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Research article

Impact of dosing strategy on clinical outcomes of patients with lupus nephritis initially treated with lower-than-recommended-dose cyclophosphamide

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ABSTRACT

Aim: Cyclophosphamide is the mainstay treatment for patients with lupus nephritis (LN); it can be prescribed at lower doses than the recommended regimen to avoid side effects. We aimed to investigate the impact of cyclophosphamide dosing strategies on treatment outcomes of patients with LN initially treated with a lower-than-recommended dose.

Methods: We retrospectively reviewed patients with proliferative LN (class III, IV, or mixed) initially treated with lower-than-recommended-dose cyclophosphamide. Patients who received a titrated dose of cyclophosphamide $\geq$0.5 g/m^2 were categorized into the titrate group, while those who received doses <0.5 g/m^2 were categorized into the non-titrate group. The primary outcome was primary renal response (PRR) at 52 weeks.

Results: Of the 78 patients included, 47 were assigned to the titrate group and 31 to the non-titrate group. The titrate group had a higher proportion of PRR achievement (23 of 47 patients [48.9 %] vs. 7 of 31 patients [22.6 %] in the non-titrate group). After adjusting for potential confounders, a baseline urinary protein-to-creatinine ratio $\geq$3 g/g (OR, 0.3; 95 % CI, 0.1–0.9; P = 0.030), and titrating the dose of cyclophosphamide to $\geq$0.5 g/m^2 (OR, 4.7; 95 % CI, 1.5–15.2; P = 0.010) were independent factors for PRR. Additionally, the titrate group had a lower rate of infection (8 of 47 patients [17.0 %] vs. 12 of 31 patients [38.7 %], respectively; OR, 0.3; 95 % CI, 0.1–0.9; P = 0.036) and death associated with LN (4 of 47 patients [8.5 %] vs. 8 of 31 patients [25.8 %], respectively; OR, 0.3; 95 % CI, 0.1–0.9; P = 0.047) compared with the non-titrate group. LN flare and the need for rescue therapy did not differ between the groups.

Conclusion: For patients with LN initially treated with lower-than-recommended-dose cyclophosphamide, titration of the cyclophosphamide dose $\geq$0.5 g/m^2 was beneficial on renal response, while reducing infection leading to hospitalization and LN-associated death.

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1. Introduction

Lupus nephritis (LN) is a major risk factor for morbidity and mortality in patients with systemic lupus erythematosus [1]. The optimal approach for its treatment is an area of active research; currently, the standard treatment for LN results in just 10–40 % complete remission, and as many as 30 % of patients will progress to end-stage renal disease (ESRD) [2]. Furthermore, the incidence of adverse events from treatment ranges 42.8–97.3 % and leads to discontinuation rates as high as 44.4 % [3]. Thus, effective induction therapy is important to induce remission with a low risk of adverse events.

For patients with focal or diffuse LN, the standard intravenous dose of 0.5–1 g/m^2 cyclophosphamide given monthly, is one of the most studied and effective treatment regimens, with long-term data showing persistent benefits [4]. However, infection complications from cyclophosphamide use were reported to be as high as 77 %, with a mortality rate ranging 2.7–20 %.

Owing to inter-patient variability in cyclophosphamide pharmacokinetics, pharmacogenetics, and pharmacodynamics, establishing a dose-response relationship is challenging. Various studies have identified patient factors such as renal function [5,6], albumin level [7], genetic polymorphism [8,9], body surface area [9], and cyclophosphamide dosage [9] as significant influencers of cyclophosphamide pharmacokinetics. In addition, the pharmacogenetic relationship between genetic polymorphism and cyclophosphamide has been shown to trigger clinically important toxicities—including myelotoxicities [10]—leading to ovarian failure [11] and hemorrhagic cystitis [12]. Therefore, the optimal dosage of cyclophosphamide should be patient-specific.

Concerns over adverse events from the use of the standard cyclophosphamide dose and inter-patient variability led some clinicians to prescribe a lower-than-recommended dose of cyclophosphamide (LDC); i.e., less than 0.5 g/m^2 per month. Thus, it would be appropriate to investigate the potential of LDC for LN treatment. However, there is limited available data on LDC, with only one study reporting the use of monthly intravenous cyclophosphamide at a dosage of 500 mg [13]. Unfortunately, this study did not provide information regarding the dose of cyclophosphamide per body surface area for the population under investigation.

We hypothesized that dose titration with the recommended dose of cyclophosphamide in patients initially treated with LDC could improve therapy effectiveness without increasing the incidence of adverse events. Thus, we aimed to investigate the effect of dose titration on clinical remission and serious adverse events in patients with LN initially treated with LDC.

2. Materials and methods

This retrospective cohort study was performed using the database of Hatyai Hospital, a regional tertiary center in southern Thailand. We identified all adults (aged >18 years) who were diagnosed between 2012 and 2021 with biopsy-proven LN class III, IV, based on the International Society of Nephrology, Renal Pathology Society (ISN/RPS) 2004 classification; mixed classes III + V and IV + V were also included. All patients were treated with a first dose of intravenous cyclophosphamide <0.5 g/m^2; subsequently, the dose was regularly titrated every month. The subsequent doses of cyclophosphamide were to be equal to or greater than the previous dose, except in cases where an adverse event, such as leukopenia, necessitated a dose reduction. The patients who received cyclophosphamide ≥0.5 g/m^2 in the second or third doses were included in the titrate group, while those for whom all doses of cyclophosphamide were <0.5 g/m^2 were categorized as the non-titrate group. All patients in both groups received 6 monthly doses of cyclophosphamide. After the completion of the induction phase, patients received azathioprine or mycophenolate mofetil as a maintenance regimen. In patients with relapse LN who previously responded to cyclophosphamide, we administered cyclophosphamide again unless they had received a high cumulative dose, were planning to become pregnant, or preferred to switch to an alternative regimen. Patients who had received treatment with intravenous cyclophosphamide, oral cyclophosphamide, mycophenolate mofetil, or prednisolone at a dosage exceeding 15 mg/day within the last 6 months were excluded from the study. Additionally, patients who had received any immunosuppressive agents other than steroids and cyclophosphamide during the induction phase, or agents other than azathioprine or mycophenolate mofetil during the maintenance phase—such as calcineurin inhibitors or biologic agents—were excluded from the study. We excluded patients who had received continuous hemodialysis for more than 2 weeks before receiving cyclophosphamide, were pregnant, or had other concurrent autoimmune conditions. Other active medical conditions leading to study exclusion included severe cardiovascular disease, liver dysfunction, chronic obstructive pulmonary disease, bone marrow insufficiency unrelated to systemic lupus erythematosus (SLE), active bleeding disorders, or current infections requiring intravenous or oral antibiotics. Additionally, patients who had previously failed both cyclophosphamide and mycophenolate mofetil induction for LN were also excluded. Additionally, patients who died due to causes unrelated to LN, such as accidents, as well as those who were lost to follow-up, were excluded. This study was approved by the Institutional Review Board of Hatyai Hospital (HYH EC 034-65-01) and carried out according to the Declaration of Helsinki. The need for written informed consent was waived, given the retrospective nature of the study and patient anonymization before the analysis.

2.1. Outcome measures

The primary outcome measured in this study was primary renal response (PRR), which included a urinary protein-creatinine ratio (UPCR) of <0.7 g/g; an estimated glomerular filtration rate (eGFR) no less than 20 % of the value before the renal flare, or ≥60 mL/min per 1.73 m^2 of the body surface area; and no use of rescue therapy at 52 weeks. We used this as the primary outcome because data have shown that proteinuria <0.7 g/day at month 12 after therapy initiation is the best predictor for favorable long-term kidney outcomes [14,15].

The secondary outcome included relapse LN, rescue therapy, infection leading to hospitalization, death associated with LN, and end-stage renal disease (ESRD). Relapse LN was defined as recurrent inflammatory activity requiring alternative or more intensive

treatment, accompanied by any of the following parameters: active urine sediment (glomerular hematuria with red and/or white blood cell casts, white blood cells in the absence of infection), increased urine protein excretion, and/or increased serum creatinine. Rescue therapy was defined as switching to or additional use of immunosuppressive drugs beyond the scheduled course of cyclophosphamide and maintenance therapy or receiving prednisolone at more than 10 mg/day by week 24. Death associated with LN was defined as death resulting from complications of infection, renal failure, or active SLE. Lastly, ESRD was defined as the initiation of maintenance dialysis, receipt of kidney transplantation, or a sustained decrease in eGFR to less than 15 mL/min per 1.73 m^2 of the body surface area.

2.2. Statistical analysis

Categorical variables are reported using frequency statistics, and significant differences between the two groups were tested using Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous variables are summarized using descriptive statistics, and significant differences were assessed using Student's t-test or the Wilcoxon rank-sum test. To identify the impact of "achievement of titrating cyclophosphamide to the optimal dose" on the primary and secondary endpoints, logistic regression analysis was performed. After univariate analysis, variables such as sex, age, body mass index (BMI), LN classification, achievement of titrating cyclophosphamide to the optimal dose, antimalarial drug use, serum creatinine, baseline UPCR, and other variables with P-values <0.1 were included in the multivariate analyses. P-values <0.05 indicated statistical significance. All data analyses were conducted using Stata (Version 15.1, College Station, TX: StataCrop LLC).

3. Results

A total of 78 patients were enrolled in this study: 47 in the titrate group and 31 in the non-titrate group. One patient was lost to follow-up in the former, while three were lost in the latter group. Additionally, one patient in the titrate group died from causes unrelated to LN. Baseline demographic and clinical characteristics are shown in Table 1. The mean ± SD age was 34.2 ± 11.9 years. Overall, 94.9 % of the patients were female, and the distribution of LN classes was as follows: 12.8 %, III; 9.0 %, III + V; 70.5 %, IV; 7.7 %, IV + V. There was a trend toward higher serum creatinine (median: 1.6 vs. 0.9 mg/dL, P = 0.084) and lower eGFR (median: 62.5 vs. 83.0 mL/min/1.73 m^2, P = 0.066) in the non-titrate group compared to the titrate group. Additionally, patients in the titrate group received a higher mean dose of cyclophosphamide (mean: 0.5 vs. 0.3 g/m^2, P < 0.001) and had higher hemoglobin (mean: 10.3 vs. 9.2 g/dL, P = 0.010) and platelet levels (mean: 263 vs. 207 × 10^9/L, P = 0.009) than those in the non-titrate group. No difference was observed in the percentage of patients who received azathioprine or mycophenolate mofetil during the maintenance phase between the two groups.

3.1. Primary and secondary endpoints

The results concerning primary and secondary endpoints are provided in Table 2. At week 52, significantly more patients in the up-titrate group achieved PRR than those in the non-titrate group (23 of 47 patients [48.9 %] vs. 7 of 31 patients [22.6 %]; odds ratio

Table 1
Baseline demographics and clinical characteristics of patients with lupus nephritis.

Variable	Total (N = 78)	Titrate group (N = 47)	Non-titrate group (N = 31)	P-value
Age, years, mean (SD)	34.2 (11.9)	34.5 (12.3)	33.8 (11.6)	0.821
Female sex (%)	74 (94.9)	45 (95.7)	29 (93.5)	1.000
BMI, kg/m^2, mean (SD)	23.8 (5.9)	23.8 (6.1)	23.9 (5.6)	0.947
BSA, m^2, mean (SD)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	0.495
LN class				
III, n (%)	10 (12.8)	5 (10.6)	5 (16.1)	0.507
III + V, n (%)	7 (9.0)	4 (8.5)	3 (9.7)	1.000
IV, n (%)	55 (70.5)	33 (70.2)	22 (71)	1.000
IV + V, n (%)	6 (7.7)	5 (10.6)	1 (3.2)	0.393
Antimalarial drug (%)	66 (84.6)	40 (85.1)	26 (83.9)	1.000
Serum creatinine, mg/dL, median (IQR)	1.2 (0.6–1.5)	0.9 (0.7–1.2)	1.6 (0.8–2.3)	0.084
eGFR, mL/min/1.73 m^2, median (IQR)	76.1 (41.0–106.5)	83.0 (56.0–107.0)	62.5 (30.9–95)	0.066
Baseline UPCR, g/g, median (IQR)	2.9 (1.2–4.1)	3.0 (1.8–4.5)	2.9 (1.8–3.9)	0.923
Average dose of cyclophosphamide, g/m^2, mean (SD)	0.4 (0.1)	0.5 (0.1)	0.3 (0.1)	<0.001
White blood cell, × 10^3/μL, median (IQR)	9.2 (6.9–11.5)	9.6 (7.0–12.3)	9.1 (5.9–11.2)	0.388
Absolute neutrophil count, × 10^3/μL, median (IQR)	7.4 (4.8–9.7)	7.3 (5.3–9.7)	7.5 (3.8–10.4)	0.748
Hemoglobin, g/dL, mean (SD)	9.9 (2.0)	10.3 (1.7)	9.2 (2.1)	0.010
Platelet, × 10^9/L, median (IQR)	243 (182–284)	263 (210–313)	207 (156–267)	0.009
Albumin, g/dL, mean (SD)	2.6 (0.6)	2.6 (0.7)	2.5 (0.6)	0.670
Follow-up time, years, median (IQR)	2 (1–5)	3 (1–4)	2 (1–5)	0.649
Maintenance therapy (%)				
Mycophenolate mofetil, n (%)	27 (43.6)	17 (36.2)	10 (32.3)	0.810
Azathiopine, n (%)	42 (53.8)	29 (61.7)	13 (41.9)	0.107

SD, standard deviation; IQR, interquartile range; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-creatinine ratio; LN, lupus nephritis.

Table 2
Impact of titrate dosing strategy on primary and secondary endpoints.

Endpoint	Total (N = 78)	Titrate group (N = 47)	Non-titrate group (N = 31)	Difference	Adjusted odds ratio (95 % CI)[a]	P -value
	number (percent)			(percentage points)		
Primary endpoint						
Primary renal response at 52 weeks	30 (38.5)	23 (48.9)	7 (22.6)	26.3	4.7 (1.5–15.2)	0.010
Secondary endpoints						
Relapse lupus nephritis	18 (23.1)	13 (27.7)	5 (16.1)	11.6	1.7 (0.5–5.8)	0.390
Rescue therapy	21 (26.9)	10 (21.3)	11 (35.5)	−14.2	0.4 (0.1–1.1)	0.075
Infection leading to hospitalization	20 (25)	8 (17)	12 (38.7)	−21.7	0.3 (0.1–0.9)	0.036
Death associated with lupus nephritis	12 (15.4)	4 (8.5)	8 (25.8)	−17.3	0.3 (0.1–0.9)	0.047
End-stage renal disease	10 (12.8)	3 (6.4)	7 (22.6)	−16.2	0.3 (0.1–1.6)	0.168

[a] The odds ratios with 95 % confidence intervals and P-values were calculated using a logistic regression model for the comparison between the titrate and non-titrate groups, adjusting for sex, age, body mass index, lupus nephritis classification, antimalarial drug use, serum creatinine, and urinary protein-creatinine ratio.

[OR], 4.7; 95 % confidence interval [CI], 1.5–15.2; P = 0.010). There was no significant difference in relapse of LN (13 of 47 patients [27.7 %] vs. 5 of 31 patients [16.1 %]; OR, 1.7; 95 % CI, 0.5–5.8; P = 0.390) and rescue therapy (10 of 47 patients [21.3 %] vs. 11 of 31 patients [35.5 %]; OR, 0.4; 95 % CI, 0.1–1.1; P = 0.075) between the two groups. Additionally, patients in the up-titrate group had fewer cases of infections leading to hospitalization than those in the non-titrate group (8 of 47 patients [17.0 %] vs. 12 of 31 patients [38.7 %]; OR, 0.3; 95 % CI, 0.1–0.9; P = 0.036) and fewer cases of death-associated LN (4 of 47 patients [8.5 %] vs. 8 of 31 patients [25.8 %]; OR, 0.3; 95 % CI, 0.1–0.9; P = 0.047). There was no significant difference in ESRD (3 of 47 patients [6.4 %] vs. 7 of 31 patients [22.6 %]; OR, 0.3; 95 % CI, 0.1–1.6; P = 0.168) between the two groups.

3.2. Univariate baseline predictors of primary renal response (PRR)

The baseline predictors for PRR at 52 weeks are shown in Table 3. Only three baseline factors (antimalarial drug, UPCR ≥3 g/g, and up-titrate dose ≥0.5 g/m^2) were identified as PRR predictors at 52 weeks; ORs: 9.1 (95 % CI, 1.1–74.8, P = 0.040), 0.3 (95 % CI, 0.1–0.9, P = 0.026), and 3.3 (95 % CI, 1.2–9.1, P = 0.022), respectively.

3.3. Multivariate baseline predictors of PRR

In the multivariate model, which included age, sex, BMI, lupus class, antimalarial drug use, serum creatinine, UPCR, and up-titrate, persistent associations with PRR at 52 weeks were found for baseline UPCR ≥3 g/g (OR, 0.3; 95 % CI, 0.1–0.9; P = 0.030), and up-titrate dose ≥0.5 g/m^2 (OR, 4.7; 95 % CI, 1.5–15.2; P = 0.010).

4. Discussion

In this retrospective cohort study of patients with proliferative LN who initially received LDC, we showed that administering LDC

Table 3
Univariate and multivariate logistic regression analyses for predicting factors of primary renal endpoint at 52 weeks.

Variable	Univariate analysis			Multivariate analysis		
	Crude odds ratio	95 % CI	P-value	Adjusted odds ratio	95 % CI	P-value
Male sex	0.8	0.0–8.8	0.825	0.3	0.0–4.3	0.387
Age, per 1 year increase	1.0	1.0–1.1	0.590	1.0	1.0–1.1	0.259
BMI, per 1 kg/m^2 increase	1.0	0.9–1.0	0.276	1.0	0.9–1.1	0.427
Lupus nephritis Class						
III	1	(reference)	–	1	(reference)	–
IV	0.8	0.3–2.4	0.694	0.7	0.2–2.5	0.584
Use of antimalarial drug	9.1	1.1–74.8	0.040	8.8	0.9–85.2	0.061
Serum creatinine, per 1 mg/dL increase	0.8	0.5–1.2	0.292	1.0	0.6–1.8	0.971
Baseline UPCR						
<3	1	(reference)	–	1	(reference)	–
≥3	0.3	0.1–0.9	0.026	0.3	0.1–0.9	0.030
Up-titrate dose ≥ 0.5 g/m^2	3.3	1.2–9.1	0.022	4.7	1.5–15.2	0.010
Leukopenia	2.4	0.0–15.6	0.344			
Infection	0.4	0.2–1.9	0.418			

CI, confidence interval; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-creatinine ratio.

through the entire induction phase elicits poor results and that a titrate dosing strategy can improve PRR. Interestingly, patients in the titrate dose group had fewer cases of infections leading to hospitalization and risk of LN-associated death. The up-titrate dose was also an important factor for predicting PRR.

Using high doses of cyclophosphamide further increases the risk of infection [16], which is the leading cause of death in patients with LN [17]. Many clinicians opt to use LDC as the first dose to evaluate the patient's response to medication toxicities, such as leukopenia, gastrointestinal reaction, and infection. However, there is a paucity of data on the effectiveness and safety of using LDC. Sigdel et al. [13] conducted a prospective cohort study in 41 Nepalese patients with LN receiving pulse intravenous cyclophosphamide 500 mg for six pulses monthly: 18 patients (43.9 %) achieved complete remission and 16 (39.02 %) achieved partial remission. Unfortunately, no information regarding the dose of cyclophosphamide per body surface area was provided in this study. Compared with the result for the non-titrate group in our study, which received approximately 500 mg of cyclophosphamide, their study showed a more favorable result. We speculated that ethnicity with different genetic backgrounds plays a role in the difference in findings.

Since the National Institutes of Health (NIH) regimen shows cyclophosphamide's efficacy for treating LN [18], efforts to maximize its effectiveness while avoiding toxic side effects have been made. One such effort is Euro-lupus regimens, which have shown comparable efficacy while reducing toxicities [19]. However, genetic polymorphisms can influence the patient's response to the cyclophosphamide treatment at standard doses and cause serious adverse effects. This is because cyclophosphamide is a prodrug, and its active compounds may be affected by genetic polymorphisms [20,21]; this has been shown in different clinical conditions, such as those for LN [22], hematopoietic cell transplants [23], diffuse large-B cell lymphoma [24], and breast cancer [25]. Therefore, starting with LDC to avoid serious adverse events and titrating according to patient response could be an alternative regimen strategy for LN patients. In our study, the titrate dosing strategy demonstrated an acceptable renal response at week 52 without increasing the incidence of adverse events, and it was flexible and personalized for LN treatment. This regimen may be suitable for patients who are fragile, have a history of adverse events from cyclophosphamide, or are already receiving a high cumulative dose of cyclophosphamide.

We found more cases of infections leading to hospitalization and death-associated LN in the non-titrate group than in the titrate group. Additionally, the non-titrate group had more patients in non-remission, exposing them to more severe inflammatory conditions. Studies have shown that severe inflammatory conditions can lead to an impaired gut barrier and micro-bacterial dysbiosis, thus predisposing to opportunistic infection [26]. Furthermore, patients in the non-titrate group may be exposed to a prolonged course of high-dose corticosteroids. This is supported by a retrospective cohort study by Ichinose et al. [27], in which the achievement of complete remission at 12 months after induction therapy was associated with a better survival rate for patients with LN. Thus, even partial remission in LN may provide better results for patients and renal survival [28].

Although the difference was not significant, serum creatinine levels and eGFR were found to be numerically higher and lower, respectively, in the non-titrate group than in the titrate group. After adjusting for potential confounders, including eGFR, up-titration of cyclophosphamide remained an independent factor for PRR after LDC regimen initiation. This finding underscores the potential implications of up-titrating the LDC regimen, as it is more personalized than the fixed-dose regimens in Euro-Lupus studies. By gauging cyclophosphamide-related complications and titrating to patient responses, this approach improves remission rates while avoiding severe infection complications and death compared to LDC without titration. Furthermore, this study highlights that using LDC without titration is hazardous. This regimen led to an increased rate of LN-associated infection and death. Clinicians should be encouraged to always dose cyclophosphamide per body surface area to avoid using an LDC without proper recognition.

This study had some limitations. First, as a retrospective cohort study, it lacked data on some potential confounding factors, including socioeconomic status, duration of LN, renal pathology activity and chronicity index, steroid doses during the induction and maintenance phases, involvement of other organs, disease activity index (SLEDAI-2K), and complement levels. Therefore, some important factors such as pathological parameters or disease activity index were not included in the prediction of PRR. Furthermore, with no available data on non-serious adverse events, it remains unknown whether starting with an LDC can reduce them. However, cyclophosphamide toxicities are dose-related, which means starting with LDC can also help avoid non-serious adverse events. Second, owing to the limitations of retrospective data, we cannot specify the attending physician's reason behind a titration or non-titration strategy, and we did not have a group of patients who used a standard dose of cyclophosphamide to compare with the titrate group. Therefore, we could not ascertain that the titrate group had comparable efficacy with lower adverse events compared with a group that received a standard dose of cyclophosphamide. Third, compared with that in a previous study with a similar outcome, our primary outcome (48.9 % in the up-titrate group and 38.5 % in the entire cohort) showed a comparable result with primary efficacy renal response at week 52 from the BLISS-LN trial (47 % in the belimumab group and 35 % in the placebo group) [29]. However, future prospective randomized controlled trials are needed to evaluate the renal response of the titration strategy compared with other cyclophosphamide regimens. Finally, our findings from the Thai population may not be generalizable to other populations.

In summary, starting with LDC and titrating to patient response may be an alternative regimen for LN treatment; the use of LDC without titration results in low renal response without decreasing the incidence of serious adverse events. Future studies are required to compare the efficiency of the titrate regimen to that of other cyclophosphamide regimens.

Abbreviations table

Abbreviation	Definition
eGFR	Estimated glomerular filtration rate

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Abbreviation	Definition
ESRD	End-stage renal disease
LDC	Lower-than-recommended dose of cyclophosphamide
LN	Lupus nephritis
PRR	Primary renal response
SLE	Systemic lupus erythematosus
UPCR	Urinary protein-to-creatinine ratio

Ethical statement

This study was conducted following the Declaration of Helsinki. The Institutional Review Board of Hatyai Hospital (HYH EC 034-65-01) approved this study. All patient data were analyzed in anonymity. Patient consent was waived by the ethics committee, as no individual data were published, nor was any intervention performed on patients.

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Data availability statement

The original anonymous dataset is available on request from the corresponding author at busmdcu58@gmail.com.

CRediT authorship contribution statement

Kittiphan Chienwichai: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aniwat Choomnirat:** Formal analysis, Data curation. **Sorawat Sangkaew:** Formal analysis. **Nutthapong Sunanthamethee:** Formal analysis, Data curation. **Arunchai Chang:** Writing – review & editing, Software, Methodology, Formal analysis, Conceptualization, Formal analysis, Data curation.

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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