Prognostic of modified early warning score for identification of deteriorating patients on general wards

Mr. Ratapum Champunot

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Health Development
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ค่าการทำนายของ modified early warning score ในการระบุตัวผู้ป่วยที่มีอาการทรุดลงในตึกผู้ป่วยสามัญ

นายรัฐภูมิ ชามพูนท

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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.....Dean of the Faculty of Medicine

(Professor Suttipong Wacharasindhu)

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.....Thesis Advisor

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.....Examiner

(Assistant Professor Chulalak Komoltri, Ph.D.)

.....External Examiner

(Somboon Tansuphaswasdikul, M.D.)

รัฐภูมิ ชามพูนท : ค่าการทำนายของ modified early warning score ในการระบุตัวผู้ป่วยที่มีอาการทรุดลงในตึกผู้ป่วยสามัญ (Prognostic of modified early warning score for identification of deteriorating patients on general wards) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: นพ. กฤษณ์ พงศ์พิรุฬห์, 45 หน้า.

ค่าการทำนายของ modified early warning score ในการระบุตัวผู้ป่วยที่มีอาการทรุดลงในตึกผู้ป่วยสามัญ

วัตถุประสงค์: การเกิดเหตุการณ์ไม่พึงประสงค์ในโรงพยาบาลส่วนใหญ่มักจะมีสัญญาณเตือนนำมาก่อนสักระยะหนึ่ง โดยเป็นการเปลี่ยนแปลงทางสรีรวิทยาที่ทรุดลง MEWS ถูกแนะนำให้มาใช้เป็นเครื่องมือช่วยเหลือในการค้นหาสัญญาณเตือน แม้ว่าจะมีหลักฐานคำแนะนำที่มีคุณภาพสูงอย่างจำกัดในการแสดงให้เห็นถึงความไว ความจำเพาะ และประโยชน์ของ MEWS ก็ตาม คะแนนSOS เป็นเครื่องมือที่ปรับจาก MEWS และถูกนำมาใช้ในจังหวัดพิษณุโลกประเทศไทย การศึกษานี้ต้องการประเมินความสามารถในการทำนายของคะแนน SOS ณ ที่ 4, 8, 12, 24 ชั่วโมงก่อนที่เหตุการณ์ไม่พึงประสงค์จะเกิดขึ้น

วัสดุและวิธีการ: ได้ดำเนินการศึกษาแบบมีกลุ่มควบคุมซ้อนใน(nested case-control) ของผู้ป่วยผู้ใหญ่ที่มีเหตุการณ์ไม่พึงประสงค์ในหอผู้ป่วยทั่วไปและเสียชีวิตในระหว่างเดือนมิถุนายนถึงเดือนกรกฎาคม พ.ศ. 2558 โดยจับคู่ 1: 2 กับผู้ป่วยควบคุม ที่อยู่ในหอผู้ป่วยเดียวกัน วันและเวลาเดียวกัน และรอดชีวิตหลังจากที่จำหน่าย ข้อมูลทั้งหมดได้จากฐานข้อมูลและการตรวจค้นเวชระเบียนย้อนหลัง การประเมินประสิทธิภาพในการจำแนกของคะแนน SOS ในแต่ละช่วงเวลาใช้ลักษณะการวิเคราะห์ ROC ร่วมกับพื้นที่ที่สอดคล้องกันใต้เส้นโค้ง (AUC) ของคะแนน SOS ณ ที่ 4, 8, 12, 24 ชั่วโมงก่อนที่จะเกิดเหตุการณ์ไม่พึงประสงค์และ มีการวิเคราะห์ค่าความไวและความจำเพาะของคะแนน SOS ในแต่ละช่วง

ผลการศึกษา: จากข้อมูลผู้ป่วยผู้ใหญ่ทั้งหมด 5666 ราย ได้มีการคัดเลือกป่วยเสียชีวิต 41 รายให้เป็นกลุ่มตัวอย่างและจับคู่กับผู้ป่วย 82 รายที่รอดชีวิตที่ได้รับการคัดเลือกให้เป็นกลุ่มควบคุม จากการวิเคราะห์พบว่า ภาวะการหายใจล้มเหลวเฉียบพลัน (68.3%) เป็นเหตุการณ์ไม่พึงประสงค์ที่พบบ่อยที่สุด มีผู้ป่วยอายุรกรรมถูกคัดเข้าร่วมการศึกษามากกว่าผู้ป่วยศัลยกรรม (85.4% เทียบกับ 14.6%) คะแนน SOS ณ ที่ 4 ชั่วโมงก่อนเกิดเหตุการณ์ไม่พึงประสงค์เป็นค่าที่ดีที่สุดสำหรับทำนายเหตุการณ์ไม่พึงประสงค์โดยมีค่าของ AUC เท่ากับ 0.972 (95% CI, 0.949-0.995) อย่างไรก็ตาม คะแนน SOS ณ ที่ 8, 12, 24 ชั่วโมงก่อนเกิดเหตุการณ์ไม่พึงประสงค์ยังคงเป็นค่าที่ดีสำหรับทำนายเหตุการณ์ไม่พึงประสงค์ (AUC 0.906, 0.915, 0.860 ตามลำดับ) ค่า SOS คะแนน≥ 4 ณ ที่ 4 ชั่วโมงก่อนที่เหตุการณ์ไม่พึงประสงค์ คือ ค่าที่ดีที่สุด ที่ใช้สำหรับทำนายเหตุการณ์ไม่พึงประสงค์ โดยมีความไว 82.9%, ความจำเพาะ 95.1% และประสิทธิผลการวินิจฉัย 91.1% สำหรับ ค่า SOS คะแนน≥ 4 ณ ที่ 8, 12, 24 ชั่วโมงก่อนเกิดเหตุการณ์ไม่พึงประสงค์ยังคงมีค่าการทำนายที่ดีสำหรับเหตุการณ์ไม่พึงประสงค์โดยมีความจำเพาะ 95.1%, 96.3%, 92.7% ตามลำดับ อย่างไรก็ตามพบว่าความไวจะลดลงเมื่อเวลาก่อนที่เหตุการณ์ไม่พึงประสงค์เพิ่มขึ้นในกรณีที่ใช้คะแนน SOS ≥ 4 เพื่อเป็นค่าที่ใช้ทำนาย

สรุป: คะแนน SOS ณ ที่ 4, 8, 12, 24 ชั่วโมงก่อนเกิดเหตุการณ์ไม่พึงประสงค์ มีความสามารถในการคาดการณ์ที่ดีสำหรับผู้ป่วยที่มีเหตุการณ์ไม่พึงประสงค์ในหอผู้ป่วยทั่วไป SOS คะแนน≥4 เป็นค่าที่เหมาะสมสำหรับในการใช้ค่านี้เป็นจุดตัดของเกณฑ์ที่จะเริ่มต้นการดำเนินการแก้ไขเหตุการณ์ไม่พึงประสงค์ SOS คะแนน≥4 มีความสามารถในการคาดการณ์เหตุการณ์ไม่พึงประสงค์ที่ดี ไม่ว่าจะเป็นที่ ณ เวลาใดใน 24 ชั่วโมงก่อนเกิดเหตุการณ์ไม่พึงประสงค์

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา 2558 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

5574810030 : MAJOR HEALTH DEVELOPMENT
KEYWORDS: ADVERSE EVENT, DETERIOATION, EARLY WARNING SCORES, PROGNOSTIC, GENERAL WARDS

RATAPUM CHAMPUNOT: Prognostic of modified early warning score for identification of deteriorating patients on general wards. ADVISOR: KRIT PONGPIRUL, Ph.D., 45 pp.

Prognostic of modified early warning score for identification of deteriorating patients on general wards

Objective: Most in-hospital adverse events do not happen without warning but are preceded by some period of physiological instability and clinical deterioration. MEWS have been introduced despite limited high quality evidence to demonstrate their sensitivity, specificity and usefulness. SOS score is a MEWS that is used in Phitsanulok, Thailand. This study assessed the predictive ability of SOS score at 4, 8, 12, 24 hours before adverse events (T_0).

Materials and Methods: We conducted a nested case-control study of adult patients who had adverse events in a general ward and died during June-July 2015 matched 1:2 with control patients who stayed in the same ward, same date and time and survived after discharge. Data were obtained from administrative databases and retrospective chart review. Discrimination of the SOS score at each time was assessed within receiver characteristic (ROC) analyses for admission SOS score and SOS score at 4, 8, 12, 24 hours before adverse events and corresponding area under the curve (AUC). The sensitivities and specificities of different cutoff thresholds were investigated.

Results: 41 patients who died were selected to be the case group and 82 patients who survived were selected to be the control group, all from 5666 adult patients. Acute respiratory failure (68.3%) was the most common adverse event. More medical patients were enrolled in study than surgical patients (85.4% vs 14.6%). The SOS score at 4 hours before adverse events is the best predictor for adverse events with an AUC of 0.972 (95% CI, 0.949-0.995). However, the SOS score at 8, 12, 24 hours before adverse events are still good predictors for adverse events (AUC 0.906, 0.915, 0.860 respectively). The SOS score ≥ 4 at 4 hours before adverse events is the best cut-off value for adverse events with a sensitivity 82.9%, a specificity 95.1% and a diagnostic effectiveness 91.1%. The SOS score ≥ 4 at 8, 12, 24 hours before adverse events are still good cut-off values for adverse events with a specificity 95.1%, 96.3%, 92.7%, respectively. However, sensitivity fell when the time before adverse events was increased if the SOS score ≥ 4 to be the cut-off value was used.

Conclusions: The SOS score at 4, 8, 12, 24 hours before adverse events is a good predictive ability for patients who had adverse events in a general ward. The SOS score ≥4 is reasonable for using this value to be cut-off point of trigger threshold to initiate action for worsening adverse events. The SOS score ≥4 had a good predictive ability regardless of the time intervals leading up to 24 hours before adverse events.

Field of Study: Health Development Student's Signature .....

Academic Year: 2015 Advisor's Signature .....

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CHAPTER I

Introduction

1.1 Background and Rationale

Failure to identify changes in deteriorating patients and act upon them can result in an increased severity of illness and then worsening morbidity and mortality. Critical physiological changes have been described in 51–86% of patients who suffered a subsequent cardiopulmonary arrest in the general wards, often several hours before the arrest. The previous data suggest that most in-hospital cardiopulmonary arrests do not happen without warning. Most are preceded by some period of physiological instability and clinical deterioration, which are either not recognized or inadequately treated.[1-4]

The early warning score (EWS) was developed as a track and trigger tool for the prompt identification of seriously ill patients. The scoring system was developed because not all unwell patients can be monitored in intensive care or high dependency units. It allows deteriorating patients to be identified, before physiological deterioration has become too profound.[5-10] The Early Warning Score is a simple physiological scoring system that can be calculated at the patient's bedside, using parameters which are measured in the majority of patients. It was based on the regular assessment of five basic physiological parameters by trained nursing staff (mental response, pulse rate, systolic blood pressure, respiratory rate and temperature). For patients who are postoperative or unwell enough to be recorded, a sixth parameter, urine output, can also be added (Table 1). It gives a reproducible measure of how "at risk" a patient is.

Early warning scores are sometimes also referred to as Patient at Risk scores (PARS) or Modified Early Warning Scores (MEWS). The Modified Early Warning Score (MEWS) has been widely adopted throughout the world. In July 2007, the National Institute for Clinical Excellence (NICE) definitive guidance on "Acutely ill patients in hospital" recommends as a priority that physiological track and trigger systems should be used to monitor all patients in acute hospital settings.[11] In July 2012, The Royal College of Physicians in the UK launched National Early Warning Score (NEWS) for standardizing the assessment of acute illness severity in the NHS.[12] In Thailand, a

modified early warning scoring system was developed from a number of sources, including a previously validated scoring system and other local examples.[13, 14] Values of each parameter (assigns from zero to three points) was modified to reflect our patients' higher acuity and to avoid excessive false-positive triggers. The final scoring system was modified and launched with new nomenclature, "SOS (search out severity) score" (Table 2).[15] Changing the nomenclature of EWS was anticipated to facilitate the recognition of physiological deterioration.

The original EWS was not presented as a predictor of outcome. The EWS was designed to help for bedside evaluation in a short time of impending critically ill patients. Predictive capabilities of MEWS for worse outcomes and adverse events vary between different studies, and little is known regarding common practices concerning the measurement of vital signs on nursing wards.[16-22] The place (e.g. emergency department), the time (e.g. on admission) of the sampling point for physiological variables to calculate the score, and the predictive value of EWS scores for patient outcomes (e.g. cardiac arrest), are the important factors that make predictive capabilities vary between different studies.[23] This study investigated the predictive abilities of MEWS before the adverse events to identify hospitalized patients at risk, and focus on predictive abilities of MEWS score for adverse events of patients in general hospital wards. This study will focus on the most in-hospital adverse events that do not happen without warning, but are preceded by some period of physiological instability and clinical deterioration. The more challenging questions in this study are "What is the proper cut-off value" and "what is the best time to use MEWS score for the patients in general hospital wards, before adverse events occur?"

Table 1 Modified Early Warning Score (MEWS)

MEWS Score	3	2	1	0	1	2	3
Temp (core)		≤35.0	35.1-36.0	36.1-38.0	38.1-38.5	>38.6	
Pulse/Apex		≤40	41-50	51-100	101-110	111-130	≥ 131
Systolic Blood Pressure	<70	71-80	81 - 100	101 - 199		>200	
Respiratory rate		<8		9-14	15-20	21-29	>30
SPO2	≤85	85-89	90-93	>94			
CNS response (AVPU)		New confusion /agitation		Alert	Voice	Pain	Unrespon -sive
Urine output	<500ml/ 24hours	<750ml/24 hours	1000-750 ml/ 24hours				

Table 2 Search Out Severity Score (SOS)

score	3	2	1	0	1	2	3
Temp		≤35	35.1-36	36.1-38	38.1-38.4	≥38.5	
Sys BP	≤80	81-90	91-100	101-180	181-199	≥200	Vasopressor
HR	≤40		41-50	51-100	100-120	121-139	≥140
RR	≤8	ventilator		9-20	21-25	26-35	≥35
Neuro			New Confusion Agitation	A Alert	V Respond to voice	P Respond to pain	U unresponsiveness
Urine/day or Urine/8 hr or Urine/4 hr or Urine/1 hr		≤500 ≤160 ≤80 ≤20	501-999 161-319 81-159 21-39	≥ 1,000 ≥ 320 ≥160 ≥40			
Vasopressor = patient use vasopressor to maintain hemodynamics e.g. Dopamine, Norepinephrine, Dobutamine, Adrenaline Ventilator = patient used ventilator for respiratory support							

CHAPTER II

Literature reviews

2.1 Review of the related literature

All related literature was searched via PubMed Clinical Queries, Trip database and Google search engine by using keywords in this research (adverse event, deterioration, early warning scores, predictive value, general wards) and then searched across related citation articles. Papers related to research involving adult inpatients outside critical care areas and emergency departments were included, if in English and if full texts were available. We focused on clinical studies and systematic reviews in the last 20 years.

Research has shown that patients in general hospital wards often show early signs and symptoms, such as changes in breathing and pulse, when their condition is getting worse.[1-4] One Way to identify and treat patients who are deteriorating is to introduce Early Warning Score System (EWS/MEWS) to record physiological observations. This review of literatures will focus on the predictive value of MEWS for the identification of deteriorating patients.

Most clinical studies derived and validated a risk prediction model by using admission MEWS, but in most real world situations, predictive values can change after admission.[5-8] MEWS derived from ward vital signs before adverse events would likely have improved accuracy for detecting clinical deterioration. Some studies used maximum MEWS or mean MEWS before adverse events, but didn't identify lead time before the adverse events from which MEWS were collected, so it may be that MEWS were used from one day or one month before adverse events. These studies didn't represent the true predictive value of MEWS that were used as a track and trigger tool to identify deteriorating patients before becoming too profound.

A recent systematic review[23] (table 3) found 8 observational studies (6 prospective cohort and 2 case–control) reported the predictive values of EWS scores for the outcomes of interest (death and cardiac arrest within 48 hours of measurement). These studies confirm those of previous case series, demonstrating

that patients begin to show abnormal physiology several hours prior to the event, and suggesting that many patients can be identified prior to profound, enabling potentially life-saving interventions. These studies used only patients experiencing cardiac arrest on the general wards to represent cases that had adverse events. No study reported on the predictive ability of EWS for respiratory failure or shock. In our opinion, other events e.g. acute respiratory failure or shock, should be included for adverse events in general wards, because cardiac arrest is a profound event for which it is too late for early intervention. Most studies selected control subjects admitted during a specified period of time that may not have coincided with their matched case patient admission, and matched on characteristics other than the admission type or ward, such as age and sex, which makes control subjects less representative of the hospitalized population and therefore the results are less useful in clinical practice.

Past systematic reviews[18-22] (as a result of the poor methodological quality of the included studies) found a lack of evidence to support the benefits of MEWS for the early identification of patients who are getting worse. MEWS have been introduced despite limited high quality evidence to demonstrate their sensitivity, specificity and usefulness. To date the research evidence on MEWS tools in predicting patient outcomes or impending critical illness is poor, and the extent to which the existing tools are valid or reliable predictors of deterioration is unknown.[19] The findings from these systematic reviews are important as they demonstrate the need for further high quality research in the area, before the widespread promotion of MEWS can be recommended.

Table 3 Observational studies of the predictive value of MEWS[23]

Study	Population	Outcome measurement	Predictive ability
Churpek et al. 2012	Medical/surgical patients	Cardiac arrest	AUC 0.78 (95%CI, NR)
Churpek et al. 2012	Medical/surgical patients	Cardiac arrest	AUC 0.77 (95%CI, 0.71-0.82)
Kellett and Kim 2012	Medical (non-ICU)/surgical patients	Mortality	AUC 0.93 (95%CI, 0.91-0.95)
Opio et al. 2013	Medical patients	Mortality	AUC 0.89 (95%CI, 0.82-0.95)
Prytherch et al. 2010	General medicine and emergency patients	Mortality	AUC 0.89 (95%CI, 0.88-0.89)
Rothschild et al. 2010	Medical and medicine subspecialty inpatients	Cardiac arrest	AUC NR
Smith et al. 2013	General medical patients	Mortality and cardiac arrest	AUC 0.86 (95%CI, 0.85-0.87)
Churpek et al. 2014	Hospital ward patients	Cardiac arrest	AUC 0.88 (95%CI, 0.88-0.89)

CHAPTER III

Research methodology

3.1 Research questions:

3.1.1 Primary research question

Can a modified early warning score (SOS score) at 4-hours before the adverse events, identify hospitalized patients at risk (would have adverse events)?

3.1.2 Secondary research question

Can a modified early warning score (SOS score) at 8-hours, 12-hours and 24-hours before the adverse events, identify hospitalized patients at risk (would have adverse events)?

3.2 Objectives:

3.2.1 Primary objective

Predictive abilities of a modified early warning score (SOS score) at 4-hour before the adverse events to identify hospitalized patients at risk

3.2.2 Secondary objective

Predictive abilities of a modified early warning score (SOS score) at 8-hour, 12-hour and 24-hour before the adverse events to identify hospitalized patients at risk

3.3 Conceptual Framework

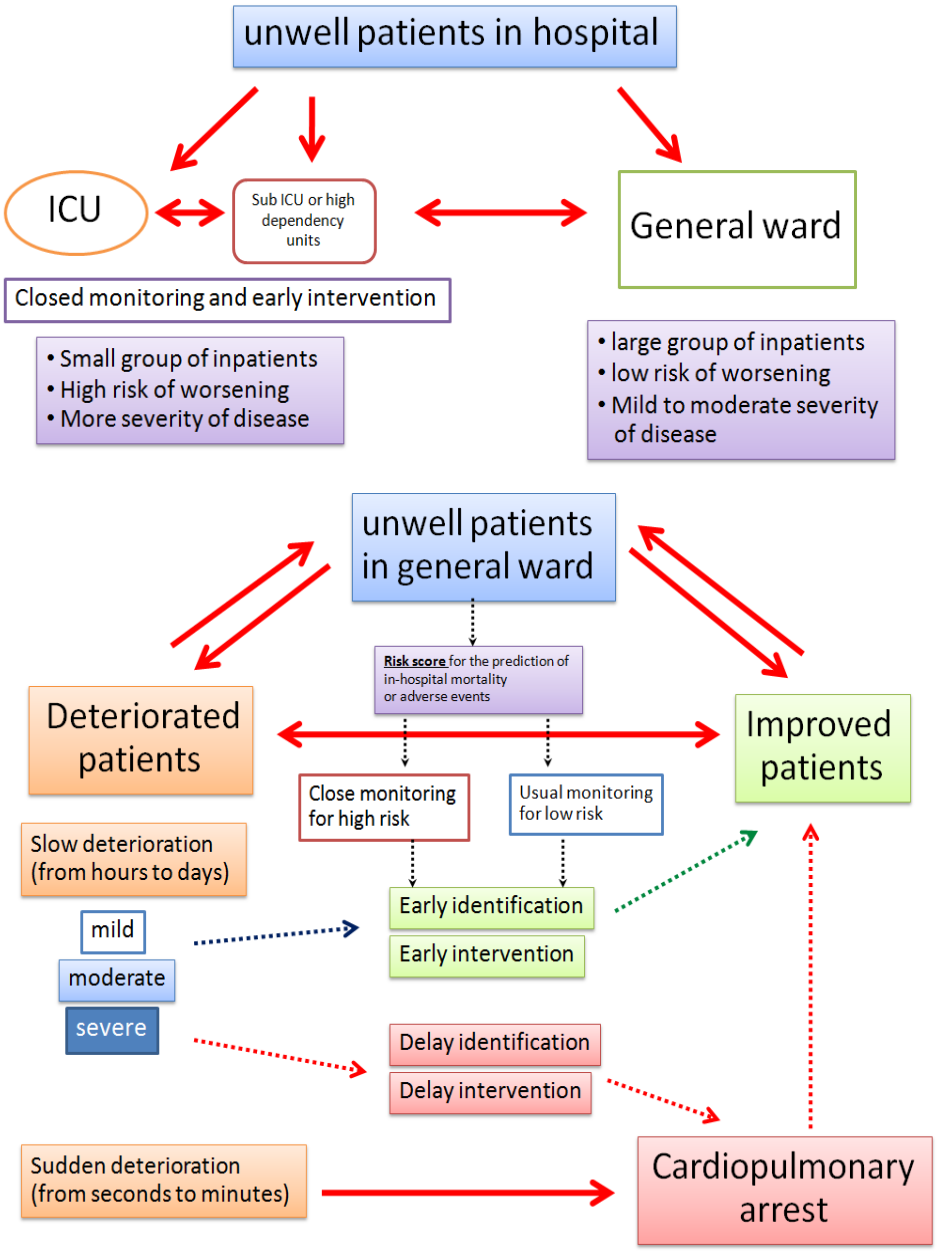


Figure 1 Conceptual Framework

Keywords:
adverse event, deterioation, early warning scores, prognostic, general wards

3.4 Operational Definition

A. Early warning score (EWS)

A simple scoring system used at general ward level based on careful routine physiological measurement of heart rate, blood pressure, respiratory rate, temperature and conscious level, each with an upper and lower score of 0–3 points from which a total score is calculated.

B. Modified early warning score (MEWS)

A scoring system, modified from EWS, that is based on the same physiological data as EWS but different in level for each score calculated.

C. Search out severity score (SOS)

MEWS used in Buddhachinaraj Phitsanulok hospital but with changed nomenclature.

D. Adverse events

One of the following events
(1) Cardiopulmonary arrest
Loss of a palpable pulse with attempted resuscitation
(2) Acute respiratory failure
Need for mechanical ventilation
(3) Shock
Systolic blood pressure less than 90 mmHg or diastolic blood pressure less than 60 mmHg or mean blood pressure less than 65 mmHg recorded more than 2 times, or need vasopressor drug (dopamine, norepinephrine, adrenaline) more than 15 minutes.

E. Sudden deteriorated patient

Patient who had sudden deterioration before adverse events. Subjective clinical judgment with duration before adverse events (from seconds to minutes) was used to define sudden events.

3.5 Research design

Retrospective Nested case-control study by using a population based sample (Retrospective chart review)

3.6 Research Methodology

3.6.1 Population and Sample

Target population; all unwell, hospitalized patients in general wards
Study population; patients that were admitted in general ward in June-July 2015 by dividing in 2 groups

1. ***Group of patients that had adverse events (case)***

All admitted patients who died (status post discharge was summarized as dead) and endured one of the following adverse events in general ward: (1) cardiopulmonary arrest (2) acute respiratory failure (3) shock

2. ***Group of patients that didn't have adverse events (control)***

All admitted patients who survived after discharge (status post discharge was summarized as improved or transferred) and matched with each case that had adverse events by matching criteria. The first priority of the matching criteria, in selecting control patients for each case is the patient is using the same ward, the same date and the same time of each case patient's adverse events. After that, 2 control patients of each case patient's adverse events were selected, and matched further by using the nearest age of each case patient (case-control ratio is one to two).

3.6.2 Patient Selection

Inclusion criteria

Adult patients (age 15 or more) that were admitted in general ward in June-July 2015

Exclusion criteria

- Patients who had a length of stay in general ward less than 48 hours
- Patients with incomplete epidemiological or discharge data.
- Patients who had the following adverse events before admission or in the first 24 hours after admission:

(1) Cardiopulmonary arrest

(2) Acute respiratory failure
(3) Shock

- Patient who had sudden deterioration (from seconds to minutes) before adverse events.
- Patient who had been documented as a palliative care patient.
- Patient who had adverse events outside general ward (adverse events occurred in ICU, OR, CCU and other special units)

Case patients were selected by the following processes

- All adult patients (≥15 years old) that were admitted in general ward in June-July 2015 were selected as a study population.

- Selected all died patients (status post discharge was summarized as dead) who admitted in general ward more than or equal 2 days in June-July 2015 were assigned as potentially eligible case patients.

- Chart reviews were done and excluded who had one of the following criteria

- Patients with incomplete epidemiologic or discharge data.
- Patients who had the following adverse events before admission or in the first 24 hours after admission:
  (1) cardiopulmonary arrest
  (2) acute respiratory failure
  (3) shock
- Patient who had sudden deterioration (from seconds to minutes) before adverse events.
- Patient who had been documented as a palliative care patient.
- Patient who had adverse events outside general ward (adverse events occurred in ICU, OR, CCU and other special units).

Control patients were selected by the following processes to minimize selection bias

- All adult patients (≥15 years old) that were admitted in general ward in June-July 2015 were selected as a study population.

- Selected all survived patients after discharge (status post discharge was summarized as improved or transferred), who were admitted in general ward more than or equal 2 days in June-July 2015, were assigned as potentially eligible control patients.
- 4 Control patients were matched with each case that had adverse events by matching criteria. The first priority of the matching criteria, in selecting control patients for each case, is the patient is using the same ward, the same date and the same time of each case patient's adverse events. After that, 4 control patients of each case patient's adverse events were selected and matched further by using the nearest age of each case patient.

- Chart reviews were done for exclude patients who had one of the following criteria
  - Patients with incomplete epidemiologic or discharge data.
  - Patients who had the following adverse events before admission or in the first 24 hours after admission:
    (1) cardiopulmonary arrest
    (2) acute respiratory failure
    (3) shock
  - Patient who had been documented as a palliative care patient.

- After that, 2 control patients of each case patient's adverse events were selected, and matched further by using the nearest age of each case patient (case-control ratio is one to two).

3.6.3 Sample size calculation

Sample size determination for diagnostic accuracy studies involving bi-normal receiver operating characteristic (ROC) curve indices was used for calculating sample size.[24, 25] The sample size estimation is based on area under the ROC curves (AUC) of at least 0.8. We estimated predictive ability of SOS score by AUC at least 0.8 from the previous study.[10] We used Power (1- Beta) = 0.9 and Alpha (significant level) = 0.05. Our study matched 1:2, case:control subjects. After being calculated, the sample size in the case group should be 20 cases, and 40 controls.

3.6.4 Data collection

- All data were collected by the following processes to minimize selection bias.

- All adult patients' data (grouped by clinical service in June – July 2015) were obtained from administrative databases in tertiary care hospital with 1,000 inpatient beds.
- All demographic data (age, gender, admission ward, admission date, discharge ward, discharge date, length of stay, discharge type) were extracted from administrative databases in excel format.
- Principle investigator select case patients by inclusion and exclusion criteria.
- Patient demographic data of case patients were obtained from administrative databases and retrospective chart review and collected in record form part 1 by principle investigator.
- Date and time of adverse events (T_0) were collected in record form part 1 by principle investigator.
- Principle investigator matched 2 control patients with each case by matching processes and criteria as above.
- Patient demographic data of control patients were obtained from administrative databases and retrospective chart review and collected in record form part 1 by principle investigator.
- All vital parameters of each case and control patients were collected at admission and 24 hours, 12 hours, 8 hours, 4 hours before time of adverse events (T_0).
- Vital parameters of the nearest time will be replaced if the vital parameters of the exact time couldn't be found.
- All vital parameters that included heart rate (beats per minute), systolic blood pressure (millimeters of mercury), respiratory rate (breaths per minute), temperature (degrees Celsius), neurologic (new agitation, A, V, P, U) and urine output (ml) were collected and then calculated into SOS score. (Record form part 2).
- All research staffs who collected data will be audited (demonstrated how to gather information from chart review for 10 charts) by principle investigator.
- Research staffs who collected data didn't know which record form are identified as case or control patients. (single blinded data collection)
- All data in record form part 1 and 2 were input into SPSS program for further analysis.

3.6.5 Data Analysis

Baseline characteristics of cases are reported as means with standard deviations, or medians and interquartile ranges (if the assumption of normal distribution was violated) for continuous variables. Categorical variables are reported as numbers and percentages. Baseline data of case and control patients was shown to compare as means with standard deviations, or medians and interquartile ranges (if the assumption of normal distribution was violated) for continuous variables. Categorical variables are reported as numbers and percentages. Discrimination of the SOS score at each time was assessed within receiver characteristic (ROC) analyses for admission SOS score and SOS score at 24 hours, 12 hours, 8 hours, 4 hours before adverse events (T_0) and corresponding area under the curve (AUC). The sensitivities and specificities of different cutoff thresholds were investigated for predictors with an AUC of at least 0.6. CIs for the AUC, sensitivity, and specificity of SOS score were calculated using bootstrapping, a nonparametric method that involved taking 1,000 samples of the data with replacement to obtain an empirical sampling distribution. Statistical analyses were completed using SPSS version 15. This study used the STARD checklist for reporting on diagnostic accuracy.

3.6.6 Ethical Considerations

This research protocol will be submitted for approval by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and the Faculty of Medicine, Buddhachinaraj Hospital. The scientific, educational, and/or societal value and the ethical consideration in terms of respecting the participants' welfare and dignity and their right to privacy and confidentiality will be considered.

Practices implemented to keep the participant's confidentiality are to use study codes on data documents and keep a separate document that links the study code to subjects' identifying information locked separately, back up data documents in separated hard drive, assign security codes to computerized records, and limit access to identifiable information.

3.6.7 Expected Benefit and Application

By identifying the SOS score that should be used to be the predictors of adverse events, our study provides direction regarding which cut point of the SOS score to

use in the future activation criteria. In addition, our findings will suggest that for many patients there is ample time prior to adverse events to provide potentially life-saving interventions.

3.6.8 Obstacle

-This study is a single-center study at a tertiary care hospital, the results may not be generalizable to some hospitals.
-This study is a retrospective study. There will be problems in some patients in collecting all data (missing data) used for analyses, so this study needs to exclude patients with incomplete epidemiologic or discharge data.
-The case-control design of this study has the potential for bias related to differential exposure assessment, as it is unclear whether vital sign measurement was different for cases compared to controls.
-The value of vital signs was recorded manually, so sometimes there is the potential to have distorted input or wrong values.

CHAPTER IV

Results

All 5666 adult patients were admitted in general wards in June-July 2015. After excluding 2461 patients who had a length of stay less than 2 days, and 77 patients whose status post discharge was summarized to be other than dead, improved and transferred, all 213 patients who died were assigned to be selected for cases that had adverse events and all 2915 patients who survived were assigned to be selected for match control with each case that had adverse events. Among all patients who died, 172 were excluded by exclusion criteria, and then 41 patients were selected to be in the case group. Of All 2915 patients who survived, 82 were selected to be the control group (case-control ratio is one to two) by using matching criteria with each case of the 41 patients who died that were selected to be in the case group (figure 2). General characteristics of the cases and controls are shown in table 4. Acute respiratory failure (68.3%) is the most common adverse events in the case group. Seventy eight percent of cases died from septic shock. Both groups of patients have low SOS scores at admission, because this study has already excluded patients who

had adverse events before admission or in the 24 hours after admission. Gender of controls did not match exactly with cases because the neurosurgical ward in our hospital does not use separate ward for males and females. Figure 3 shows box plots that compared SOS score at 4, 8, 12, 24 hours before adverse events of the case and control group. Bar graph in Figure 4, 5, 6, 7 show distribution of SOS score at 4, 8, 12, 24 hours before adverse events of the case and control group.

Comparison of SOS score discrimination at different time

Area under the curve (AUC) was used to evaluate discriminatory power for time interval before adverse events. An SOS score at 4 hours before adverse events is the best predictor for adverse events with an AUC of 0.972 (95% CI, 0.949-0.995). However, SOS scores at 8, 12, 24 hours before adverse events are still good predictor for adverse events (AUC 0.906, 0.915, 0.860 respectively) as shown in table 5.

Comparison of SOS score discrimination at different points (value)

Sensitivity, specificity and diagnostic effectiveness were used to evaluate discriminatory power for the value of SOS scores before adverse events. An SOS score ≥ 4 at 4 hours before adverse events is the best cut-off value for adverse events with a sensitivity of 82.9%, a specificity of 95.1% and a diagnostic effectiveness of 91.1%. An SOS score ≥ 4 at 8, 12, 24 hours before adverse events are still good cut-off values for adverse events with a specificity of 95.1%, 96.3%, 92.7%, respectively. However, sensitivity fell when the time before adverse events was increased, if a SOS score ≥ 4 was used to be the cut-off value, as shown in table 5.

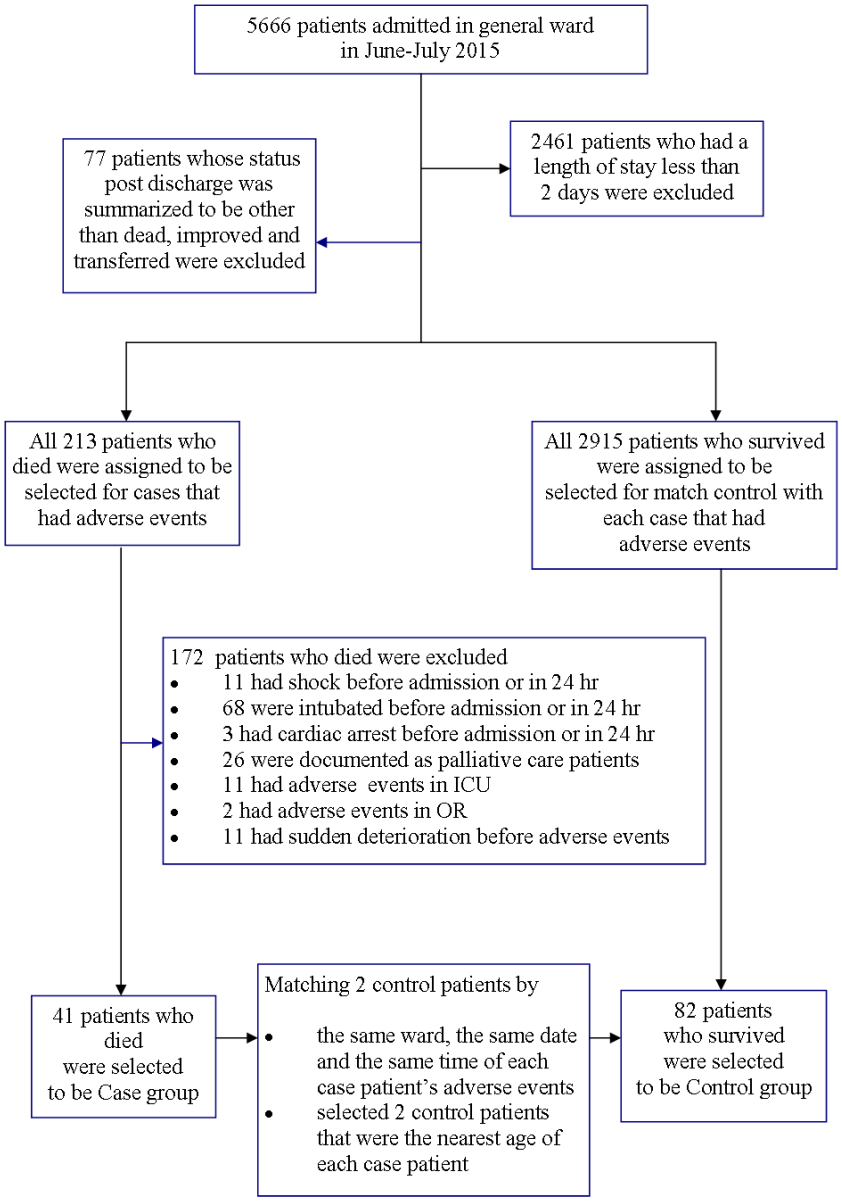
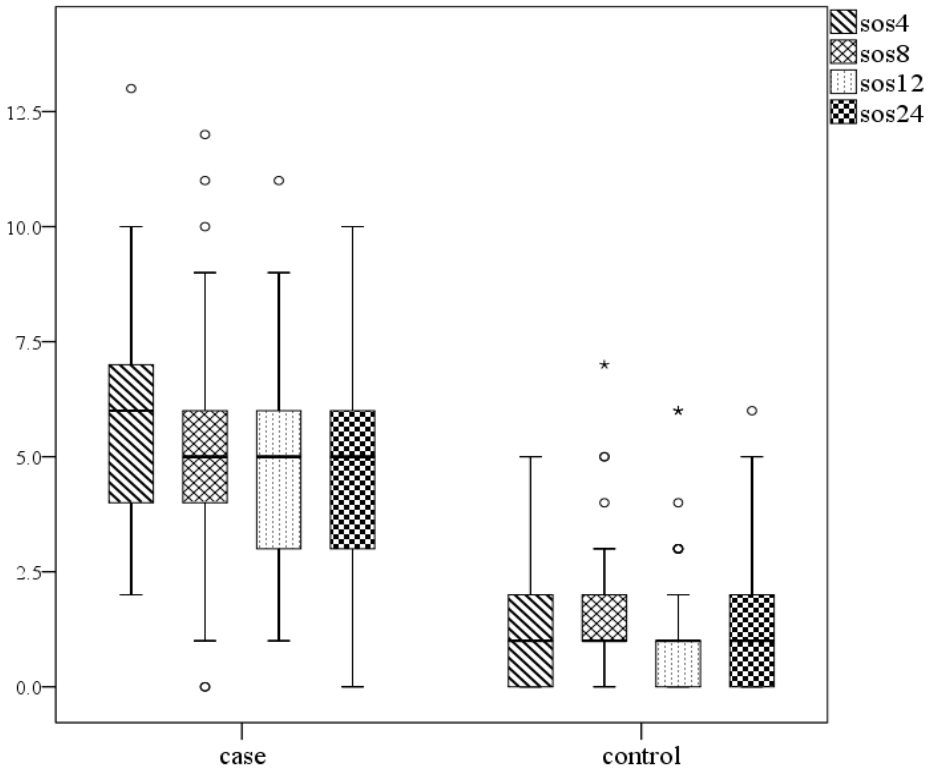


Figure 2 Diagram to report flow of participants through the study

Table 4 General characteristics of cases having adverse events and controls

Characteristic	Number (%)	
	Cases (n=41)	Controls (n=82)
Age-yr, Mean±SD	65±16.9	58±15.8
Gender		
Male	19 (46.3%)	37 (45.1%)
Female	22 (53.7%)	45 (54.9%)
Type of patients		
Medical conditions	35 (85.4%)	70 (85.4%)
Surgical conditions	6 (14.6%)	12 (14.6%)
SOS score admission, median (IQR)	2 (1-3)	1 (0-2)
Type of adverse events		
Acute respiratory failure	28 (68.3%)	
Cardiac arrest	5 (12.2%)	
Septic shock	5 (12.2%)	
Other shock	3 (7.3%)	
SOS score value, median (IQR)		
4 hours before adverse events	6 (4-7)	
8 hours before adverse events	5 (4-6.5)	
12 hours before adverse events	5 (3-6.5)	
24 hours before adverse events	5 (3-6)	
Shift time of adverse events		
Morning (8.30-16.30)	15 (36.6%)	
Evening (16.30-0.30)	13 (31.7%)	
Night (0.30-8.30)	13 (31.7%)	
Died from septic shock	32 (78%)	
Length of stay-days, median (IQR)	7 (3-19)	

Figure 3 Box plots of SOS score at 4, 8, 12, 24 hours before adverse events of cases and controls



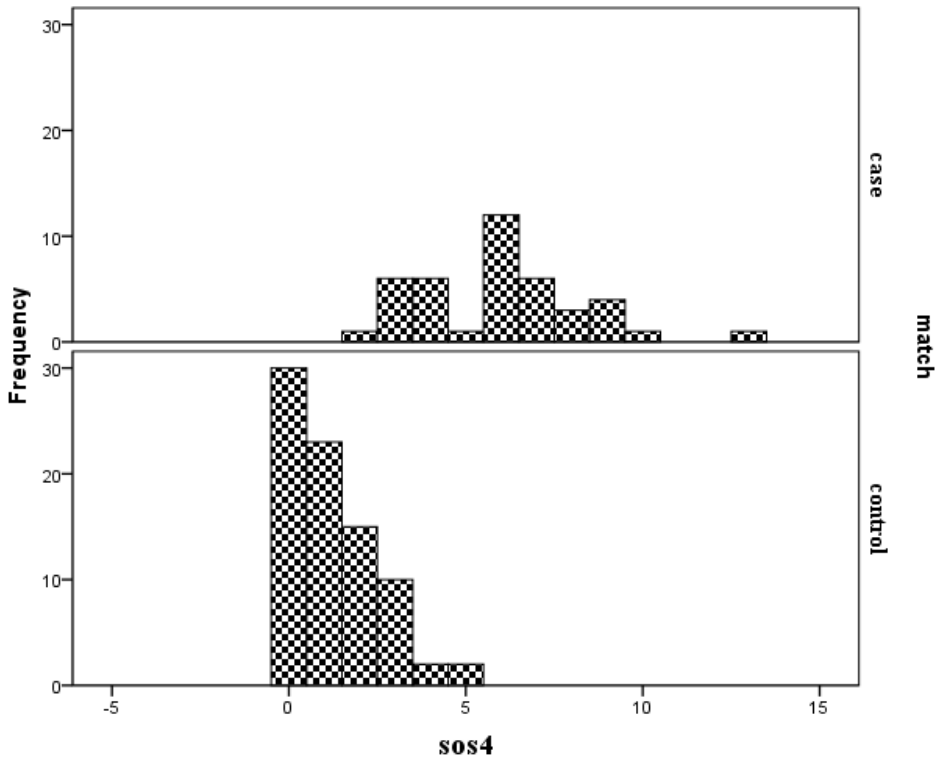


Figure 4 *Distribution of SOS score at 4 hours before adverse events in cases and controls*

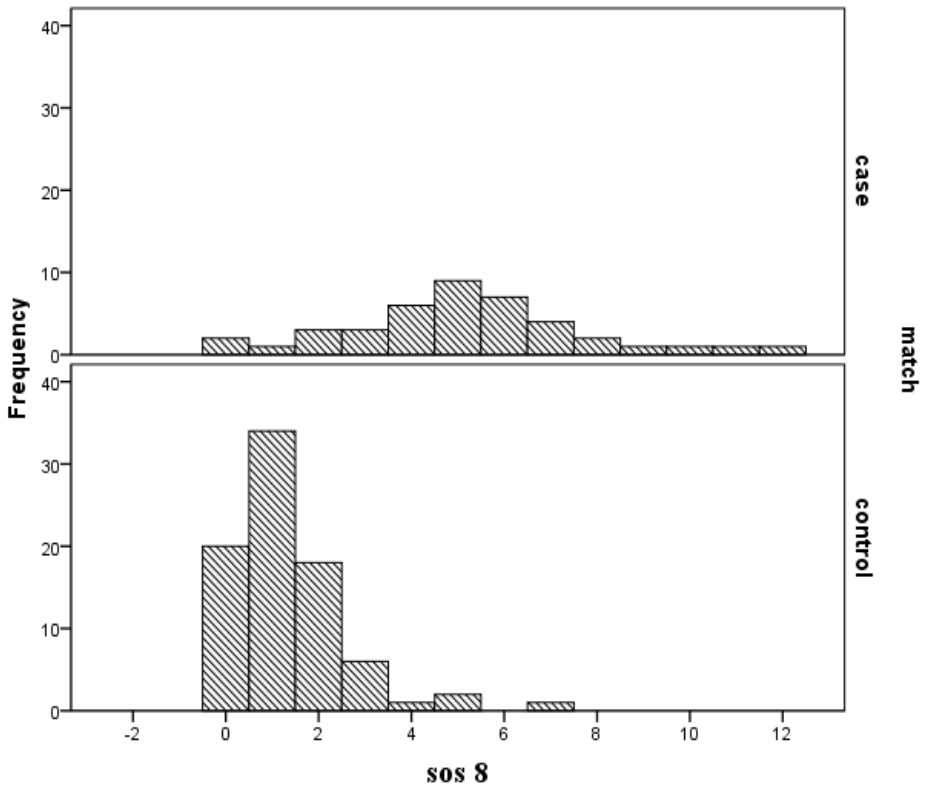


Figure 5 Distribution of SOS score at 8 hours before adverse events in cases and controls

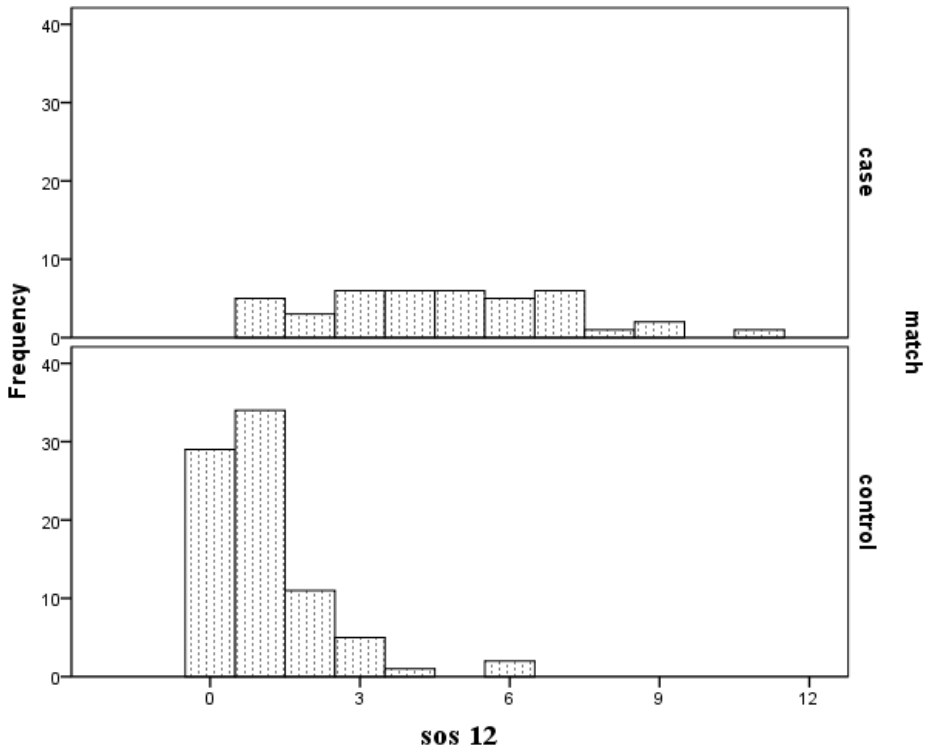


Figure 6 Distribution of SOS score at 12 hours before adverse events in cases and controls

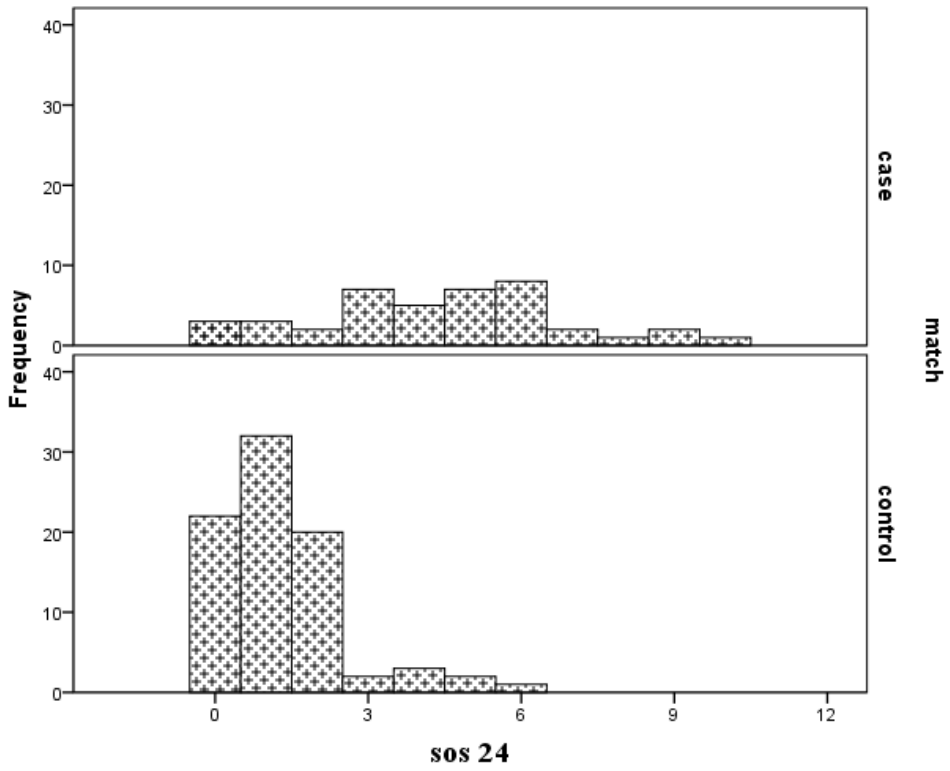


Figure 7 Distribution of SOS score at 24 hours before adverse events in cases and controls

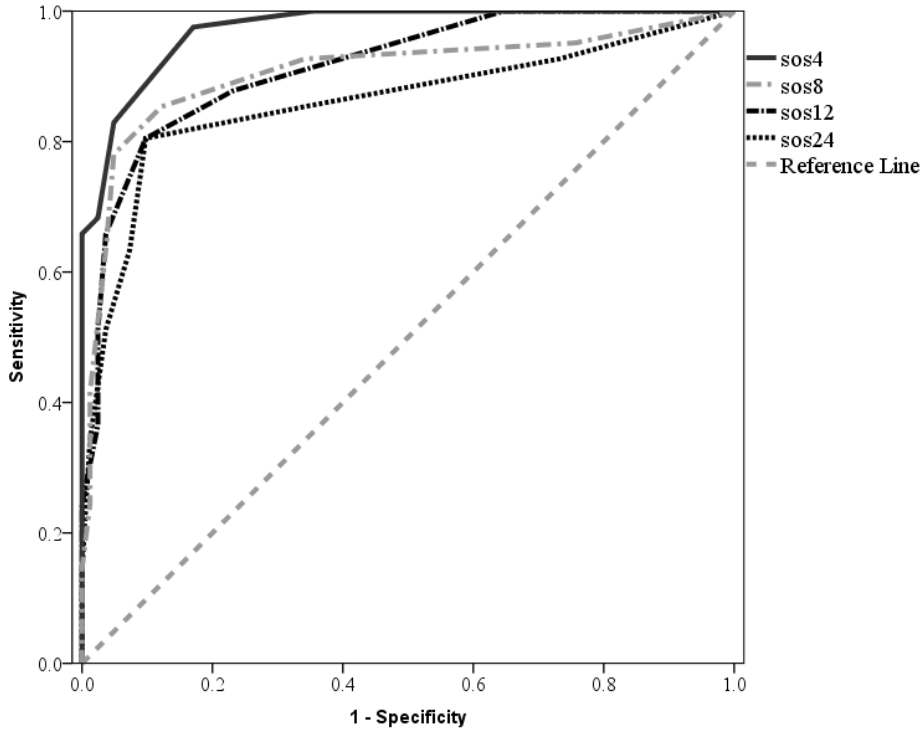


Figure 8 Receiver Operating Characteristics (ROC) curves of SOS score at 4, 8, 12, 24 hours before adverse events for discriminating case and control group

Table 5 Comparison discrimination ability at each cut-off of SOS score at 4, 8, 12, 24 hours before adverse events (AEs)

SOS score	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, %	Area under ROC curve (95% CI)
4 hr before AEs				0.972 (0.949-0.995)
SOS ≥ 2	100 (91.4-100)	64.6 (53.3-74.9)	76.4	
SOS ≥ 3	97.6 (87.1-99.9)	82.9 (73.0-90.3)	87.8	
SOS ≥ 4	82.9 (67.9-92.8)	95.1 (87.9-98.7)	91.1	
SOS ≥ 5	68.3 (51.9-81.9)	97.6 (91.5-99.7)	87.8	
SOS ≥ 6	65.9 (49.4-79.9)	100 (95.6-100)	88.6	
8 hr before AEs				0.906 (0.839-0.974)
SOS ≥ 2	92.7 (80.1-98.5)	65.9 (54.5-75.9)	74.8	
SOS ≥ 3	85.4 (70.8-94.4)	87.8 (78.7-93.9)	86.9	
SOS ≥ 4	78.0 (62.4-89.4)	95.1 (87.9-98.7)	89.4	
SOS ≥ 5	63.4 (46.9-77.8)	96.3 (89.7-99.2)	85.4	
SOS ≥ 6	41.5 (26.3-57.9)	98.8 (93.4-99.9)	79.7	
12 hr before AEs				0.915 (0.862-0.968)
SOS ≥ 2	87.8 (73.8-95.9)	76.8 (66.2-85.4)	80.5	
SOS ≥ 3	80.5 (65.1-91.2)	90.2 (81.7-95.7)	86.9	
SOS ≥ 4	65.9 (49.4-79.9)	96.3 (89.7-99.2)	86.2	
SOS ≥ 5	51.2 (35.1-67.1)	97.6 (91.5-99.7)	82.1	
SOS ≥ 6	36.6 (22.1-53.1)	97.6 (91.5-99.7)	77.2	
24 hr before AEs				0.860 (0.779-0.942)
SOS ≥ 2	85.4 (70.8-94.4)	65.9 (54.5-75.9)	72.3	
SOS ≥ 3	80.5 (65.1-91.2)	90.2 (81.7-95.7)	86.9	
SOS ≥ 4	63.4 (46.9-77.9)	92.7 (84.7-97.3)	86.2	
SOS ≥ 5	51.2 (35.1-67.1)	96.3 (89.7-99.2)	81.3	
SOS ≥ 6	34.1 (20.1-50.6)	98.8 (93.4-99.9)	77.2	

CHAPTER V

Discussion

Adverse events that occur in the hospital can be divided in 2 ways. The first way is the acute sudden adverse events that occur rapidly in a few seconds or a few minutes. Because acute sudden adverse events occur suddenly in a few seconds or a few minutes, no time should be wasted for thinking or making judgments, so an experienced and well-trained team is the key factor to improve outcomes of patients in this group.[19, 21]

A strategy to prevent acute medical adverse events in the hospital is to use a specific risk score or to estimate the risk of these events in patients that are likely to have acute medical adverse events. However, you should first know which group of patients is likely to have acute medical adverse events, and then estimate the risk to these patients by specific tools or risk score. If the patients are in low risk group after classified by risk scores, routine monitoring and intervention will be done in these patients. If the patients are in a high risk group, they should be closely monitored to keep in touch, and interventions that can reduce the risk of acute medical adverse events should be done. Even though prevention strategy was already done in all patients, unexpected acute sudden adverse events could still occur in the hospital. Strategies to treat acute sudden adverse events are necessarily hard and harsh, fast and furious, performed by an effective and experienced team, which might conclude these sudden events with a good outcome.

The second way of adverse events is sub-acute adverse events that occur and progress slowly in a few hours or a few days. Sub-acute adverse events occur more commonly than acute types. These sub-acute adverse events occur frequently in general wards, however early detection and early resuscitation increases the likelihood of a good prognosis for patients in these groups.

The main difference between sub-acute and acute sudden adverse events is time. When sub-acute adverse events occur, they can progress from the small to big catastrophic events in a few hours or a few days. Tools for monitoring and early

detection are the most important thing in the strategy for treatment of sub-acute adverse events. MEWS is a simple and effective tool already in place, which all nurses can use to monitor and detect these sub-acute adverse events as part of routine practice, because sub-acute medical adverse events occur frequently and can happen in every patient with unspecific diseases.[17, 18]

This study emphasized the advantages of using MEWS for the early detection of deteriorating patients in general wards. Results from this study indicated that SOS scores (which is one type of MEWS used in Thailand) have a good predictive ability for adverse events in patients that are admitted in general wards. From data of the recent systematic reviews, there is no study reported on the predictive ability of MEWS for acute respiratory failure[23]. This is the first study that reported on the predictive ability of MEWS for adverse events in general wards that included acute respiratory failure or shock. Our study confirmed MEWS can be used for early detection in other adverse events, because cardiac arrest is a profound event that is too late for early intervention. We reported SOS score at 24, 12, 8, 4 hours before adverse to identify patients with more needs for immediate resuscitations and managements, so that early intervention could be done before adverse events occurred. Therefore, all patients in general hospital ward should be monitored by MEWS in order to early detect and resuscitate deteriorating patients. However, education and training should be provided to ensure staff have the competencies in monitoring, measurement, interpretation and response to the MEWS.[11]

Moseson and colleagues reported multiple scoring systems that have been developed in Intensive Care Unit (ICU), had superior performances in predicting mortality in hospital.[26] “What is the best scoring system?” Sometimes, it was not about the development of a completely novel tool, but simple and effective tools already in place, which all nurses can monitor and detect these sub-acute adverse events as part of routine practice, because sub-acute adverse events occur frequently, and can happen in every patient with unspecific diseases. [17, 18] Routine measurement of the SOS score can be done easily in general wards. The time taken to calculate SOS score is less than 30 seconds after routine measurements of vital signs.

Single parameter system is a simple, but has low sensitivity, low positive predictive value but high specificity, so could be potentially to result in excessive alarms without true adverse events. From the recommend of NICE guideline[11], multiple-parameter or aggregate weighted scoring systems should be used for track and trigger systems because these scoring system demonstrate a range of sensitivities

and specificities depending on the cut-off score used. From the results of AUC, sensitivity, specificity and diagnostic effectiveness (accuracy) in this study, the SOS score should be one of the tools for early detection of adverse events in general wards. The SOS score ≥4 is a reasonable value to use to be the cut-off point of trigger threshold to initiate action for worsening adverse events. This study showed that the SOS score ≥4 had a good predictive ability regardless of the time intervals leading up to 24 hours before the adverse events.

The SOS score is the most optimum score that allow monitoring clinical progress in general hospital ward, at least in Thailand context. The SOS score uses six physiological parameters to assess illness severity: temperature, systolic blood pressure, pulse rate, respiratory rate, level of consciousness and urine output. The SOS score can represent disturbance of all vital systems in the body e.g. central nervous system, respiratory system, cardiovascular system, renal and metabolic system. The clarity to identification of deteriorating patients can be enhanced and magnified by the SOS score, because deteriorating patients will have abnormal values in multiple physiological parameters more common than single physiological parameter in isolation[20]. The SOS score indicate "new onset confusion" in the level of consciousness parameter and weighted score of 1 because some patients may be confused but alert e.g. patient with alcohol withdrawal. Because the SOS score allow monitoring of clinical progress, so weighting score when the patients use vasopressor for maintain hemodynamics or use ventilator for support respiratory failure is reasonable. The SOS score don't indicate and weight score for oxygen saturation values because measurement of oxygen saturation by pulse oximetry is not routinely used in clinical assessment in low to middle income country, and respiratory rate monitoring can be represented the disturbance of respiratory system.

Urine output is another physiological parameter that added in the SOS score. Urine output is one of the three windows for tissue perfusion monitoring and important in many clinical settings[27]. Urine output is not routinely recorded for every patient in general wards. Our SOS protocol will add the urine output parameter to the SOS calculation in the cases that have an SOS score ≥ 2. Smith and Oakey found that urine output is the most inconsistently recorded data.[28] However, Hammond and coworkers found that urine output monitoring can improve after MEWS implementation.[29] Our study prove that urine output monitoring can be recorded routinely when the patients have an SOS score ≥ 2 after SOS score implementation. There are no studies that prove adding urine output in the MEWS calculation will increase discriminative power of MEWS. However, we found that the

SOS score had a higher predictive ability when compared with past studies that used MEWS which didn't add urine the output to calculation.[12] Further study should evaluate the value of adding the urine output in the MEWS calculation.

In Thailand, the SOS score is well-known for the early detection of septic patients, but with no clear cut-off value for early aggressive intervention. Adverse events in this study included septic shock (12.2%) and 78% of patients who had adverse events died from septic shock. MEWS was used in the early detection septic patients,[30, 31] but there is no strong evidence to clarify MEWS to be a sepsis screening tool. Our study might increase indirect evidence for using MEWS as a screening tool for sepsis.

While this study confirmed that SOS scores have the predictive ability to identify patients at risk of clinical deterioration, there is limited high-level data on the impact of their implementation on patient outcomes.[23, 32] Further study to test the impact of intervention under the SOS score protocol should be done.

The limitation of our study is design of methodology. Although RCTs are considered the strongest form of evidence, the complexity of introducing a MEWS system, with an accompanying educational program and audit, might suggest that a single RCT of a MEWS might be almost impossible. It would be impracticable to randomize individual patients on the same ward to receive different levels of monitoring.[33, 34] This study should be done in cohort design, but in view of ethical considerations, we cannot perform this study in a cohort manner because, if we suspected someone will deteriorate, we should do something to prevent it, and then adverse events will not occur. This is the main problem and is why this study had to be done in a retrospective nested case-control design.[35]

We excluded patients who were already worse before admission, or who had worsened in the 24 hours after admission for separate good patients in the first 48 hours after admission. The baseline SOS score at the time of admission of case and control in this study help to confirm the good status of patients before admission. We excluded patients who were admitted into, or who had adverse events in settings other than the general medicine or surgical wards such as ICU, and did not include acute sudden adverse events, because these were outside of our proposed scope. Thus, this study showed the real predictive ability of the SOS score, when it was used on the right patient (patients who had sub-acute adverse events), in the right place (in general wards) and at the right time (4-24 hours before adverse events). However, it will be at risk for "over-fitting" data to the population under study. Our study may exaggerate the predictive ability of models and, furthermore,

may not be broadly applicable to all populations. Another thing that should be reminded in our study is that positive and negative predictive values are largely dependent on disease prevalence in the examined population. Therefore, if we used the SOS score in the real world practice, positive and negative predictive values from our study will be changed when used the SOS score in other setting with a different prevalence of the disease in the population. Despite good discriminative ability, this studies also found clinically important trade-offs in sensitivity and specificity of the SOS score when using specific scores as a cut-off value. A range of sensitivities and specificities depending on the cut-off value used. However, in this study showed that SOS score ≥4 had a high sensitivity and specificity (sensitivity of 82.9%, specificity of 95.1%) at 4 hours before adverse events.

CHAPTER VI

Conclusion

The SOS score at 4, 8, 12, 24 hours before adverse events has a good predictive ability for patients who had adverse events in general wards. The SOS score ≥4 is a reasonable value to use to be the cut-off point of trigger threshold, to initiate action for worsening adverse events. SOS score ≥4 had a good predictive ability regardless of the time intervals leading up to 24 hours before adverse events.

Appendix A

Institutional Review Board approval

เอกสารรับรองโครงการวิจัยในมนุษย์

เอกสารรับรองโครงการวิจัยในมนุษย์ 82/56
คณะกรรมการจริยธรรมเกี่ยวกับการวิจัยในมนุษย์
โรงพยาบาลพุทธชินราช พิษณุโลก

ชื่อโครงการ ค่าการทำนายของ modified early warning score ในการระบุตัวผู้ป่วยที่มีอาการทรุดลงในหอผู้ป่วยสามัญ

ชื่อหัวหน้าโครงการ นายแพทย์ธีรฐภูมิ ชามพูนท

เลขที่โครงการ/รหัส -

สังกัดหน่วยงาน กลุ่มงานอายุรกรรม โรงพยาบาลพุทธชินราช พิษณุโลก

การรับรอง ขอรับรองโครงการวิจัยดังกล่าวข้างบนนี้ได้ผ่านการพิจารณาและรับรองจาก คณะกรรมการจริยธรรมเกี่ยวกับการวิจัยในมนุษย์โรงพยาบาลพุทธชินราช พิษณุโลก เมื่อวันที่ 30 ส.ค. 2556

ลงนาม
(นายแพทย์ธีระ ศิริอาชาพันธ์)
ประธานคณะกรรมการจริยธรรมเกี่ยวกับการวิจัยในมนุษย์

Appendix B

Case Record Form

Part 1 Baseline data

Code .....
(case นำหน้าด้วย A ตามด้วยรหัส control นำหน้าด้วย B,C ตามด้วยรหัส)

อายุ .....
เพศ 1 male 2 female
Event เกิดที่ 1 ward สามัญ 2 ICU
Event เกิดที่ Ward .....
ประเภทผู้ป่วย 1 medical condition 2 surgical condition
Event 1 cardiac arrest 2 respiratory failure
3 septic shock 4 shock อื่น
เสียชีวิตจาก severe sepsis or septic shock 1 yes 2 no
เวรที่เกิด Event 1 เวรเช้า 2 เวรบ่าย 3 เวรดึก
วันที่เกิดเหตุการณ์ ..... เวลา.....
แพทย์ได้พบผป.ก่อนเกิดเหตุการณ์ครั้งสุดท้าย..... ชม.
Length of stay.....วัน
LOS ..... Days before event (นอนรพ.กี่วันก่อนเกิดเหตุการณ์)

Part 2 data for SOS score calculation

Time before	Temp	Sys BP	HR	RR	Neuro	Urine	Total SOS
Admit value							
Admit score							
4 hr value							
4 hr score							
8 hr value							
8 hr score							
12 hr value							
12 hr score							
24 hr value							
24 hr score							

Appendix C

STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies

STARD Checklist

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	
	4	Study objectives and hypotheses	
METHODS			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	
Participants	6	Eligibility criteria	
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	
	8	Where and when potentially eligible participants were identified (setting, location and dates)	
	9	Whether participants formed a consecutive, random or convenience series	
Test methods	10a	Index test, in sufficient detail to allow replication	
	10b	Reference standard, in sufficient detail to allow replication	
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	
	15	How indeterminate index test or reference standard results were handled	
	16	How missing data on the index test and reference standard were handled	
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	
RESULTS			
Participants	19	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	
	21a	Distribution of severity of disease in those with the target condition	

	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	

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ภาคผนวก

VITA

Name: Ratapum Champunot

Date of Birth: July 19, 1975

Place of Birth: Phitsanulok, Thailand

Educational Records:

June 1992 - March 1998

Medical Degree, Faculty of Medicine.

Chiangmai University, Chiangmai, Thailand .

June 2001- June 2002

Certificate in Post Graduate Education in Internal medicine

Chiangmai University, Chiangmai, Thailand .

June 2001 – June 2004

Diploma, Thai Broad of Internal Medicine . Thai Medical

Council (Faculty of Medicine Chaingmai Thailand)

June 2004 – June 2006

Diploma,Thai Broad of Pulmonary and

Critical care in Respiratory Medicine

(Faculty of Medicine Chaingmai Thailand)

June 2006 – June 2007

Diploma,Thai Broad of Critical care medicine

(Faculty of Medicine Chulalongkorn University Thailand)

Employment Chronology:

1998-1999 : Physician, Srisakate Hospital, Srisakate

1999-2000 : Physician, Khunhan Hospital, Srisakate

2000-2001 : Physician, Nuenmaprang Hospital, Phitsanulok

2001-Present : Physician, Buddhachinaraj Hospital, Phitsanulok

Current Position

1) Attending Physician(staff)

Pulmonary and Critical Care consultant

Department of Internal Medicine

Buddhachinaraj Hospital (1,000 beds, tertiary care hospital)

Phitsanulok, Thailand 65000

2) Committee of Thai Society of Critical Care Medicine