score of the MoCA ranged from 0 to 30 points. Subjects who had the highest educational level below or Grade 6 received 1 point. The elimination point for normal cognition in the Thai elderly was over 24.

***Measures for the caregiver* consisted of two parts: Interviewed the caregivers by a qualified clinician.**

The Thai version of the Disability Assessment for Dementia scale (DAD-T) [16] has 40 questions divided into four basic ADL aspects and six instrumental ADL aspects. The DAD-T scores ranging from 0.0 - 100.0%. If the subject scores 100.0% score, this means that he/she can do all activities of daily living by him/herself.

The Neuropsychiatric Inventory Questionnaire-Thai version (NPI-Q Thai) [17] was developed from Neuropsychiatric Inventory (NPI) by Cummings (1994). [18] It is an informant-based instrument that measures the presence and severity of 12 NPS domains in patients with cognitive impairment including delusions, hallucinations, agitation or aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep problems, and changes in appetite. It has been translated and culturally modified for Thai people. The caregiver indicated the presence or absence of NPS in the patient during the previous month. The NPI-Q considered the severity of the NPS and caregiver's distress. The severity scale had scores ranging from 1 to 3 points (1 = mild; 2 = moderate; and 3 = severe) and the scale for assessing caregiver distress had scores ranging from 0 to 5 points (0 = no distress; 1 = minimal distress; 2 = mild distress; 3 = moderate distress; 4 = severe distress; and 5 = extreme distress). The NPI-Q has proven valid and has good levels of interscale correlation between NPI and NPI-Q.

***Statistical analysis***

Data were analyzed using SPSS 22.0. The categorical measures were summarized using frequencies and percentages, and the continuous measures were described by means and standard deviations. The associations between categorical variables were assessed using Chi square test or Phi coefficients. Differences in cognitive tests between subjects with and without NPS were checked with *t* - tests. The predictors of cognitive impairment were analyzed by multiple regression analysis. All tests were performed at a significance level of 0.05.

## Results

### *Subjects' characteristics*

The subjects comprised 100 elderly people (65 females; 35 males; mean age of 71.3 years, age range = 52 - 89 years). They had a medical disease and psychiatric disorder, 96.0% and 22.0%, respectively. The most common medical disease in this population was dyslipidemia (55.0%). Most subjects also showed signs that others could notice that they had memory and attention problems (Table 1).

The TMSE scores ranged from 24 to 30 (mean = 27.8; SD = 1.8), the MoCA scores range from 11 to 24 (mean = 21.7; SD = 2.9), and the average score of the DAD-T was 96.6% (range = 57.5 - 100.0%; SD = 6.9) (Table 1).

### *Prevalence of neuropsychiatric symptoms (NPS)*

The prevalence of at least one NPS from the NPI-Q was 65.0% with at least two domains of the symptoms at 50.0%, and at least three domains of the symptoms at 36.0%. Thus, the mean number of the NPS domains was 2.1 (SD = 2.3, min = 0, and max = 9). The mean of the severity of the NPS was 2.9 (SD = 3.6, min = 0, and max = 16) and the mean of the caregiver's distress was 3.4 (SD = 5.7, min = 0, and max = 29).

**Table 1.** Subjects' characteristics.

| Characteristics | n (%) or mean ± SD |
|---|---|
| **Gender** | |
| Male | 35 (35.0) |
| Female | 65 (65.0) |
| Age (years), mean ± SD | 71.3 ± 7.5 |
| Education: bachelor's degree or above | 53 (53.0) |
| Marital status: marriage | 66 (66.0) |
| Medical underlying diseases* | 96 (96.0) |
| Hyperlipidemia | 55 (55.0) |
| Psychiatric underlying diseases** | 22 (22.0) |
| Drug for medical condition | 83 (83.0) |
| lipid-lowering drug | 46 (46.0) |
| Use of psychotropic drug | 39 (39.0) |
| **Family history** | |
| Dementia | 22 (22.0) |
| Psychiatric diseases | 10 (10.0) |
| Duration of cognitive impairment (years) | 4.4 ± 4.7 |
| **History of cognitive impairment** | |
| Others notice patient's memory problem | 59 (59.0) |
| Others notice patient's attention problem | 29 (29.0) |
| **Caregiver** | |
| Female | 65 (65.0) |
| Being with patient (years) | 24.0 ± 15.2 |
| Frequency of meeting patient: 7days/week | 68 (68.0) |
| TMSE | 27.8 ± 1.8 (min 24, max 30) |
| MoCA | 21.7 ± 2.9 (min 11, max 24) |
| DAD-T | 96.6 ± 6.9 (min 57.5, max 100) |
| DAD-T< 100.0% | 38 (38.0) |

*hypertension (53), diabetes (23), cardiovascular diseases (19), and neurological diseases (12)
**depression (11), anxiety (8), insomnia (2), and bipolar disorder (1)

The NPS from NPI-Q had 12 domains. It was found that the most common NPS was irritability (33.0%), the second was sleep problems (31.0%), the third was anxiety (29.0%) whereas the lowest prevalence was hallucination (6.0%) (Figure 1).

***Relationship of the presence of neuropsychiatric symptoms (NPS) in mild cognitive impairment (MCI) patients***

The comparison between MCI patients with NPS and without NPS was made by a Chi square test. It was found that there were no significant differences among the two groups in gender, marital status, educational level, underlying disease, and family history of dementia, or mental illness. The presence of NPS had a statistically significant relationship with using a lipid-lowering drug ($P = 0.03$) and history that others noticed that the subjects had memory/attention problems ($P = 0.016$ and 0.017, respectively) (Table 2). This study found that MCI patients who used lipid-lowering drug had significantly increased anxiety and aberrant motor behavior domains of NPS ($\chi^2 = 6.26$, $P = 0.01$ and $\chi^2 = 6.38$, $P = 0.01$, respectively).

In the *t* - test analysis, it was found that the MCI patients of the NPS group had lower total MoCA ($P = 0.02$), TMSE ($P = 0.006$), and DAD-T scores ($P < 0.001$), which were statistically significant (Table 3). There were no significant differences in age between those with and without NPS.

In multiple regression analysis, it was found that agitation and apathy significantly predicted DAD-T, MoCA and TMSE scores ($P < 0.001$, $< 0.001$, and 0.001, respectively; all inversely associated) (Table 4).

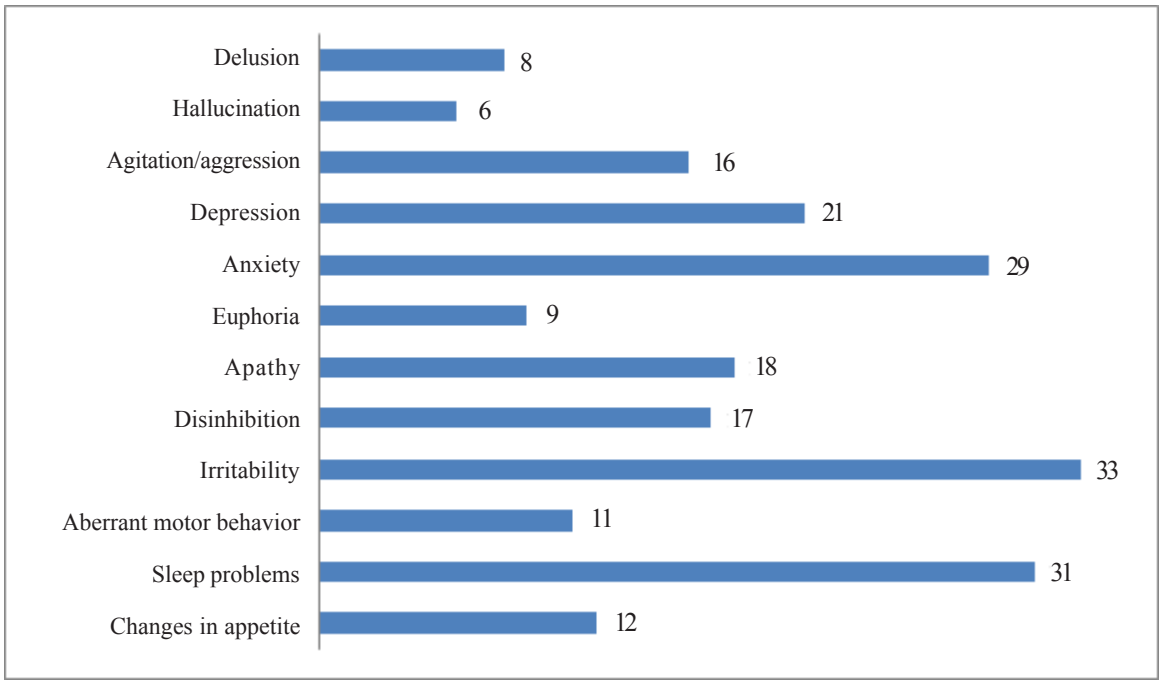


**Figure 1.** Prevalence of neuropsychiatric symptoms (12 domains).

**Table 2.** Factors related to NPS in MCI patients by Chi-square or Fisher's Exact test.

| Factors | NPS | | | | $\chi^2$ or Phi | *P* - value |
|---|---|---|---|---|---|---|
| | Absence ( n = 35 ) | | Presence ( n = 65 ) | | | |
| | n | % | n | % | | |
| **Gender** | | | | | | |
| Male | 10 | 28.6 | 25 | 71.4 | 0.978 | 0.320 |
| Female | 25 | 38.5 | 40 | 61.5 | | |
| **Educational level** | | | | | | |
| Below bachelor's degree | 21 | 44.7 | 26 | 55.3 | 3.653 | 0.056 |
| Bachelor's degree or above | 14 | 26.4 | 39 | 73.6 | | |
| **Marital status** | | | | | | |
| Single/divorce/widow | 12 | 35.3 | 22 | 64.7 | 0.002 | 0.965 |
| Marriage | 23 | 34.8 | 43 | 65.2 | | |
| **Medical underlying diseases** | | | | | | |
| No | 2 | 50.0 | 2 | 50.0 | 0.064 | 0.521 [a] |
| Yes | 33 | 34.4 | 63 | 65.6 | | |
| **Psychiatric underlying diseases** | | | | | | |
| No | 27 | 34.6 | 51 | 65.4 | 0.023 | 0.879 |
| Yes | 8 | 36.4 | 14 | 63.6 | | |
| **lipid-lowering drug** | | | | | | |
| No | 24 | 44.4 | 30 | 55.6 | 4.603 | 0.032* |
| Yes | 11 | 23.9 | 35 | 76.1 | | |
| **Cognitive enhancer** | | | | | | |
| No | 25 | 33.8 | 49 | 66.2 | 0.185 | 0.667 |
| Yes | 10 | 38.5 | 16 | 61.5 | | |
| **Drug for psychiatric condition** | | | | | | |
| No | 22 | 36.1 | 39 | 63.9 | 0.078 | 0.780 |
| Yes | 13 | 33.3 | 26 | 66.7 | | |
| **Dementia in family** | | | | | | |
| No | 29 | 37.2 | 49 | 62.8 | 0.740 | 0.390 |
| Yes | 6 | 27.3 | 16 | 72.7 | | |
| **Psychiatric disease in family** | | | | | | |
| No | 33 | 36.7 | 57 | 63.3 | 0.105 | 0.295 [a] |
| Yes | 2 | 20.0 | 8 | 80.0 | | |
| **Others notice patient's memory problem** | | | | | | |
| No | 20 | 48.8 | 21 | 51.2 | 5.801 | 0.016* |
| Yes | 15 | 25.4 | 44 | 74.6 | | |
| **Others notice patient's attention problem** | | | | | | |
| No | 30 | 42.3 | 41 | 57.7 | 5.662 | 0.017* |
| Yes | 5 | 17.2 | 24 | 82.8 | | |
| Duration of cognitive impairment | | | | | | |
| ≤ 5 year | 31 | 37.8 | 51 | 62.2 | 1.575 | 0.209 |
| > 5 year | 4 | 22.2 | 14 | 77.8 | | |

*$P < 0.05$, **$P < 0.01$, [a] = Phi coefficient

**Table 3.** Factors related to NPS in MCI patients by *t* - Test.

| Factors | NPS | Mean ± SD | Mean Difference | *P* - value |
|---|---|---|---|---|
| Age (years) | Absence | 70.00 ± 7.34 | - 2.046 | 0.194 |
| | Presence | 72.05 ± 7.52 | | |
| MoCA | Absence | 22.54 ± 2.21 | 1.281 | 0.022* |
| | Presence | 21.26 ± 3.24 | | |
| TMSE | Absence | 28.49 ± 1.58 | 1.055 | 0.006** |
| | Presence | 27.43 ± 1.89 | | |
| DAD_T | Absence | 99.50 ± 1.58 | 4.433 | < 0.001** |
| | Presence | 95.07 ± 8.16 | | |

*$P < 0.05$, **$P < 0.01$

**Table 4.** Predictive of cognitive function and ADL (by multiple regression).

| Dependent variables | Predictors | B | SE | *t* | *P* | F | df | *P* | Partial Eta squared |
|---|---|---|---|---|---|---|---|---|---|
| MoCA | Agitation | - 1.951 | 0.863 | - 2.26 | 0.027 | 8.64 | 3/70 | < 0.001 | 0.27 |
| | Apathy | - 2.255 | 0.775 | - 2.91 | 0.005 | | | | |
| | Delusion | - 2.454 | 1.191 | - 2.06 | 0.043 | | | | |
| TMSE | Apathy | - 1.399 | 0.519 | - 2.70 | 0.009 | 7.23 | 2/71 | 0.001 | 0.17 |
| | Agitation | - 1.218 | 0.534 | - 2.28 | 0.026 | | | | |
| DAD-T | Agitation | - 9.552 | 1.858 | - 5.14 | < 0.001 | 17.83 | 3/70 | < 0.001 | 0.43 |
| | Apathy | - 6.580 | 1.794 | - 3.67 | < 0.001 | | | | |
| | Age | -0.200 | 0.100 | -2.01 | 0.049 | | | | |

## Discussion

In the current study, the prevalence of NPS in patients with MCI was found in a slightly large number (65.0%). In compliance with previous studies in other countries; for example, the systematic review by Gallagher D, *et al*. [6] the prevalence of NPS was found to be 35.0 - 85.0%. As for the cross-sectional study by Trivedi SC, *et al*. [8] in India, the prevalence was 63.7%. Meanwhile, the study by Panasathit M, *et al*. [9] in Thailand showed a prevalence of 75.0%. This study discovered that 50.0% and 36.0% of patients suffered from NPS by more than two and three domains, respectively. The tendency was in a greater number than in the result of Panasathit study[9], which studied MCI patients whose TMSE and MoCA scores were closer to the current study but found at least two NPS of 30.0% and three NPS of 27.5%. This is probably because the most caregivers of this research was a female who lived with the patients (24 years on average); therefore, they could provide more details. In this study, it was found that the mean of the NPS domains was 2.11, which was close to the result of Edwards ER, *et al*. [7] in California that found the mean number of NPS to be 2.3.

According to this present study, the NPS that were mostly found were irritability (33.0%), sleep problems (31.0%) as the second, and anxiety (29.0%) as the tertiary. The symptom which was rarely found was hallucinations (6.0%). Similarly, the previous study had applied the NPI-Q evaluation to assess the NPS; for instance, the study by Phanasathit M, *et al*. [9], which studied 40 patients. The most found NPS were sleep problems (37.5%), irritability, anxiety, and changes in appetite (25.0% each). The study of Forrester SN, *et al*. [19] in the USA stated that the most found NPS were depression (22.0%), irritability (21.0%), anxiety (18.0%), and sleep problems (17.0%). Meanwhile, the study of the prevalence of NPS evaluated by NPI also provided a similar result to the study of Edwards ER, *et al*. [7], which found the most NPS were anxiety (39.3%), sleep problems (35.2%), and depression (34.9%).

Even though the results of this study found the hierarchy and volume of prevalence differing from other studies, they were still slightly different as the information of the common NPS were similar. In other words, irritability, anxiety, sleep problems, and

depression were mostly found and might relate to each other. In reference to the study of Peters KR, *et al*. [20] in Canada, the NPS were divided into two aspects: mood cluster and frontal cluster. The highest frequency of the NPS in accordance with this study and the aforementioned all belonged in the mood cluster. Kevin discovered that patients with MCI possessed symptoms in the mood cluster more than the frontal cluster, which differed from patients with dementia, as the symptoms of the frontal cluster were almost entirely found to have apathy and aberrant motor behavior. [3] Furthermore, according to Lanctôt KL, *et al*. [21] , the three phases of NPS were mainly associated with the severity of dementia. For this study, the NPS at phases 1 to 2 were mainly found while phase 3 (delusions, hallucinations, euphoria, and motor disturbance) was a small group. The study results might indicate that recent NPS originate from the disability of the brains' work, specifically in the frontal lobe, which deals with executive, judgment, problem solving, and inhibition. The elderly who have no problems with the frontal lobe rarely have NPS whereas during MCI, the frontal lobe weakens, and decision-making and inhibition decrease. Hence, anxiety and emotional symptoms are frequently found but when entering dementia, the frontal lobe will function with many errors and the patients will demonstrate more psychosis symptoms.

As for the data of the assessments, the factors in the TMSE and MoCA evaluations with patients with MCI with the NPS had a mean lower than the group without NPS symptoms. This conformed to the previous data, which realized the relationship of the cognitive impairment's severity and NPS. In addition, this conformed to the information stating that dementia patients had more NPS than patients with MCI while the patients with MCI had more NPS than the general elderly. [8, 22] Besides, some domains of NPS had a special link to cognitive impairment. This study found that agitation and apathy were the most predictors for cognitive impairment. Similar to Richard study[23], who found that apathy increase the risk of progression from MCI to Alzheimer's disease.

It was revealed that one out of two patients had the record informing that others had seen that they had a problem about memory and one out of three patients had the record informing that the patients had a problem with attention. This might represent the severity of the cognitive impairment, as others could see it. The data relating to the presence of the NPS was quite significant. For this reason, this required giving priority to the short and simple questions as a means to explore the NPS and treat the patients appropriately. Furthermore, to diagnosis the patients with MCI, they had to perform their daily activities normally. However, according to this current study, the patients who participated in the research must have recorded that they could perform all of their daily activities. On the other hand, as a result of the DAD-T evaluation, 38.0% of the subjects did not receive a score of 100.0%. In this study, the DAD-T score was highly related to the presence of NPS. In consequence, the treatment of this patient group should have focused on asking about their ability in doing daily activities or add the DAD-T evaluation as the standard diagnosis of a patient with MCI.

With regards to the other factors, the study found that the patients who used a lipid-lowering drug encountered more significant NPS. As for the information about the lipid-lowering drug belonging in the statin group and PCSK9 inhibitor group, they affected dementia and caused other mental disorders. Nowadays, research results conflict with each other due to the fact that many studies support the relationship of statin and depression, but many have found no relationship between these two issues. [24 - 26] Moreover, there are a few current studies about the relationship between the PCSK9 inhibitor with mental disorders. There are also a lot of studies about the NPS' mechanism of a lipid-lowering drug in both groups that is associated with interrupting the production of brain cholesterol. This information might require a doctor to be more aware of the importance of a patient's medication, especially the lipid-lowering drug of patients in a mental disorder department of a hospital.

The strength of this study was the selection of the NPI-Q tool as the standard validation. A NPI-Q tool is capable of differentiating the person who has never had NPS or a mental disorder, but any symptom changes within a month might be a result of cognitive impairment. From the interview with the doctors who were trained to use the tool and the direct interview with the subjects who were the caregivers of the patients, the mean of staying with the patients was 5.9 days/week and staying with the patients for 24 years on average. The caregivers probably recognized the old characters of their patients and were able to describe the difference relating to NPS within one month before the interview. Therefore, their

information has the probability to be very credible. In terms of limitations, due to the fact that this was a descriptive research, it only demonstrated the prevalence of NPS and the relating factors. The study could not indicate any causal relationships. Moreover, as the study specifically researched on patients who came for treatment as outpatients in King Chulalongkorn Memorial Hospital, which is a tertiary-care hospital, it was regularly found that the patients had more severe symptoms than a general institute or hospitals that were not at the tertiary-care level. This study did not exclude the patients with psychiatric disorders, so we cannot indicate whether NPS is caused by the existing psychiatric disorders or the mild cognitive impairment. Thus, the result of this study needed to focus on this fact.

The further study should increase the sample size in order to clarify the significance of some factors that would tend to have a relationship with NPS, but were not significant in this study. Subjects may be recruited from a multicenter, which can be more applied to the general population. Additional information should be accounted for type of lipid-lowering drug, psychoneurobiological profile and neuroimaging to explore the mechanisms that cause NPS in MCI patients. A analytical study should be designed to find the causal relationship between the factors and NPS in MCI patients.

## Conclusion

NPS are very common in Thai MCI patients. Therefore, the management of patients with MCI should always be assessed for NPS, as they are often found to be in the mood-symptoms group; such as, irritability, worry, depression and sleep problems. Adequate NPS management should be undertaken to reduce these symptoms and the caregiver's distress.

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## Conflicts of interest

The authors, hereby, declare no conflict of interest.

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