Risk Factors in Neuroleptic Malignant Syndrome: A 10-year Case-control Study of Neuroleptic Use in Patients in Charoenkrung Pracharak Hospital

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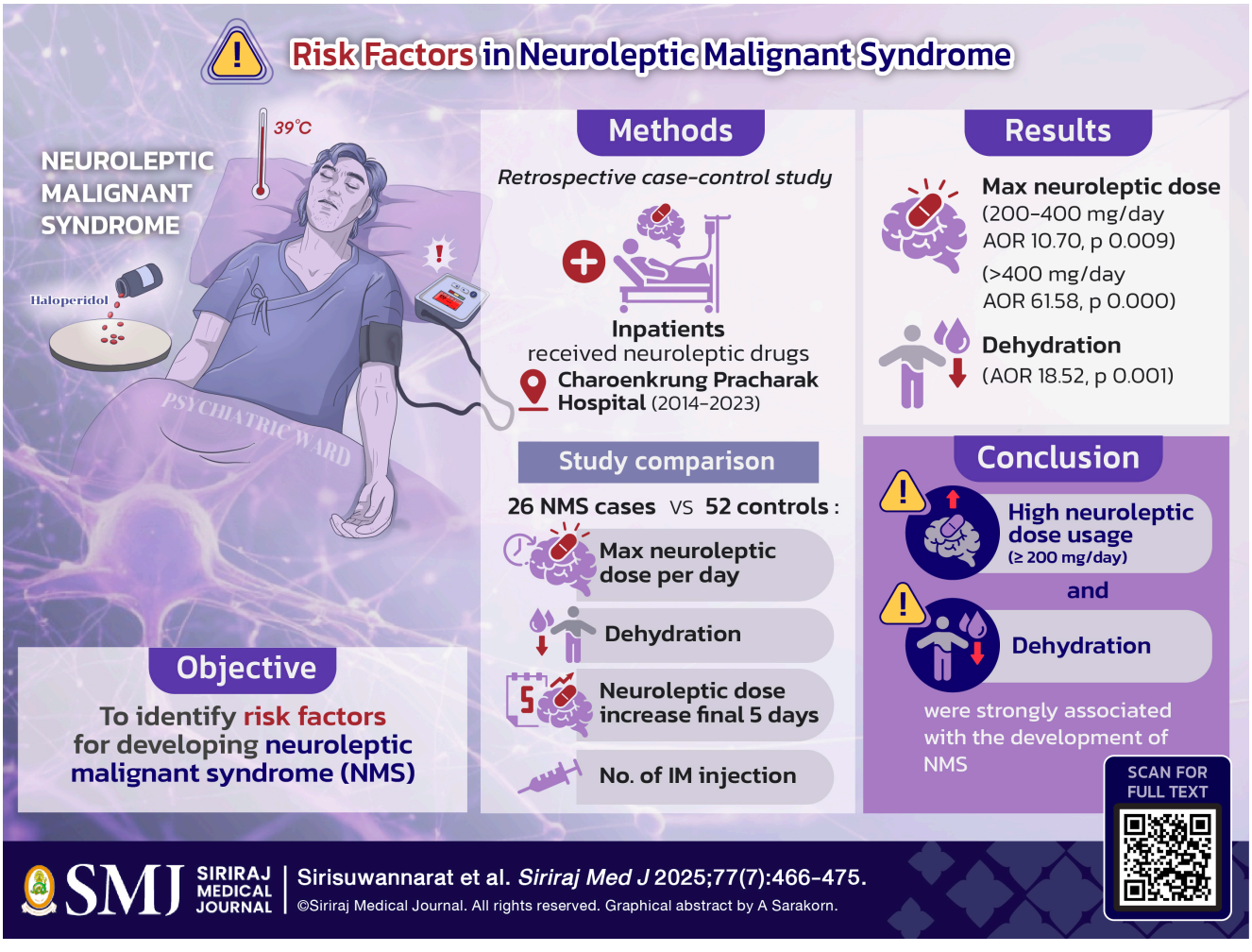

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ABSTRACT

Objective: To identify the risk of using high doses of neuroleptics in the development of neuroleptic malignant syndrome (NMS). Additionally, we examined other potential risk factors, including age, psychiatric diagnosis, route of neuroleptic administration, dose escalation over a short period, psychomotor agitation, dehydration, and electrolyte imbalance.

Materials and Methods: A case-control study was performed, comprising 26 NMS cases matched with 52 controls by sex and time of admission to the hospital over a 10-year data-collection period. A retrospective chart review was conducted to compare the two groups using conditional logistic regression analysis.

Results: The maximum neuroleptic dose (adjusted OR 10.70, 95%CI 1.79–64.00 for a neuroleptic dose of 200–400 mg/day and adjusted OR 61.58, 95%CI 6.87–552.19 for a neuroleptic dose > 400 mg/day) and dehydration (adjusted OR 18.52, 95%CI 3.22–106.62) were found to be significant risk factors for developing NMS.

Conclusion: The risk factors for developing NMS were found to be receiving a high dose of neuroleptics per day and dehydration.

Keywords: Neuroleptic malignant syndrome; maximum neuroleptic dose; neuroleptic increase final 5 days; delirium; dehydration; electrolyte imbalance (Siriraj Med J 2025; 77: 466-475)

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare fatal adverse effect of taking neuroleptic drugs. This syndrome is characterized by three main symptoms: generalized muscle rigidity with akinesia, autonomic nervous system (ANS) dysregulation, and alteration in mental status.[1] The incidence rate ranged from 0.02% to 3.2%.[2] The mortality rate was reported as high as 10%–55%.[3] Currently, the most effective approach to avoid NMS is prevention through raising awareness of the potential risks. Identifying the risk factors has been of great interest.

Previous research into the risk factors for developing NMS has been done by the first case series of Addonizio et al. U.S. in 1986.[4] Later, the first case-control study was published by Keck et al. U.S. in 1989[5], who concluded that the risk factors correlated with NMS were the use of a high dose of neuroleptic drugs within a short period of time and intramuscular neuroleptic injection; however, that study had some limitations, including its small sample size, which limited the analysis of the statistically significant independent variables.

Since then, there have been many studies performed in various formats, including case series, cross-sectional, and case-control methodologies, aimed at determining the potential risk factors associated with NMS. One good quality study was done by Sachdev et al. in 1997[6] with an Australian population and an adequate sample size (25 cases and 50 controls) that showed that receiving a high neuroleptic dose per day was a risk factor for developing NMS. This study also found that dehydration was another key risk factor like in a study of Chen et al.[7] which suggested that dehydration was the risk factor for NMS.

Many experts have studied about risk factors for developing NMS. "Maximum neuroleptic dose" (Maximum dose of neuroleptic per day) was one of the most interesting factors. The previous studies[5,6,8,9] found that maximum neuroleptic dose was the associated factor to cause NMS but all these studies emphasize only increasing dose was the risk but did not study which dose level that being the risk. The study by Su YP et al.[10] and Guinart et al.[11] were the large and most recent studies that studied more about which dose level that might be the risk but their finding had different outcomes. SU YP et al. concluded that maximum neuroleptic dose was not associated with increasing the risk of NMS but Guinart et al. concluded that neuroleptic dose more than 2 DDDs (defined daily dose) increase the risk of developing NMS.

About the class and potency of neuroleptic drugs, we found three large case-control studies which had results in the same direction that likelihood of developing NMS did not differ by neuroleptic class (first-generation antipsychotics VS second-generation antipsychotics).[7,11,12] About the potency of neuroleptic drug, Nielsen et al.[13] found that high- or mid-potency first-generation antipsychotics and second-generation antipsychotics indicated an increased risk of NMS. However, since it did not directly compare the two potencies, we cannot conclusively determine whether potency itself is a risk factor for developing NMS.

Regarding the form of neuroleptic use, intramuscular neuroleptic injection was frequently reported as a significant risk factor for developing NMS in most studies.[5,9] Only

one study[6] reported non-significant results. Concerning long-acting neuroleptic injection, the majority of studies found no statistically significant association with NMS.[9-12,14]

In terms of "increasing the neuroleptic dose over a short period", many studies have emphasized this factor.[5,6,8,15] However, the outcomes have been controversial. Keck et al.[5] and Berardi et al.[8] reported positive findings supporting this as a risk factor, whereas Sachdev et al.[6] and Langan et al.[15] found no significant association. Langan et al. specifically concluded that "increasing the neuroleptic dose over a short period" is not a risk factor for developing NMS.

In Thailand, the focus area of this research, there have been prior case reports and case series about NMS, Taemeeyapradit et al.,1989[16] and Kooptiwoot et al.,1999[17] were the first and second case reports in Thailand but, to the best of our knowledge, no case-control study has yet been performed in Thai population. However, four big case series studies were performed. The first case series was by Wae-alee et al. in 1996[18], who found that changes in the amount or type of neuroleptic drug used were associated factors for developing NMS. The second case series was performed by Tantiphlachiva in 1999[19], who found that the associated factors for developing NMS were an agitated state, dehydration, long-acting neuroleptic injection, and intramuscular neuroleptic injection. The third case series was performed by Kasantikul et al. in 2006[20] who found that the associated factor for developing NMS was dehydration. The fourth, and most recent, case series was performed by us in 2020.[21] In our study, we postulated that old age, delirium, and alcohol dependency were associated risk factors for developing NMS.

In conclusion, from reviewing the past literature, the following factors have been put forward as risk factors for developing NMS: male sex[7], old age[21], psychiatric diagnosis[22-26], delirium[7,8], alcohol dependence[21], intravenous neuroleptic injection[8], intramuscular neuroleptic injection[5,9], long-acting neuroleptic injection[19], maximum neuroleptic dose[5,6,8,9,11,15], increase in neuroleptic dose in a short period[5,8], changes in the amount or type of neuroleptic drug[18], psychomotor agitation[5,6,8,9,19], dehydration[6,7,19,20], mechanical restraint or locked in open seclusion[6], extra pyramidal symptoms[7,8], and electrolyte imbalance.[27]

Nevertheless, despite significant advances in the literature regarding risk factors for NMS, there remain some limitations. For example, smaller studies often provide detailed information on each case and control but they lack sufficient statistical power to reach definitive conclusions. Conversely, larger studies may have adequate statistical power but frequently lack detailed data essential for ensuring reliability. Additionally, the two largest and most recent studies examining the maximum neuroleptic dose reported conflicting outcomes, resulting in uncertainty about whether the maximum neuroleptic dose is a definitive risk factor for NMS. Furthermore, most previous case-control studies were conducted in Western populations. Upon reviewing the literature, we found that non-white ethnic groups have a twofold increased risk of NMS[10], potentially related to genetic differences in the CYP2D6 gene, as Caucasian populations typically possess more normal-function CYP2D6 alleles compared to Asian, African, or African American populations.[28,29] Due to these varying outcomes and genetic differences between Caucasian and non-white populations (including Asians), it was essential to perform a case-control study that has adequate sample size for the main objective and detailed data collection specifically targeting the Thai population to enhance the reliability of our findings.

In our opinion, we consider that the "maximum neuroleptic dose at a high level" may be the greatest risk factor for developing NMS based on our review of the literature, whereby this factor has the strongest evidence to support this as a risk factor. Also, previous studies mostly did not identify the exact dose that would represent a risk factor for NMS. Consequently, these inspired us to set the primary outcome as "the level of neuroleptic dose that would represent a risk factor for developing NMS". Our secondary outcomes were the other factors that might be risk factors for NMS, such as age, psychiatric diagnosis, intramuscular neuroleptic injection, long-acting neuroleptic injection, neuroleptic increase final 5 days (increase in neuroleptic dose in a short period), psychomotor agitation, dehydration, and electrolyte imbalance.

MATERIALS AND METHODS

The study protocol was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (BMAHREC); Approval number: S015hc/67_EXP.

We initially identified all the neuroleptic-treated inpatients in our hospital from 2014 to 2023 who were diagnosed with NMS according to ICD-10 code G210, then selected only the cases that matched the DSM-5 criteria.[30] After all the cases (patients with neuroleptic use who were diagnosed with NMS by DSM-5 criteria) had been identified, systematic sampling (as shown in Fig 1) was performed to select 26 NMS cases (as the calculated required sample size, see below) for the statistical analysis. We chose 52 control patients (matched to the cases by

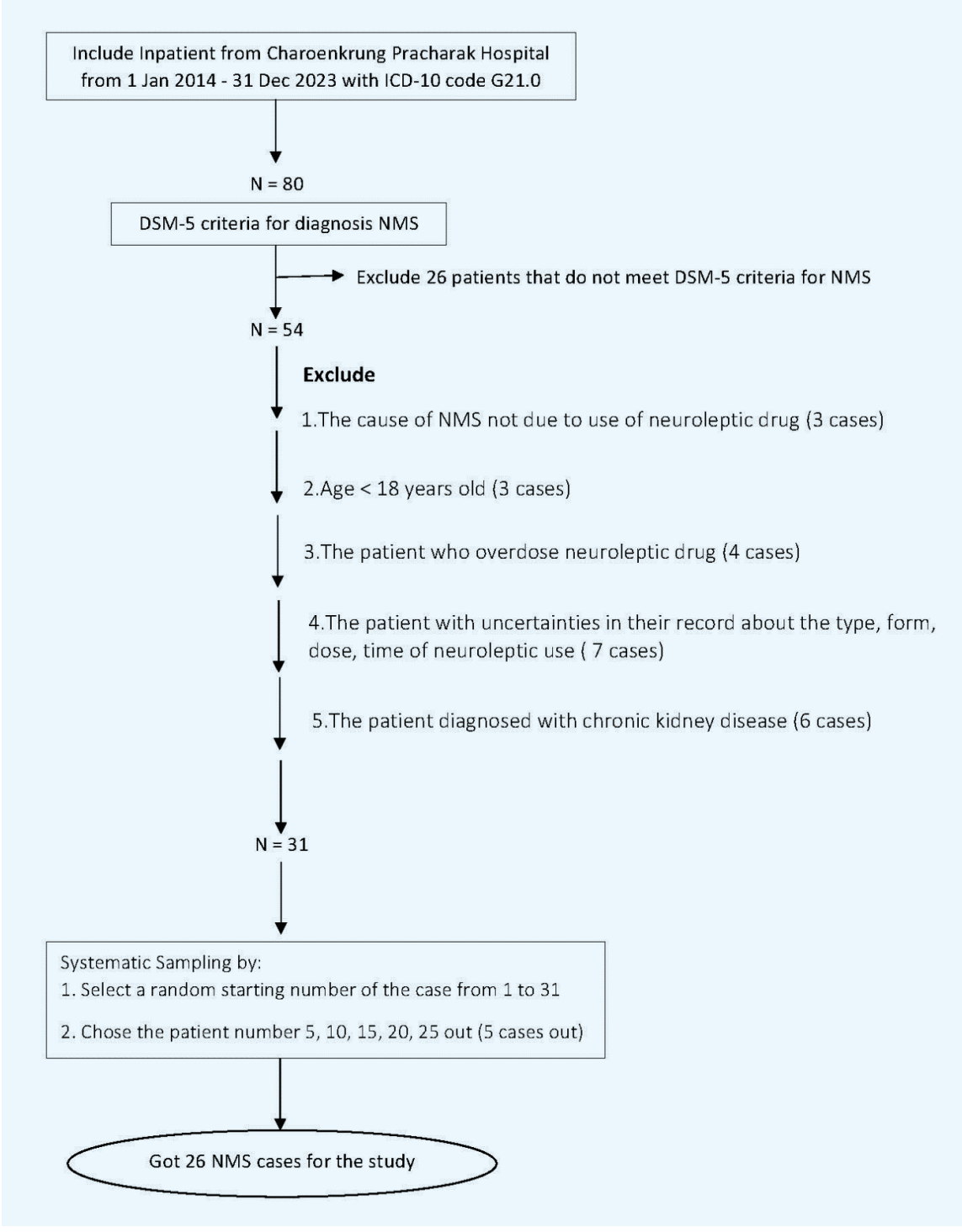

Fig 1. Systematic sampling flowchart for including NMS cases to this study.

gender and date of admission to the hospital). All the patients were treated at the inpatient unit of Charoenkrung Pracharak Hospital. We excluded patients who were aged <18 years old, who did not use neuroleptic drugs, intentionally took an overdose of neuroleptic drugs, patients with missing laboratory data or a psychiatric diagnosis, and patients with uncertainties in their records about the type, form, dose, and time of neuroleptic use.

The definitions of some variables are as follows:

1. Maximum neuroleptic dose (mg per day): the dose of neuroleptics used on the day with the highest dose within 2 weeks preceding the end point[31] (see definition of "the end point" below). The total neuroleptic dose was converted to chlorpromazine equivalents dose (using Davis's schedules[32]).

- For intravenous neuroleptic use: doses were

converted to chlorpromazine equivalents by estimating the intravenous administration to be 3 times as potent as oral dosing, as determined by Davis's schedules.[32]

- For intramuscular neuroleptic use: doses of haloperidol 5 mg intramuscular were converted to haloperidol 8.3 mg oral (reference from Hertfordshire Partnership University NHS Foundation Trust).

- For long-acting neuroleptic use:

- haloperidol decanoate 100 mg intramuscular was considered equivalent to 10 mg oral haloperidol[33];
- fluphenazine decanoate 25 mg intramuscular was considered equivalent to 300 mg oral chlorpromazine.[9]

2. Neuroleptic increase final 5 days: neuroleptic dose increases during the 5 days preceding the end point.

- For a dose increase compared to the starting point: use '+' symbol (e.g., +50 mg);

- For a dose decrease compared to the starting point: use '-' symbol (e.g., -50 mg).

3. Number of intramuscular neuroleptic injections: number of intramuscular neuroleptic injections received during the 2 weeks preceding the end point.[31]

4. Long-acting neuroleptic injection: "use" or "no use" of long-acting neuroleptics within 1 month preceding the end point.[9]

5. Psychiatric diagnosis: defined following the ICD-10 codes.

6. Delirium: defined as "delirium" following the ICD-10 code "F05" within 2 weeks preceding the end point.[31]

7. Psychomotor agitation: excessive and purposeless motor activity, requiring medication or restraint or seclusion within 2 weeks preceding the end point.[31]

8. Dehydration: 1) hematocrit or blood urea nitrogen concentration (BUN) > 50% of the normal range or 2) serum creatinine > 1.2 mg/dL[8] preceding the end point (rules out patients diagnosed with chronic kidney disease who might show a permanent BUN or serum creatinine increase to prevent misinterpreting this as dehydration).

9. Electrolyte imbalance: hyper-hyponatremia with blood sodium level > 145 or < 136 mmol/L, and hyper-hypokalemia with blood potassium level > 5.1 or < 3.5 mmol/L preceding the end point.

The definition of "the end point" (for variable numbers 1–9 above)

- for cases: the onset of NMS[8];

- for controls: the hospital day corresponding to the day of onset of NMS in the cases.[8]

The date used for recording the laboratory data for variable numbers 8–9 was recorded within ±3 days, when available.[8]

Sample size

We calculated the required sample size for our study based on the study by Sachdev et al.[6] as a reference (see Table 1 in Sachdev et al.: "Case-control study of neuroleptic malignant syndrome"). The "maximum neuroleptic dose" was used to calculate the required number of cases and controls as follows.

$$n_1 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_1^2 + \frac{\sigma_2^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_2}{n_1},\ \Delta = \mu_1 - \mu_2$$

$$\mu_1 = mean\ in\ group1$$
$$\mu_2 = mean\ in\ group2$$
$$\sigma_1 = S.D.\ in\ group1$$
$$\sigma_2 = S.D.\ in\ group2$$
$$\mu_1 = 958.3$$
$$\mu_2 = 488.1$$
$$\sigma_1 = 821.1$$
$$\sigma_2 = 334.4$$

n1 = cases n2 = controls

$$\gamma = ratio = \frac{2}{1}$$
$$\alpha = 0.05\ ;\ \beta = 0.2$$
$$n_1 = \frac{[Z_{1-\frac{0.05}{2}} + Z_{1-0.2}]^2[(821.1)^2 + \frac{334.4^2}{2}]}{(958.3 - 488.1)^2}$$

$$n_1 = 26$$
$$n_2 = 52$$

The sample size for cases was 26, controls was 52 based on the calculated formula as above.

Statistical analysis

Comparative analyses of the two groups were conducted using different statistical methods based on the type of data. For continuous variables with a normal distribution, the T-test was employed, while the Wilcoxon signed-rank test was utilized for data that were non-normally distributed or for noncontinuous discrete variables. Fisher's exact test was applied to assess the differences in dichotomous variables. The data are presented herein as frequencies and as mean values accompanied by their standard deviations (mean ± SD). Relationships between variables were analyzed through conditional logistic regression, which is known to be suitable for case-control studies where one case is matched to two control subjects (A 1:2 case-control ratio was chosen to improve statistical power while

TABLE 1. Differences in risk factors for developing neuroleptic malignant syndrome between patients with the syndrome (N=26) and the controls (N=52): continuous variables.

Variables	Case		Control		Crude Odds Ratio				Adjusted Odds Ratio			
Continuous	Mean	SD	Mean	SD	Odds ratio	P-value	95% Confidence interval		Odd Ratio	P-value	95% Confidence interval	
Age	57.23	18.02	63.96	17.97	0.98	0.098	0.95	1.00				
Maximum neuroleptic dose (mg/day)	534.32	314.90	114.31	314.91	1.01	0	1.00	1.01				
- Neuroleptic level 0–200 mg/day	106.80	54.80	67.63	44.31	NS	NS	NS	NS				
- Neuroleptic level 200–400 mg/day	254.92	127.49	92.43	70.89	8.20*	0.002	2.13	31.63	10.70*	0.009	1.79	64.00
- Neuroleptic level >400 mg/day	795.24	363.92	471.67	49.07	35.53*	0	7.46	169.33	61.58*	0.000	6.87	552.19
No. of intramuscular injections	0.62	0.77	0.15	0.78	2.47*	0.037	1.06	5.79	0.85	0.712	0.37	1.97
Neuroleptic dose increase final 5 days	46.80	147.92	-3.80	147.92	1.00	0.170	1.00	1.01				
- Neuroleptic increase < 0 mg	33.04	147.18	-70.45	55.00	NS	NS	NS	NS				
- Neuroleptic increase ≥ 0 mg	95.51	186.97	28.57	83.00	3.72*	0.050	0.98	14.16	9.65	0.070	0.83	111.84

* = statistically significant

Abbreviations: N = Number of patients; NS = not statistically significant; OR = Odds Ratio; SD = Standard deviation

maintaining feasibility in data collection.) The results are reported as odds ratio with 95% confidence intervals (95% CI) to indicate statistical significance. The analyses were performed using STATA version 17.0.

RESULTS

In total, 26 inpatients from Charoenkrung Pracharak Hospital who were diagnosed with NMS during January 1, 2014, to December 31, 2023 were added in our study, in line with the required sample size determined above. The data of these patients were compared to those of the control group, comprising 52 inpatients. The mean age for the cases was 57.23 ± 18.02 years old, and for the controls was 63.96 ± 17.97 years old, with the proportions of males and females as 53.85% males and 46.15% females in both groups. The main psychiatric diagnosis for both the cases and controls was delirium (cases = 57.69%, controls = 65.38%). The second main psychiatric diagnosis was schizophrenia for both the cases and controls (cases = 38.46%, controls = 25.00%). There was no statistically significant difference found for all types of psychiatric diagnosis.

Table 1 and Table 2 present comparisons of the cases and controls for different variables. Four variables showed statistical significance: 1) maximum neuroleptic dose (categorized into 200–400 mg/day: crude OR = 8.2,

TABLE 2. Differences in risk factors for developing neuroleptic malignant syndrome between patients with the syndrome (N=26) and the controls (N=52): categorical variables.

Variables Categorical		Case N	Case %	Control N	Control %	Crude Odds Ratio				Adjusted Odds Ratio			
						Odds ratio	P-value	95% Confidence interval		Odds ratio	P-value	95% Confidence interval	
Sex	Male	14	53.85	28	53.85	Matched variable							
	Female	12	46.15	24	46.15								
Psychiatric diagnosis	Schizophrenia	10	38.46	13	25.00	2.44	0.083	0.89	6.72				
	Bipolar disorder	2	7.69	1	1.92	4.25	0.247	0.37	49.20				
	Major depressive disorder	1	3.85	1	1.92	2.04	0.619	0.12	33.98				
	Organic mental syndrome	3	11.54	9	17.31	0.62	0.508	0.15	2.53				
	Anxiety	1	3.85	1	1.92	2.04	0.619	0.12	33.98				
	Substance use disorder	0	0.00	3	5.77	NS	NS	NS	NS				
	Delirium	15	57.69	34	65.38	0.89	0.843	0.27	2.89				
	Mental retardation	3	11.54	0	0	NS	NS	NS	NS				
	Alcohol dependence	6	23.08	11	21.15	6.65	0.109	0.66	67.43				
Pre-NMS conditions	Agitation	13	50.00	31	59.62	0.79	0.627	0.31	2.04				
	Dehydration	14	53.85	6	11.54	8.94*	0.000	2.84	28.20	18.52*	0.001	3.22	106.62
	Electrolyte imbalance	18	69.23	31	59.62	1.41	0.505	0.16	3.83				
Others related to treatment	Long-acting neuroleptic injections	3	11.54	0	0	0.67	0.414	0.26	1.75				

* = statistically significant

Abbreviations: N = Number of patients; NS = Not statistically significant; OR = Odds ratio; S.D. = Standard deviation

95% CI = 2.13–31.63 and >400 mg/day: crude OR = 35.53, 95% CI = 7.46–169.33); 2) number of intramuscular injections (crude OR = 2.47, 95% CI = 1.06–5.80); 3) neuroleptic increase final 5 days (≥0 mg: crude OR = 3.72, 95% CI = 0.98–14.16); 4) dehydration (crude OR = 8.94, 95% CI = 2.84–28.20). Next, we performed conditional logistic regression analysis for these four significant variables. The results (Tables 1 and Table 2) revealed three significant variables (P<0.05): 1) maximum neuroleptic dose 200–400 mg/day (adjusted OR = 10.70, 95% CI = 1.79–64.00); 2) maximum neuroleptic dose exceeding 400 mg/day (adjusted OR = 61.58, 95% CI = 6.87–552.19); and 3) dehydration (adjusted OR = 18.52, 95% CI = 3.22–106.62). For our primary outcome, we found evidence that the greater the increase in neuroleptic dose per day, the stronger the statistical significance, implying that the factor "maximum neuroleptic dose" was a great risk for developing NMS.

For the secondary outcomes, only dehydration was statistically significant between the two groups (adjusted OR = 18.52, 95% CI = 3.22–106.62), while the factors: age, psychiatric diagnosis, delirium, alcohol dependence, neuroleptic increase final 5 days, intramuscular neuroleptic injection, long-acting neuroleptic injection, psychomotor agitation, and electrolyte imbalance did not differ significantly between the two groups.

DISCUSSION

From our study, the most significant factors correlated with the risk of developing NMS were the **maximum neuroleptic dose** and **dehydration**. Our study suggests that NMS appears to occur in patients who have received high doses of neuroleptics or are dehydrated. These findings accorded with the trends reported in previous studies[5,6,8,9,11] who reported that receiving a high neuroleptic dose per day was a risk factor for NMS. We also found evidence that the higher the neuroleptic dose, the stronger the statistical results. Our findings implied that the factor "maximum neuroleptic dose" was the greatest risk factor for developing NMS [maximum neuroleptic dose of 200–400 mg/day had an adjusted OR of 10.7 (P = 0.009, 95% CI = 1.79–64.00) while a maximum neuroleptic dose exceeding 400 mg/day had an adjusted OR of 61.58 (P = 0.000, 95% CI = 6.87–552.19)]. Our study results were in line with a previous case series of 13 NMS cases reported[15], who found that a "rapid dose escalation of neuroleptic" might be less correlated to the development of NMS than a "higher daily cumulative neuroleptic dose."

Regarding the number of intramuscular neuroleptic injections, our study found a statistically significant difference between the two groups when we performed univariable logistic regression (crude OR = 2.47, 95% CI = 1.06–5.79) but was not statistically significant when we performed multivariable logistic regression (adjusted OR = 0.85, 95% CI = 0.37–1.97), which was in contrast to previous studies[5,9], who found that intramuscular neuroleptic injection tended to be a risk factor for NMS.

Among the variables, the number of intramuscular neuroleptic injections and an increase in neuroleptic dose in the final 5 days showed trends toward significance, but did not reach this when we considered the adjusted odds ratio. In particular, a quite strong adjusted odds ratio of 9.65 was found for the neuroleptic increase final 5 days, but its p-value was 0.07, exceeding the significance threshold of $p < 0.05$. Our outcome was probably due to the high correlation between the three variables; maximum neuroleptic dose, rate of dose increase, and route of neuroleptic usage in this small sample, which made it difficult to see the impact of each variable separately. Increasing the sample size, or studying only one variable and matching other variables that have a high correlation with it could improve the statistical reliability. For example, if we aimed to study intramuscular neuroleptic injection as a possible risk factor, we could match the maximum neuroleptic dose and the rate of dose increase.

Our data suggest that dehydration independently contributes to the risk of NMS, aligning with the findings in previous studies[6,7,19,20] which strongly suggested that dehydration is a significant risk factor for developing NMS.

For the factor "age" our study showed a different outcome from in the previous study[21] this might because our study mostly consists of elderly patients in both the cases and controls, so we could not identify a difference in this factor.

No statistically significant difference was found among all the types of psychiatric diagnosis (Table 2), which was a different outcome from the reviewed literature studies in refs[22-26] stating that psychiatric diagnosis was a risk factor for developing NMS. Then, we concluded that the psychiatric diagnosis is not being the risk factor for NMS. Surprisingly, we found no significant difference for the factor "delirium" and "alcohol dependence", unlike in the reviewed literature studies[7,8] that delirium was the risk for NMS and unlike in the reviewed literature study[21] that alcohol dependence was a risk factor for NMS. The reason that in our study these factors showed no statistical significance, which may have been due to different in characteristics of the sample group from normal population that in our study both the cases and controls were mostly under delirious and alcohol dependent state, so we could not identify a difference between the two groups.

In terms of "long-acting neuroleptic injection" as a factor, we found no statistical significance among the two groups, unlike in the case series.[19] But our study tends to has the same outcome as the study of SU YP et al.[10] which found that depot flupentixol has no significant association to be the cause of NMS, also in the same direction as previous studies[9,11,12,14] which found that long-acting neuroleptic injection was not associated with an increased frequency of NMS.

For the factor of psychomotor agitation, there was no statistical significance found in our study, unlike the results in previous studies[5,6,8,9,19], who all reported that psychomotor agitation was a risk factor for NMS. The difference might be because in our study both the cases and the controls were mostly in an agitated state and our definition of psychomotor agitation was less specific to detect a differentiation between the groups. Future studies should investigate this factor further, and should consider a more specific definition in rating the severity of agitation to rule out cases where agitation was present but not severe enough to cause NMS.

Regarding electrolyte imbalance, this could be due to the fact that all our controls were inpatients, who are generally in weakened states also suggested in previous

study.[27] As a result, nearly all the controls selected also had electrolyte imbalance, with high percentages of electrolyte imbalance found in both the cases (69.23%) and the controls (59.62%). Therefore, the results showed no statistical significance between the two groups in our study. To improve the representation, a more diverse control group could be included to ensure a broader variety of participants.

Strengths and limitations of the present study

The main strengths of this study were its design as a case-control study, which is considered the most reliable methodology for rare syndromes like NMS, and also our delving deeply into each factor with an adequate sample size (NMS cases=26) to address our main objective, which was to prove that a high neuroleptic dose is a risk factor for developing NMS. Specifically, we achieved this by evaluating "the maximum neuroleptic dose" as a risk factor for NMS. This study chose an inpatient department (IPD) population, which allowed us to easily obtain all the data needed for the study, especially details on the dose, the route, and the period of neuroleptic administrations. By using an adequate sample size, our results allowed us to determine the statistical significance in the main objective, and we were able to prove that receiving a high neuroleptic dose is indeed a risk factor for developing NMS. We also found that being in a state of "dehydration" is a risk factor for NMS too.

There are some limitations of our study to note with some factors, such as neuroleptic increase final 5 days, number of intramuscular neuroleptic injections, whereby the results showed trends toward significance, but did not show statistical significance, possibly due to an inadequate sample size. We advise that further study should be done with an increased sample size to create a greater possibility of accurately determining the correlation between these factors and NMS. Also, the sample group in this study mostly consists of elderly patients, most of whom have delirium and did not use long-acting neuroleptic injection, the findings may not be generalizable to other populations, such as younger patients. Regarding alcohol dependence, the lack of statistical significance could be attributed to the similar characteristics between the cases and controls, as both groups primarily included alcohol-related conditions. Consequently, we were unable to distinguish alcohol dependence as an independent risk factor between the two groups.

CONCLUSION

According to our study, we found four statistically significant risk factors between the two groups (cases and controls) for developing NMS, which were a maximum neuroleptic level higher than 200 mg/day, dehydration, number of intramuscular injections, and neuroleptic increase final 5 days (≥0 mg). However, after calculating the adjusted odds ratio to smooth out the confounding factors, we found that only **a maximum neuroleptic dose higher than 200 mg/day and dehydration were risk factors for developing NMS**. Our findings suggest avoiding the use of high-dose neuroleptics and dehydration in patients administered with neuroleptic drugs.

Data Availability Statement

The data supporting the findings of this original article are available within the article.

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DECLARATIONS

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Conflict of Interest

The author declares that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

Registration Number of Clinical Trial

None

Author Contributions

Conceptualization and methodology, S.S.; Data collection, S.S.; Formal analysis, S.S.; Visualization and writing – original draft, S.S.; Writing – review and editing, S.S.

Use of Artificial Intelligence

Artificial Intelligence tool was not used in this manuscript.

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