## **ORIGINAL RESEARCH**



## Pre-hospital Prognostic Factors of 30-Day Survival in Sepsis Patients; a Retrospective Cohort Study

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Abstract: Introduction: According to excising findings, if the emergency management system (EMS) operation will be developed, the survival outcome of sepsis patients might improve. This study aimed to evaluate the pre-hospital associated factors of survival in sepsis patients. Methods: This retrospective cohort study was conducted on patients diagnosed with sepsis, coded with the Thailand emergency medical triage protocol and criteria-based dispatch symptom group 17. Information on the 30-day survival rate of patients was obtained from the electronic medical records. Pre-hospital factors associated with 30-day survival were analyzed using univariate and multivariate logistic regression analyses and were reported using odds ratio (OR) with 95% confidence interval (CI). Results: 300 patients diagnosed with sepsis were enrolled. Among them, 232 (77.3%) survived within 30 days. Non-survived cases had significantly older age (p = 0.019), lower oxygen saturations (92.5% vs. 95.0%; p = 0.003), higher heart rate (p = 0.001), higher respiratory rate (p < 0.012) 0.001), lower level of consciousness (p < 0.001), higher disease severity based on qSOFA score (p = 0.001), and higher need for invasive airway management (p = 0.001) and supplementary oxygen (p = 0.001). The survival rate improved by 3.5% with every 1% increase in pre-hospital oxygen saturation (adjusted OR = 1.035, 95% CI: 1.005-1.066, p = 0.020) and the survival probabilities of patients who responded to voice (adjusted OR = 0.170, 95% CI: 0.050-0.579, p = 0.005), those who responded to pain (adjusted OR = 0.130, 95% CI: 0.036-0.475, p = 0.002), and those who were unresponsive (adjusted OR = 0.086, 95% CI: 0.026–0.278, p-value < 0.001) were lower than patients who were alert. Conclusion: The 30-day survival rate of patients with sepsis managed by the EMS team was 77.3%. Pre-hospital oxygen saturation and level of consciousness were associated with the survival of patients with sepsis who were managed in the pre-hospital setting.

Keywords: Emergency medical services; emergency treatment; sepsis; survival

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## 1. Introduction

Sepsis is a leading cause of death worldwide. Its incidence rate is approximately 48.9%, which is lower than that of accident-related mortality. Based on previous studies worldwide, variations in the reported incidence of sepsis are caused by differences in disease definitions, study periods, types of data collected, patient groups, and public health systems in each area (1). A study in the United States of America revealed that the mortality rate of sepsis decreased from 28.6%–45.0% in 2001 to 12.3% in 2019, due to improvement in medicine and public health within 20 years (2, 3). In addition, a study with long-term follow-up found that the mortality rate of patients with severe sepsis or those with delayed evaluation and treatment is higher (3). A previous meta-analysis on studies from seven countries revealed that the mortality rate of sepsis was 17.0% and the mortality rate of severe sepsis was higher, at 26.0% (4). Research on Southeast Asian countries, including Thailand, Malaysia, and Vietnam, reported that the 28-day mortality rates of sepsis were 7.0% in patients without signs of organ dysfunction and 47.0% in those with at least four signs (5). According to the index statistics on the rate of mortality due to sepsis in the ministry

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of public health hospitals of Thailand, more than 452,480 patients presented with sepsis, and there were over 153,324 deaths recorded from 2018 to 2022 (6).

Based on the Surviving Sepsis Campaign in 2016 guidelines, sepsis is an actual medical emergency condition (7). It commonly requires emergency medical service (EMS) in the prehospital setting (8). Therefore, patients with sepsis should be managed during the pre-hospital period, and the window for the hour-1 sepsis bundle must be reduced. Sepsis can be screened and diagnosed in the pre-hospital setting. Thus, patients can receive treatment more quickly, which can consequently increase the survival rate (9, 10). If the EMS team can immediately initiate a provisional diagnosis of sepsis, perform appropriate evaluation, provide treatment, and monitor vital signs continuously at the scene and during transportation, the survival rate can increase (11). A study in Brazil showed that oxygen depletion and Sequential Organ Failure Assessment (SOFA) score of  $\geq$ 3 was associated with a lower survival rate in sepsis patients (12). A study that aimed to evaluate the epidemiology of sepsis in the pre-hospital context found that an abnormal respiratory rate and decreased level of consciousness are significantly associated with a high mortality rate (13).

Based on the above-mentioned points, this study aimed to assess the 30-day survival rate and its pre-hospital associated factors in patients with sepsis whose managements were started by EMS in the pre-hospital setting in Thailand.

## 2. Methods

#### 2.1. Study design and settings

This retrospective cohort study was conducted at the Vajira-EMS (V-EMS) unit, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand to evaluate the pre-hospital associated factors of survival in sepsis patients whose managements were started by EMS, from January 1, 2019 to October 31, 2022. The V-EMS unit is the leading EMS center among nine zone areas in Bangkok, dispatched from Erawan Center, Bangkok, networking with both public and private hospitals, with six hospitals in the responsible area, which was 50 square kilometers and a population of 500,000 (14, 15). The EMS team of the V-EMS unit comprises at least three staff, which include paramedics or emergency nurse practitioners (ENPs), which act as the operation team leader, and emergency medical technicians. During each operation, the paramedics or ENPs can operate under off- and on-line medical protocols based on the orders of emergency physicians. In the study area, the sepsis management guidelines include the use of the quick Sepsis-Related Organ Failure Assessment (qSOFA) score in the pre-hospital setting. Patients should have a score of at least 2 for the following parameters: respiratory rate (at least 22 cycles/min), systolic blood pressure (approximately 90 mmHg), and Glasgow Coma Scale (GCS) score (13) or decreased level of consciousness, and sepsis diagnosis. A diagnosis of sepsis is made based on the presence of at least two items of systemic inflammatory response syndrome (SIRS) criteria (16). According to the offline protocol for patients with sepsis, paramedics or ENPs should start oxygen supplementation with a cannula or mask with a reservoir bag and endotracheal intubation according to pre-hospital guidelines. Oxygen saturation should be maintained at  $\geq$ 94%. Venous catheterization must be performed to administer at least 30 mL/kg of crystalloid solutions (e.g., lactated Ringer's solution [LRS] and acetar) if there are no contraindications such as crepitation in both lungs and edema in both legs (systolic blood pressure maintained at  $\geq$ 90 mmHg). Moreover, reassessment is performed after every administration of 300-500 mL of fluid.

#### 2.2. Participants

Adult patients with final diagnosis of sepsis, symptom group 17red1 – 17red9, dispatched to V-EMS, aged more than 18 years, coded with Thailand emergency medical triage protocol and CBD symptom group 17, which is sepsis or septic shock and transported to emergency department, were enrolled in the study. Patients who refused treatment or transportation to the hospital, those with incomplete or missing data, and those receiving end-of-life or palliative care were excluded from the analysis.

#### 2.3. Data collection

The data of patients finally diagnosed with sepsis or septic shock were collected from the EMS patient care report, which is a record of advanced EMS operation. This form comprised data on EMS operation units, patients, and all treatments provided by the EMS teams. All data were recorded by dispatchers and paramedics or ENPs at the scene. Further, these data were a part of remuneration for the EMS operation units. Data on 30-day survival were extracted from the electronic medical records of Vajira Hospital. We collected information including demographic and clinical characteristics of the participants (such as gender; age; underlying disease; location; sepsis category; pre-hospital systolic and diastolic blood pressures, heart and respiratory rates, oxygen saturation, body temperature, level of consciousness [alert, responds to pain, responds to voice, and unresponsive], airway management, oxygen supplementation with a cannula, mask with a reservoir bag, and bag valve mask, fluid supplementation, and blood glucose level; qSOFA score; response time; on-scene time; distance from the base station to the scene; and distance from the scene to the hospital, and data on 30-day survival outcome), which were reviewed by the primary investigator from the electronic medical records.

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#### 2

#### 2.4. Outcome measures

3

The primary outcome was 30-day survival.

#### 2.5. Definition of terms

- Sepsis is a life-threatening condition caused by the host's abnormal response to infection.

Septic shock is defined as a systolic blood pressure of <90 mmHg and arrhythmia with a heart rate of >100 beats/min (17). In our study area, paramedics or ENPs suspect infection in patients with fever or a history of fever and those with symptoms indicative of infection or organ dysfunction. Further, they assess qSOFA score. If the score is at least 2, a diagnosis of sepsis is made, and the management guidelines for patients with sepsis or septic shock can be applied immediately at the scene.

- The Thailand emergency medical triage protocol and CBD severity code was used at the scene. It utilizes data obtained by evaluating the situation and symptoms of patients at the scene. Further, it uses 26 symptom groups. Symptom group 17 is defined as a diagnosis of sepsis or septic shock using 17 code red 1–9.

- Response time (min) was defined as the duration from emergency call to ambulance arrival at the scene.

- On-scene time (min) was defined as the duration from ambulance arrival at the scene to departure from the scene.

- Thirty-day survival was defined as the survival of patients with sepsis or septic shock (RC code 17 red) who were managed by EMS in the pre-hospital setting and evaluated within 30 days (from day 1 [service day] to day 30).

#### 2.6. Sample size

The sample size was estimated using the formula for infinite population proportion. A normal curve was defined as a p-value of 0.05 and an error rate of 4%. The proportion of patients was based on a previous study. The 30-day survival rate of patients with sepsis managed by EMS at the pre-hospital setting was 89.3% (10). The sample size was at least 230. Thereafter, 288 patients were added based on the following formula: nnew =  $230/(1 \ 0.20)$ . Hence, the final sample size was 300. Simple random sampling was performed to obtain a sample including patients diagnosed with sepsis in the pre-hospital setting and dispatched to the V-EMS unit.

#### 2.7. Statistical analysis

A descriptive analysis was performed to examine variable distribution. Continuous variables were expressed as mean  $\pm$ standard deviation or median and inter-quartile range (IQR) and categorical variables as frequencies and percentages. Between-group differences were evaluated using the independent t-test or the Mann–Whitney U test for numeric variables and the chi-square test or the Fisher's exact test for categorical variables.

The 30-day survival rate of patients with sepsis whose management was started at the pre-hospital setting was expressed as frequency distribution and percentage. To evaluate factors associated with the 30-day survival of patients with sepsis managed in the pre-hospital setting, crude analysis was performed using the chi-square test or the Fisher's exact test based on data appropriateness and multivariate logistic regression analysis, the result were reported as odds ratio (OR) and 95% confidence interval (CI).

The Statistical Package for the Social Sciences software for Windows, version 28.0 (IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, the USA) was used. A p-value of <0.05 was considered statistically significant.

#### 2.8. Ethical statement

This study was conducted in accordance with the 1975 Declaration of Helsinki and its 2000 revised version. It was approved by the Institutional Review Board of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA no. 220/2565). The need for informed consent was waived due to the retrospective nature of the study and anonymity of all patient data.

## 3. Results

#### 3.1. Baseline characteristics of the participants

300 patients diagnosed with sepsis were enrolled. Among them, 232 (77.3%) survived within the 30 days of follow-up. The mean age of patients was  $73.40 \pm 16.00$  years (53.7% male). Table 1 compares the baseline characteristics of studied cases between survived and non-survived cases.

The mean ages of the survivors and non-survivors were 72.34  $\pm$  16.51 and 77.01  $\pm$  13.63 years, respectively (p = 0.019). The two groups had similar conditions regarding gender distribution (p = 0.488), underlying diseases (p = 0.331), location of residence (p = 1.000), disease category (p = 0.167), pre-hospital systolic blood pressure (p = 0.111), diastolic blood pressure (p = 0.389), body temperature (p = 0.389), blood glucose (p = 0.359), the median response time (p = 0.688), the median on-scene times (p = 0.925), the median distance from the base station to the scene (p = 0.973), the median distance from the scene to the hospital (p = 0.442), and volume of hydration therapy in pre-hospital setting (p = 0.098).

Non-survived cases had significantly lower oxygen saturations (92.5% vs. 95.0%; p = 0.003), higher heart rate (p = 0.001), higher respiratory rate (p < 0.001), lower level of consciousness (p < 0.001), higher disease severity based on qSOFA score (p = 0.001), and higher need for invasive airway management (p = 0.001) and supplementary oxygen (p = 0.001).

 Table 1:
 Comparing the baseline characteristics of the participants between survivors and non-survivors

Factors	Survivors (n = 232)	Non-survivors (n = 68)	p-value
Age (years)			
Mean ± SD	72.34 ± 16.51	77.01 ± 13.63	0.019t
Gender			
Male	122 (52.6)	39 (57.4)	0.488c
Female	110 (47.4)	29 (42.6)	
Underlying disease			
No	83 (35.8)	20 (29.4)	0.331c
Yes	149 (64.2)	48 (70.6)	
Location			
Home	225 (97.0)	66 (97.1)	1.000f
Public	7 (3.0)	2 (2.9)	
Disease category			
Sepsis	203 (87.5)	55 (80.9)	0.167c
Septic shock	29 (12.5)	13 (19.1)	
Pre-hospital Vital signs			
SBP (mmHg)	129.95 ± 31.80	122.79 ± 34.82	0.111t
DBP (mmHg)	73.29 ± 19.69	73.90 ± 27.12	0.839t
Heart rate (/min)	102.22 ± 21.9	112.66 ± 25.71	0.001t
Respiratory rate (/min)	25.30 ± 6.67	28.82 ± 8.06	<0.001t
Oxygen saturation (%)	95 (92–98)	92.5 (81–97)	0.003m
Body temperature (°C)	37.79 ± 1.05	37.85 ± 0.99	0.671t
Blood glucose level (mg/dL)	144 (115–181)	145 (119.5–190.5)	0.359m
Pre-hospital level of consciousness			
Alert	97 (41.8)	6 (8.8)	<0.001c
Respond to pain	49 (21.1)	32 (47.1)	
Respond to voice	56 (24.1)	13 (19.1)	
Unresponsive	30 (12.9)	17 (25.0)	
qSOFA score			
<2	118 (50.9)	19 (27.9)	0.001c
≥2	114 (49.1)	49 (72.1)	
EMS management			
Response time (min)	12 (7–16)	12 (8.5–16.5)	0.688m
On-scene time (min)	16 (12–24)	17 (13–23)	0.925m
Base station to the scene (km)	3 (2–5)	4 (2–5)	0.973m
Scene to the hospital (km)	3 (2–5)	4 (2–6)	0.442m
Pre-hospital airway management			
No	220 (94.8)	55 (80.9)	0.001f
Endotracheal tube	10 (4.3)	7 (10.3)	
Oropharyngeal airway	2 (0.9)	5 (7.4)	
Nasopharyngeal airway	0 (0.0)	1 (1.5)	
Pre-hospital oxygen supplementation			
No	115 (49.6)	16 (23.5)	0.001c
Cannula	62 (26.7)	21 (30.9)	
Mask with a reservoir bag	47 (20.3)	25 (36.8)	
Bag valve mask	8 (3.4)	6 (8.8)	
Pre-hospital fluid supplementation			
No	83 (35.8)	14 (20.6)	0.098f
Normal saline	71 (30.6)	26 (38.2)	
Ringer lactate	73 (31.5)	27 (39.7)	
10% DN/2	5 (2.2)	1 (1.5)	

4

Data are presented as mean ± standard deviation (SD), number (%), or median (interquartile range).

SBP: systolic blood pressure; DBP: diastolic blood pressure EMS: emergency medical services;

qSOFA: quick Sepsis-Related Organ Failure Assessment. P-value corresponds to the tindependent samples t-test, mMann–Whitney U test, cchi-square test, or fFisher's exact test.

 Table 2:
 Multivariate logistic regression analysis of associated factors of survival in sepsis patients

Factors	ORadj1	95% CI	p-value
Age (years)	0.980	(0.959–1.002)	0.080
Prehospital vital sign			
Heart rate (beats/min)	0.988	(0.973–1.004)	0.143
Respiration rate (cycles/min)	0.976	(0.926–1.029)	0.372
Oxygen saturation (%)	1.035	(1.005–1.066)	0.020
Prehospital level of consciousness			
Alert	1.000	Reference	
Responds to voice	0.170	(0.050–0.579)	0.005
Responds to pain	0.130	(0.036–0.475)	0.002
Unresponsive	0.086	(0.026–0.278)	< 0.001
qSOFA Score			
<2	0.531	(0.228–1.238)	0.143
≥2	1.000	Reference	
Prehospital airway management			
No	1.000	Reference	0.383
Yes	0.621	(0.213–1.812)	
Prehospital oxygen supplementation			
No	1.000	Reference	0.362
Yes	0.697	(0.321–1.513)	
Prehospital fluid supplementation			
No	1.000	Reference	0.660
Yes	0.843	(0.395–1.8)	

Abbreviations: OR, odds ratio; ORadj, adjusted odds ratio; CI, confidence interval; NA, not applicable;

qSOFA: quick Sepsis-Related Organ Failure Assessment. Variable with a p-value of <0.050 in the univariate analysis

were included in the multivariate analysis. 1Adjusted odds ratio estimated using the multiple logistic regression model.

# 3.2. Multivariate analysis of factors associated with 30-day survival

Age, qSOFA score, and pre-hospital heart and respiratory rate, oxygen saturation, level of consciousness, airway management, and oxygen supplementation were significantly associated with 30-day survival of sepsis patients based on the univariate analysis.

Table 2 shows the findings of multivariate logistic regression analysis of factors associated with 30-day survival. Based on this analysis pre-hospital oxygen saturation level and level of consciousness were found to be the independent predictors of 30-day survival in sepsis patients. With every 1% increase in pre-hospital oxygen saturation, the survival rate improved by 3.5% (adjusted OR = 1.035, 95% CI: 1.005-1.066, p = 0.020). The survival probabilities of patients who responded to voice in the pre-hospital settings, those who responded to pain, and those who were unresponsive were 0.170 (adjusted OR = 0.170, 95% CI: 0.050-0.579, p = 0.005), 0.130 (Adjusted OR = 0.130, 95% CI: 0.036-0.475, p = 0.002), and 0.086 (Adjusted OR = 0.086, 95% CI: 0.026-0.278, p < 0.001) times lower than patients who were alert.

## 4. Discussion

The 30-day survival rate of patients diagnosed with sepsis or septic shock was 77.3%. This finding is consistent with that

of a previous study in the Netherlands. That is, the survival rate of patients with sepsis who received EMS care was 79.0%, and the mean hospitalization period was 13.5 days (18). Another study revealed that the overall 30-day survival of patients with sepsis and septic shock in the emergency department of Mexico was 83.07%. Although the survival rate decreased in the septic shock group (19), the 28-day survival rate of patients with sepsis was 53.0% in Southeast Asian countries, such as Malaysia (5). According to previous research, if the EMS operation is performed, the survival outcome of patients with sepsis might improve. Further, assistance can be provided in various processes, which include the development of appropriate and convenient pre-hospital sepsis screening tools, fluid replacement, and antibiotic initiation, which might improve patient survival (20). Nevertheless, a previous study showed that the mortality rate and length of hospital stay are different in survived cases (21).

The current study showed that pre-hospital oxygen saturation and level of consciousness were associated with 30-day survival in patients with sepsis managed by EMS. This finding is consistent with that of a previous study on the EMS of a tertiary care institution in North-Western India. Results showed that oxygen saturation was a predictive factor of survival outcome in patients with sepsis and septic shock. Moreover, patients with hypoxia had a higher mortality rate (average: 26.92%) than those with normoxia (22). A study con-

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5

ducted in the intensive care unit showed that patients who were treated at the intensive care unit and survived sepsis had a higher oxygen saturation level than those who did not survive. Moreover, patients with sepsis should receive appropriate oxygen therapy to improve survival outcome (23). With every 1% increase in pre-hospital oxygen saturation, the survival rate improved by 3.5%.

Therefore, appropriate and adequate pre-hospital oxygen supplementation was recommended. Further, indirect noninvasive oxygen delivery, which can be easily performed by the emergency medical staff, must be considered. That is, capillary refill time and cyanosis assessment is required to improve the quality of management in patients with sepsis who were managed in the pre-hospital setting. This finding was consistent with the latest standard guidelines for managing patients with sepsis or septic shock. That is, patients with septic shock must undergo regular capillary refill time assessment (24). Patients with sepsis who had low pre-hospital level of consciousness might have a significantly lower survival rate. This finding was similar to that of a previous observational study using GCS as a predictive tool for survival rate, which showed that patients with decreased level of consciousness had a significantly higher mortality rate (25).

Moreover, it is comparable to two studies in the emergency departments. The first study reported a high 30-day mortality rate after sepsis diagnosis at the emergency department among patients with a low level of consciousness. Unresponsive patients could have a higher mortality rate than responsive patients (26). The second study found that an altered mental state could classify the mortality rate in septic patients in the emergency department at 28 days and could be a predictor of survival (27). Based on the standard guidelines for managing patients with sepsis in the pre-hospital setting, the EMS staff should emphasize and focus on assessing the level of consciousness using either the GCS or the AVPU (Alert, Voice, Pain, Unresponsive) scale, whichever is appropriate in each area.

Proper neurological assessment and maintenance of level of consciousness at the scene and during hospital transport were important in improving survival outcomes in patients with sepsis.

Regarding suggestions for future research, since the present study only focused on pre-hospital factors affecting septic patients' survival at 30 days, the future research should study factors affecting the patients' survival in pre-hospital and hospital, as well as definitive care contexts, such as emergency department or intensive care unit. For health managers and policymakers, the present study presented factors important for pre-hospital management by EMS team, which affected 30-day survival of septic patients and sepsis. This type of study is substantially necessary for policy making in pre-hospital management system for specific diseases that

6

are time-sensitive and have pretty high mortality rates, such as sepsis.

## 5. Study limitations

The current study had several limitations. First, it was retrospective in nature and was conducted at a single center with two data sources. Although neutrality was tried to be maintained in every way, there might still be a risk for potential selection bias, such as biases from population selection of patients with sepsis and septic shock, selection of qSOFA score in pre-hospital diagnosis of sepsis, which were believed that these potential biases did not have a significant impact on results important for septic patients' survival.

Second, some confounding factors associated with outcomes of interest might not have been evaluated. Only data on pre-hospital management were analyzed. Nonetheless, data from the emergency department or intensive care unit in the hospital should also be considered and analyzed because they might affect survival. Third, only patients diagnosed with sepsis or septic shock who were transported to the emergency department of Vajira Hospital were analyzed. However, patients brought to the emergency departments of other hospitals should also be considered because the capability of a hospital's emergency department can affect survival outcome. Fourth, the study was conducted in a single EMS unit, which was an academic center. The present study results might not be generalizable. Further studies are needed to test the external validity of the present study results. Finally, in the study area, only qSOFA was used as a screening tool. Nevertheless, bias was tried to be reduced from the screening tool by using final diagnosis at ED as inclusion criteria, which is in accordance with the Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. The application of qSOFA was not recommended for screening patients with sepsis and septic shock. However, in the study area, only qSOFA was used, and an accurate provisional diagnosis by paramedics or ENPs at the scene could substantially affect decision-making.

## 6. Conclusion

The 30-day survival rate of patients with sepsis managed by the EMS team was substantially high (77.3%). Pre-hospital oxygen saturation and level of consciousness were associated with the survival of patients with sepsis who were managed in the pre-hospital setting. Hence, guidelines on the prehospital management of sepsis, which emphasize the need to evaluate oxygen saturation and level of consciousness during hospital transport, should be developed.

## 7. Declarations

7

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## 7.2. Conflict of interest

The authors have no conflicting interests to declare.

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### 7.4. Authors' contribution

Conceptualization: Thongpitak Huabbangyang, Chanathip Wanphen, Thanakorn Faikhao, Passakorn Banjongkit and Ratchaporn Kuchapan; Methodology: Thongpitak Huabbangyang, Rossakorn Klaiangthong and Fahsai Jaibergban; Software: Thongpitak Huabbangyang; Validation: Thongpitak Huabbangyang; Formal analysis: Thongpitak Huabbangyang; Investigation: Thongpitak Huabbangyang; Resources: Thongpitak Huabbangyang, Chanathip Wanphen, Thanakorn Faikhao, Passakorn Banjongkit and Ratchaporn Kuchapan; Data Curation: Thongpitak Huabbangyang; Writing - Original Draft: Thongpitak Huabbangyang; Writing -Review & Editing: Thongpitak Huabbangyang; Visualization: Thongpitak Huabbangyang, Rossakorn Klaiangthong and Fahsai Jaibergban; Supervision: Thongpitak Huabbangyang; Project administration: Thongpitak Huabbangyang; Funding acquisition: Thongpitak Huabbangyang. All authors read and approved the final version of manuscript.

## 7.5. Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

## 7.6. Using artificial intelligence chatbots

None.

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