Predictive Factors for Severe Chemotherapy Adverse Events in Elderly Thai Cancer Patients

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Abstract

Background: Elderly patients are at higher risk for severe chemotherapy-related adverse events (AEs), which can impair treatment continuity and cancer survival. In the Eastern Cooperative Oncology Group (ECOG) performance status (PS) is commonly used for pre-chemotherapy evaluation. Physiological decline in elderly patients, however, necessitates a comprehensive assessment. There are a few proven pre-chemotherapy factors that integrate oncologic and geriatric dimensions.

Objective: To identify additional risk factors associated with severe chemotherapy-related AEs, including socioeconomic and geriatric-related factors.

Materials and Methods: This retrospective-prospective study investigated patients with solid malignancy aged ≥60 years who received chemotherapy. Data were collected during each hospital visit. Potential factors included patient demographics, cancer characteristics, treatment plan, and geriatric assessment results. Multivariate analysis identified significant risk factors.

Results: A total of 94 elderly patients (mean age 68 years) were enrolled. Severe chemotherapy-related AEs occurred in 57% of patients (54/94). Based on adverse-event episodes, 19.1% (124/634) were classified as severe. Neutropenia and anemia were the most prevalent chemotherapy-associated AEs. Significant predictive factors included income level, ECOG PS, white blood cell (WBC) count, absolute neutrophil count (ANC), and timed up-and-go test.

Conclusion: Five additional risk factors—income level, ECOG PS, WBC count, ANC, and the timed up and go test—were identified as significant predictors of severe chemotherapy-induced AEs. These findings emphasize the need to consider factors beyond ECOG PS when evaluating the risk of severe side effects in older patients with solid tumors. Incorporating established risk factors into clinical assessments can enhance patient safety and improve therapeutic outcomes.

Keywords: Chemotherapy toxicity; Chemotherapy-related adverse events; Elderly cancer patients; Predictive factors; Geriatric assessment

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Thailand has become a highly aging society; since 2022, almost 13 million people (20% of the population) are over the age of 60[1]. Cancer is a major issue in Thailand, where the number and proportion of elderly individuals are increasing annually[2]. Incidence of cancer in the elderly population is expected to increase in the coming years[3].

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What is already known about this topic?

Elderly cancer patients often face a higher risk of severe CAEs, which can discontinue their treatment and affect their survival. Although the ECOG PS is a useful tool for evaluating patients prior to chemotherapy, it does not always correctly represent the health of senior patients. As they age, their physiological changes need more comprehensive evaluation. However, there are limited pre-chemotherapy factors that adequately integrate both oncological and geriatric considerations.

What does this study add?

This study identifies five key predictors of severe CAEs in elderly Thai cancer patients: income level, ECOG PS, WBC count, ANC, and TUGT. This research emphasizes the significance of socioeconomic factors, functional status, and specific clinical parameters, proposing a new approach to risk assessment and personalized treatment planning, which will improve patient safety and outcomes.

Chemotherapy remains a cornerstone in the treatment of solid malignancies in Thailand[4], providing notable cancer survival odds, despite the increasing popularity of targeted therapy and immunotherapy for various cancer types[5]. Geriatric patients are particularly vulnerable to significant adverse events

(AEs) associated with chemotherapy[6-12]. These adverse reactions can substantially hinder treatment continuity and can potentially contribute to premature mortality[7,12].

The Eastern Cooperative Oncology Group's (ECOG) performance status (PS) is extensively employed for pre-chemotherapy assessment, offering a standardized metric for individual function[13]. Despite its widespread use, the ECOG PS may not fully capture the complex health challenges faced by elderly patients, who often experience physiological deterioration and comorbidities[11]. From a geriatric perspective, senior patients require evaluations that consider their unique physiological, socioeconomic, and functional status[14]. Currently, there is a lack of verified methods for pre-chemotherapy evaluation that integrate both oncologic and geriatric factors, highlighting a critical gap in patient care.

This study aims to identify the risk factors for severe chemotherapy-related adverse events (CAEs) in elderly patients, focusing on socioeconomic and geriatric factors. These findings could improve patient safety and outcomes by better forecasting AEs, enhancing pre-chemotherapy evaluations, and helping physicians tailor treatment plans.

Materials and Methods

Study Design and Patients

This retrospective and prospective cohort study included patients who underwent chemotherapy at Chulabhorn Hospital in Bangkok, Thailand, between January 2023 and June 2024. Participants eligible for the study were aged 60 or older, diagnosed with a solid tumor, and prepared to initiate a chemotherapy regimen. This study also permitted the recruitment of patients receiving concurrent chemoradiotherapy. Furthermore, patients could be re-enrolled in subsequent treatment regimens if they meet the eligibility criteria. Participants who could not communicate in Thai were excluded from the study.

Methods

A research oncology nurse performed medical evaluations and geriatric assessments in the oncology outpatient unit on the day the new chemotherapy regimen commenced. Two oncology nurses responsible for geriatric assessment conducted the evaluations using the same standardized protocol.

Geriatric assessment is a multidimensional process that includes functional ability, physical health, cognition, mental health, and socio-environmental factors[14,15]. All patients received chemotherapy as scheduled by their primary oncologists. Modifications to treatment and management of AEs were the discretion of prescribing oncologists as needed. During the regimen, the incidence of AEs, modifications to chemotherapy, discontinuation of chemotherapy, dose reductions, and any delays resulting from AEs or patient preferences were recorded. Diagnosis of grade 3 to 5 toxicities or severe AEs from chemotherapy was established based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[16]. All AE grades were recorded.

Baseline patient variables included sex, age, primary cancer, stage, treatment regimen, and laboratory results. Geriatric assessment was performed the day prior to chemotherapy, involving the ECOG PS score, comorbidities, instrumental activities of daily living (IADL) score[15], Thai depression screening tool (2Q)[17], distress thermometer[18], Mini-Cog©[19,20], body mass index (BMI), Mini Nutritional Assessment (MNA®)[21], and Time Up and Go Test (TUGT)[15]. The original authors supplied a validated questionnaire in Thailand.

The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Thammasat University (approval no. MTU-EC-ES-0-066/67), and Chulabhorn Research Institute (approval no. 010/2561). Informed consent was obtained from all patients before participation.

Statistical Analysis

The sample size calculation was based on the total count of CAEs rather than on the patient population. Each predictive variable required a minimum of 10 to 20 events[22]. According to Hurria et al.[23], at least 13 parameters, including patient demographics, cancer characteristics, laboratory tests, and geriatric assessments, are hypothesized to correlate with severe AEs. To ensure adequate multivariate analysis, the study required a minimum of 130 serious AEs, determined as tenfold the expected variables.

The primary objective was to identify the factors associated with grade 3 to 5 AEs, defined as death or life-threatening AEs. Demographic and geriatric assessment data were analyzed using descriptive statistics, including mean, median, range, standard deviation, and percentage.

To identify factors associated with severe (grade 3 to 5) CAEs, univariate logistic regression analysis was employed. Variables with a p-value less than 0.2 and an area under the receiver operating characteristic curve (AUROC) with a 95% confidence interval (CI) approaching 1 were considered for multivariate

Table 1. Basic patient characteristics

Characteristics	Value
Age (years); mean±SD	68.8±6.3
Age ≥72 years; n (%)	25 (26.6)
Male; n (%)	50 (53.2)
Couple; n (%)	72 (76.6)
Education: at least bachelor's degree; n (%)	48 (51.0)
No social member activities; n (%)	84 (89.4)
Retire/unemployed; n (%)	74 (78.7)
Income (USD/month); n (%)	
≤297.8	26 (27.7)
297.9-1,489.4	55 (58.5)
>1,489.4	13 (13.8)
Living with family; n (%)	89 (94.7)
PPC; n (%)	89 (94.7)
DM; n (%)	16 (17.0)
HT; n (%)	43 (45.7)
Polypharmacy >4; n (%)	84 (89.4)
ECOG PS; n (%)	
0	50 (53.2)
1	32 (34.0)
2	12 (12.3)
Anemia; n (%)	15 (16.0)
WBC <4,000 cell/μL; n (%)	5 (5.3)
Serum albumin ≥3.5 g/dL; n (%)	89 (94.7)

Characteristics	Value
Types of cancer; n (%)	
GI & HPB	54 (57.5)
Breast	25 (26.6)
Lung	8 (8.5)
Others	7 (7.5)
Stage; n (%)	
I-II	25 (26.6)
III-IV	69 (73.4)
StCMT; n (%)	52 (56.5)
First line therapy; n (%)	61 (64.9)
Schedule duration (weeks); n (%)	
12	22 (23.4)
18	63 (67.0)
≥24	9 (9.6)
Hearing problem; n (%)	9 (9.6)
Knee pain; n (%)	41 (43.6)
Mini-Cog 4-5; n (%)	59 (62.8)
Depression; n (%)	10 (10.6)
SEFI; n (%)	22 (23.4)
Distress score >5; n (%)	28 (29.8)
Falling; n (%)	6 (6.6)
Mobile device assistant; n (%)	12 (12.8)
BMI ≥23; n (%)	47 (50)
TUGT >20 seconds; n (%)	31 (33)
Weight loss last 3 months; n (%)	65 (69.1)

USD=U.S. dollar; PPC=presence of personal consultant; DM=diabetes mellitus; HT=hypertension; ECOG=Eastern Cooperative Oncology Group; PS=performance status; WBC=white blood cell; GI=gastrointestinal; HPB=hepatopancreatobiliary; StCMT=start with standard chemotherapy dose; SEFI=Social effect from illness; BMI=body mass index; TUGT=time up and go test

Anemia: hemoglobin ≤10 in female and ≤11 in male, Metastasis: distant metastasis, Depression: presence of depression from screening, Falling: history of falling

analysis. For the multivariable analysis, multilevel logistic regression and a reduced model using the backward elimination method were used to analyze the selected factors from the univariate analysis. The results are presented as adjusted odds ratios (OR) with 95% CI. Statistical significance was set at p-value less than 0.05. All statistical analyses were performed using Stata/MP, version 18 (StataCorp LLC, College Station, TX, USA).

Results

Between January 2023 and June 2024, Chulabhorn Hospital's Oncology Clinic evaluated 94 elderly subjects (mean age 68.8, male-to-female ratio 53.2:46.8) diagnosed with solid tumors. Of the individuals, 11 died, 38 finished treatment, and 44 continued to be observed. The study documented 634 CAEs, of which 124 were categorized as grade 3 to 5 (severe or life-threatening). The study aimed for a minimum of 130 serious AEs to enable a robust multivariate analysis, identifying five principal predictors associated with grade 3 to 5 CAEs, corresponding to 50 to 100 events. As the sample size was marginally below the desired number, it was deemed sufficient for full analysis.

Baseline demographic data of the participants are shown in Table 1. The study included 94 patients with a mean age of 68.8 years (±6.3). Gastrointestinal/hepatobiliary, breast, and lung cancers were found in 54, 25, and 8 patients, respectively. Sixty-nine patients had stage III and IV cancers (17 and 52 patients, respectively). Four-fifths (76/94) had underlying diseases, namely, diabetes mellitus (17%), hypertension (45.7%), dyslipidemia, and ischemic cerebral infarction. Ninety-four percent of the participants had normal creatinine levels, and 96% had normal liver function tests. Socioeconomically, sixty-eight participants were considered above the poverty line, with monthly earnings equal to or higher than

Table 2. Common chemotherapy-related adverse events

	Grading of AEs; No. of symptom events (%)					
	1	2	3	4	1-2	3-5
HAE						
Neutropenia	0 (0.0)	42 (57.5)	22 (30.1)	9 (12.3)	42 (57.5)	31 (42.5)
Anemia	0 (0.0)	39 (79.6)	10 (20.4)	0 (0.0)	39 (79.6)	10 (20.4)
Low plt	7 (46.7)	6 (40.0)	2 (13.3)	0 (0.0)	13 (86.7)	2 (13.3)
FN	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)
NHAE						
Anorexia	48 (45.3)	41 (38.7)	17 (16.0)	0 (0.0)	89 (84.0)	17 (16.0)
Fatigue	50 (55.0)	28 (30.8)	13 (14.3)	0 (0.0)	78 (85.7)	13 (14.3)
Mucositis	15 (31.3)	24 (50.0)	9 (18.8)	0 (0.0)	39 (81.3)	9 (18.8)
HFS	8 (40.0)	4 (20.0)	9 (42.9)	0 (0.0)	12 (57.1)	9 (42.9)
PN	30 (46.2)	28 (43.1)	7 (10.8)	0 (0.0)	58 (89.2)	7 (10.8)
Diarrhea	12 (30.8)	20 (51.3)	6 (15.4)	1 (2.6)	32 (82.0)	7 (18.0)
Sepsis	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	2 (100)

AEs=adverse events; HAE=hematologic adverse event; NHAE=non-hematologic adverse events; Low plt=thrombocytopenia; FN=febrile neutropenia; HFS=hand foot syndrome; PN=peripheral neuropathy

297.9 USD. Most patients were retired or unemployed (78.7%), lived with their family (94.7%), and had a personal consultant (94.7%). Choice of treatment: 77/94 patients underwent multiple chemotherapy agents following the national guidelines provided by the National Health Security Office and the Comptroller General's Department. Quality of daily life: the 91/94 patients maintained their ability to perform basic functions during their participation period.

Treatment-related AEs are shown in Table 2. Eighty percent (510/634) of the patients experienced relatively manageable side effects, such as nausea, oral mucositis, and myalgia. The most common severe AEs were hematologic, accounting for 7.1% (45/634) of all adverse-event episodes. Among hematologic AEs, neutropenia was the most frequent, representing 52.5% (73/139). Severe non-hematologic AEs such as anorexia accounted for 2.7% (17/634).

From the univariate analysis, a total of 11 factors were identified. Multivariate analysis identified several predictors of severe CAEs (grade 3 to 5) as shown in Table 3. Patients with a monthly income >1,489.4 USD had a lower risk of severe AEs (OR 0.4, 95% CI 0.1 to 1.0, p=0.047). Patients with TUGT >20 seconds had a lower risk of severe CAEs (OR 0.4, 95% CI 0.2 to 0.8, p=0.011). A white blood cell (WBC) count <2,500 cells/μL was a significant predictor (OR 3.8, 95% CI 1.4 to 10.1, p=0.008). An absolute neutrophil count (ANC) <1,500 cells/μL was also associated with a higher risk (OR 2.2, 95% CI 1.1 to 4.4, p=0.030). An ECOG PS of 2 indicated a higher risk compared to status 0 (OR 3.2, 95% CI 1.5 to 7.1, p=0.004).

Discussion

According to the current study, 57.4% of the patients experienced severe AEs due to chemotherapy (54/94). These results are comparable to those of the studies conducted by Hurria et al.[23], Extermann et al.[8], Kim et al.[9], Feliu et al.[10], and Phaibulvatanapong et al[24]. Asian countries have a higher incidence of gastrointestinal cancers than the United States, potentially resulting in increased chemotherapy-related side effects at levels 3 to 5. The side effects of non-hematologic adverse events (NHAE) and hematologic adverse events (HAE) were also similar. Other comparison factors are listed in Table 4.

In a recent study, the ECOG PS score was identified as a risk factor for severe AEs from chemotherapy, consistent with findings from prior studies[8,24], showing that poor performance status reflects underlying frailty and deterioration of physiological function. This limits the ability of senior patients to tolerate chemotherapy. In this study, WBC count <2,500 cells/μL and ANC <1,500 cells/μL, which are related to immune system function, were significant predictors of severe AEs. Other studies[23-25] have also highlighted that cytotoxic agents can cause myelosuppression, especially neutropenia. This effect is worse in older adults with lower bone marrow reserves. Some studies[26,27] have shown that ANC during the first chemotherapy cycle is an important predictor of AE occurrence in the later cycles. There is an available guideline for using prophylactic WBC growth factors in high-risk patients[28].

Geriatric assessment was performed using the

Table 3. Multivariable analysis for parameters of severe high (grade 3-5: n=117) and low (grade 1-2: n=475) adverse event

	Grading; n (%)		Full model		Reduced model	
	High	Low	OR (95% CI)[1]	p-value	OR (95% CI)[1]*	p-value
Income (USD/month)						
≤297.8	32 (27.4)	125 (26.3)	Ref.		Ref.	
297.9-1,489.4	77 (65.8)	270 (56.8)	0.7 (0.4 to 1.4)	0.340	0.8 (0.5 to 1.5)	0.538
>1,489.4	8 (6.8)	80 (16.8)	0.4 (0.1 to 1.0)	0.060	0.4 (0.1 to 1.0)	0.047
HT						
No	80 (68.4)	257 (54.1)	Ref.			
Yes	37 (31.6)	218 (45.9)	0.7 (0.4 to 1.2)	0.148		
Schedule duration (weeks)						
12	26 (22.2)	92 (19.4)	Ref.			
18	87 (74.4)	324 (68.2)	1.5 (0.7 to 3.1)	0.287		
≥24	4 (3.4)	59 (12.4)	0.7(0.2 to 2.7)	0.610		
Distress score						
<5	87 (74.4)	304 (64.0)	Ref.			
≥5	30 (25.6)	171 (36.0)	0.8 (0.4 to 1.5)	0.523		
TUGT (seconds)						
≤20	82 (70.1)	292 (61.5)	Ref.		Ref.	
>20	35 (29.9)	183 (38.5)	0.4 (0.2 to 0.8)	0.012	0.4 (0.2 to 0.8)	0.011
WBC (cell/μL), cycle						
≥2,500	96 (82.1)	460 (96.8)	Ref.		Ref.	
<2,500	21 (17.9)	15 (3.2)	3.7 (1.4 to 10.1)	0.009	3.8 (1.4 to 10.1)	0.008
ANC (cell/μL), cycle						
≥1,500	81 (69.2)	428 (90.1)	Ref.		Ref.	
<1,500	36 (30.8)	47 (9.9)	2.1 (1.0 to 4.2)	0.044	2.2 (1.1 to 4.4)	0.030
ECOG PS, cycle						
0	49 (41.9)	247 (52)	Ref.		Ref.	
1	36 (30.8)	163 (34.3)	1.0 (0.6 to 1.9)	0.887	1.1 (0.6 to 1.9)	0.854
2	32 (27.4)	65 (13.7)	3.0 (1.3 to 6.8)	0.010	3.2(1.5 to 7.1)	0.004
Serum albumin (g/dL)						
<3.5	10 (8.5)	18 (3.8)	Ref.			
≥3.5	107 (91.5)	457 (96.2)	0.8 (0.2 to 2.6)	0.650		
Line of therapy						
First line	67 (57.3)	319 (67.2)	Ref.			
Multiple lines	50 (42.7)	156 (32.8)	0.9 (0.5 to 1.6)	0.613		
IADL						
≥8	110 (94.0)	463 (97.5)	Ref.			
<8	7 (6.0)	12 (2.5)	1.0 (0.2 to 4.9)	0.964		

OR=odds ratio; CI=confidence interval; USD=U.S. dollar; HT=hypertension; TUGT=time up and go test; WBC=white blood cell; ANC=absolute neutrophil count; ECOG=Eastern Cooperative Oncology Group; PS=performance status; IADL=instrumental activities of daily living

1 USD=33.61 Baht (January 31, 2025)

[1] Multilevel logistic regression, * Backward elimination

timed up and go test (TUGT) because of its ease of use and non-time-consuming nature. The test evaluated gait instability and risk of falling in each subject. A recent study found that subjects with a high risk from the TUGT assessment had a lower risk of developing severe AEs from chemotherapy, which may seem illogical and in contrast with the research done by Kim et al.[9], who also studied TUGT but found no such association. A possible reason is that clinicians might use extra caution in their medical practice; for example, they proactively modify chemotherapy dosages or provide supportive care for patients with higher fragility or functional impairment[29].

Income level was another significant predictor

Table 4. Comparison of variables associated with grade 3-5 chemotherapy adverse events

	Present	Hurria[23]	Extermann[8]	Phaibulvatanapong[24]	Kim[9]	Feliu[10]
Year	2024	2011	2012	2017	2018	2023
Country	Thailand	US	US	Thailand	Korea	Spain
Number	592	500	518	150	301	234
Inclusion age	60	65	70	70	70	70
Age		✓				
Income	✓					
Type		✓				
GI	50%			90%	40%	57%
Breast	27%				1%	12%
Lung	9%	30%	21%		25%	6%
StCMT		✓				
CMT≥2	✓					
Regimen			✓			✓
Duration	✓					
nHb		✓				✓
WBC	✓					
Protein ≥6.7					✓	
LDH			✓			
CrCl		✓				
Hearing		✓				
Falling		✓				
ECOG PS	✓			✓		
ADL						✓
TUGT	✓					
Med assist		✓				
Social def		✓				
Walk 1 block		✓				
DBP			✓			
Polypharmacy	✓					
No stress					✓	
HP					✓	
Obey command					✓	
MMSE			✓		✓	
MNA			✓			
Fluid/day					✓	
CONUT						✓

GI=gastrointestinal; StCMT=start with standard chemotherapy dose; nHb=normal hemoglobin; WBC=white blood cell; LDH=lactate dehydrogenase; CrCl=creatinine clearance; ECOG=Eastern Cooperative Oncology Group; PS=performance status; ADL=activities of daily living; TUGT=time up and go test; DBP=diastolic blood pressure; HP=health perception; MMSE=Mini-Mental State Exam (score 25-30); MNA=Mini-Nutritional Assessment; CONUT=controlling nutritional status (score >1)

CMT ≥2: multiple agents of chemotherapy, Regimen: chemotherapy regimen, Duration: schedule duration, Hearing: hearing impairment, Falling: history of falling last 6 months, Med assist: medical intake assist require, Social def: social deficiency from illness, Walk 1 block: limited in walking one block, No stress: no stress in last three months; Obey command: obey command accomplish; Fluid/day: oral fluid per day more than 3 cups

of severe AEs in the present study; a finding not demonstrated in other comparative studies. The cause of income level as a significant predictor in this study could be higher accessibility to healthcare, nutritional supplements, and transportation in higher-income participants. Moreover, patients with higher incomes usually seek immediate medical care despite minor symptoms, which could result in chemotherapy[30]. Some studies[31,32] have found that cancer patients often experience "financial toxicity", where treatments are expensive, and patients with limited income tend to prioritize familial issues over self-care.

A major strength of this study is the consistency of data collection and clinical practice across treating

physicians, which helps minimize variation in patient management. The incorporation of geriatric assessment parameters also provides additional prognostic insight beyond conventional oncologic factors.

This study also has limitations. As a single-center study conducted in Thai patients with solid tumors, the generalizability of the findings may be limited. Some variability among oncologists in treatment modification was unavoidable. Prophylactic G-CSF use was not routinely practiced and therefore was not captured in the dataset. Additionally, the study focused exclusively on patients receiving chemotherapy, which may limit the applicability of the findings to other cancer types or systemic treatment modalities.

Conclusion

This study identified five important factors that can lead to serious side effects of chemotherapy in older patients with solid tumors: income level, ECOG PS score, WBC count, ANC, and TUGT. Factors other than the ECOG PS score pose a significant risk of developing severe AE in elderly patients with solid cancer. Healthcare providers should consider these additional factors when planning chemotherapy for elderly patients. Future research should focus on validating these findings in larger, multicenter cohorts and developing risk assessment tools to personalize and improve the quality of care for elderly oncology patients.

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Author Contributions

JS and KS conceptualized and designed the study; NC and VP collected the data; JS, KS, and KS analyzed and interpreted the results; JS, KS, KS, and KP prepared the initial manuscripts. All authors reviewed the results and approved the final version of the manuscripts.

Clinical Trial Registration

Not applicable. This observational cohort study was not a clinical trial and therefore did not require clinical trial registration.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Data Availability Statement

The de-identified dataset supporting the findings of this study is available from the corresponding author upon reasonable request, subject to ethics committee approval and institutional data governance requirements. Public sharing of the dataset is restricted due to patient privacy concerns and ethical requirements governing the retrospective and prospective components of the study.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of the Faculty of Medicine, Thammasat University (Approval No. MTU-EC-ES-0-066/67) and the Chulabhorn Research Institute Ethics Committee (Approval No. 010/2561). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

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Use of Artificial Intelligence

Artificial intelligence (AI)-assisted tools were used solely to support English language editing and manuscript preparation during the preparation of this manuscript. Specifically, ChatGPT (OpenAI, 2025 version) was used to assist with sentence refinement, grammar checking, language polishing, and improving the clarity of scientific writing. All scientific content, including the study design, data collection, statistical analysis, interpretation of the results, and conclusions, was developed and verified exclusively by the authors. The authors take full responsibility for all content in the manuscript, including its integrity, accuracy, and originality. ChatGPT is not listed as an author in accordance with the ICMJE authorship criteria.

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