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Prognostic value of near-infrared spectroscopy in mortality and organ dysfunction in patients recovery from septic shock: The research protocol

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ABSTRACT:

Background: Sepsis or septic shock results in the alteration of blood flow at the microcirculatory level, affecting tissue oxygenation and organ function and associated with death. This study aimed to use near-infrared spectroscopy (NIRS) in conjunction with vascular occlusion test (VOT) to assess the association of microcirculatory dysfunction after recovered from septic shock and in-hospital mortality.

Methods: We conducted a prospective observational study in patients who recovered from septic shock. We performed NIRS with VOT within 24 hours of hospitalization in medical and anesthetic ICU (T0), then at the time of recovery from septic shock (D0), at day 3 (D3), day 5 (D5), and day 7 (D7) after recovery from septic shock. We recorded the de-oxygenation (DeO_2) slope, the re-oxygenation (ReO_2) slope, and the area under the hyperemic response curve (the reperfusion area). We focused on parameters of microcirculation dysfunction, in-hospital mortality, and in-hospital complications.

Hypothesis: We hypothesize that NIRS with vascular occlusion test parameters are associated with in-hospital mortality and hospital complications.

Ethics: The study protocol has been approved by the Institution Review Board of Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2020/147).

Trial registration: TCTR20220413001.

Keywords: Near-infrared spectroscopy, Recovered from septic shock

INTRODUCTION

Sepsis or septic shock is a disease that can rapidly progress and resulted in a high mortality rate. [1-2] The pathophysiology of sepsis is caused by the alteration of blood flow at the microcirculatory level, affecting tissue oxygenation and organ function and associated with death. [3] The maldistribution characteristics associated with sepsis were stagnation of capillary blood flow and reduced functional capillary density [3], making the systemic hemodynamic variables do not reflect the hemodynamic properties of microcirculation. [4]

During the recovery phase of septic shock, heart and blood vessels function has returned to a near-normal state. [5] However, microcirculation alterations in sepsis or septic shock recovery have never been determined and hard to be verified by conventional hemodynamic monitoring systems. [4]

Near-Infrared Spectroscopy (NIRS) is a tool that can detect oxygen saturation in various tissues (static method). Even though changes in static StO_2 and $ScvO_2$ during septic shock were not found to correlate well. [6] The use of NIRS in conjunction with arterial occlusion test (dynamic approach) can indicate microcirculatory function. [7] Specific alterations in dynamic measurements occur in patients with sepsis (as Figure 1). [4,5,8] The most sensitive alteration is the re-oxygenation slope after a period of stagnant hypoxia. [5]

In patients with sepsis or septic shock, the de-oxygenation (DeO_2) slope and the re-oxygenation (ReO_2) slope are lower than the healthy volunteers. Likewise, the area under the hyperemic response curve (reperfusion area) is smaller than the healthy volunteers. [7] The NIRS is non-invasive, easy to use, and can be applied in conjunction with other assessments in ICU. [9]

To date, there is no study to assess microcirculation function in recovery phase of septic shock. The prognostic value of remaining microcirculation alteration during recovery phase of septic shock to predict hard outcomes like mortality and organ dysfunction is still unknown.

We aim to identify the residual microcirculatory alteration by NIRS technique in conjunction with the arterial occlusion test in patients in the recovery phase of septic shock and analyzed the association with in-hospital mortality and organ failure.

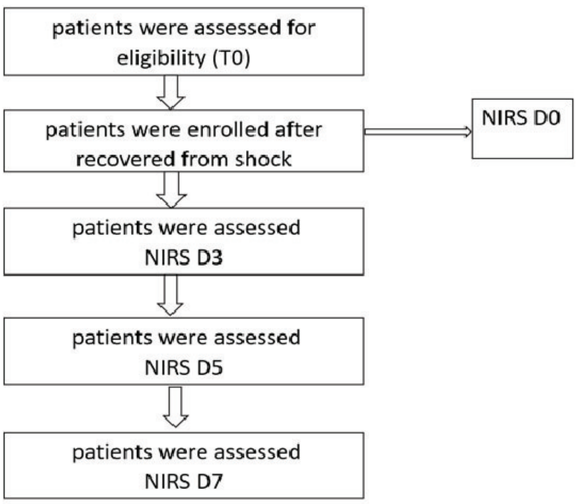

Figure 1. Study flow

KEY MESSAGES:

- To studied a predictive performance of NIRS parameters with in-hospital mortality and complications in patients surviving from septic shock

OBJECTIVES

Primary Objective

• to study correlation between in-hospital mortality in recovered subjects from septic shock and microcirculatory dysfunction

Secondary Objectives

• In-hospital complications including AKI, new sepsis and septic shock, delirium in recovered subjects from septic shock with microcirculation alteration

• Microcirculation alteration factors which determine mortality and organ dysfunction including in-hospital complication

MATERIAL AND METHODS

This study was a prospective observational study. The study protocol was approved by the Institutional Review Board of Ramathibodi Hospital, Mahidol University (COA. MURA2020/147).

Study setting

The patients were hospitalized in the medical intensive care unit (mICU) and anesthetic ICU, diagnosed with septic shock according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [10], from February 2020 to January 2022.

The definition for septic shock (10)

Patients, who met clinical criteria of sepsis, develop persistence of hypotension, and require vasopressors to optimize MAP ≥65 mm Hg, in combination with a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Eligibility Criteria for the experimental (CVI) group

Inclusion criteria

1. 18 years of age or older
2. Diagnosis of septic shock according to the Sepsis-3 criteria
3. Admission to medical ICU and anesthetic ICU within 24 hours for inclusion
4. Patients recovered from septic shock, defined from the discontinuation of all vasopressors to maintain mean arterial pressure ≥ 65 mmHg for 24 hours with one or more of the following arterial lactate criteria obtained at time point of free vasopressors and inotropes for 24 hours
    a. Restoration of lactate ≤ 2mmol/L
    b. Arterial lactate > 2 mmol/L but stable arterial

lactate at least two consecutive values within 24 hours of withdrawal vasopressors and inotropes

c. Arterial lactate > 2 mmol/L but continuous declining of arterial lactate to this value after withdraw all vasopressors and inotropes

Exclusion criteria

1. Pregnant women
2. Brain-dead patients
3. Non-resuscitated patients
4. Severe hypothermia body temperature < 28°C
5. Body mass index > 35 kg/m^2
6. Post cardiac arrest
7. Any injury to extremities that could hinder the placement of the NIRS sensor probe
8. Contraindication to NIBP measurement (tourniquet test); peripheral vascular disease, traumatized limb, limb infection, peripheral neuropathy, Raynaud's disease
9. Deny to participate in this research

Intervention

After enrollment for the study, the patients were recorded for baseline characteristics. NIRS with the vascular occlusion test was performed within 24 hours after the patients were hospitalized in ICU for septic shock (T0), then at the time of recovery from septic shock (D0), at day 3 (D3), day 5 (D5), and day 7 (D7) after recovery from septic shock. NIRS assessments with VOT were performed by only one person, the main researcher.

NIRS assessments

Nonin Medical's SenSmart™ Model X-100, Universal Oximetry System, was used with Nonin's EQUANOX Advance Model 8004CB, 4-wavelength sensors, depth 12.5 mm, to place on the thenar eminence ,selected one of the upper extremities which arterial line was not inserted, not too edema, not the same site of vasopressors infusion and confirming that the NIRS probe is attached firmly with thenar eminence. The tissue oxygen saturation (StO_2) was recorded during the arterial occlusion test, and all data were exported to files for conversion to Microsoft Excel 365 and off-line analyzed.

Vascular occlusion test

The arterial occlusion test was performed by a pneumatic cuff pressure inflated 50 mmHg above the patient's systolic blood pressure and maintained for 3 minutes. [11] This procedure produced a progressive fall in StO_2, defined as De-oxygenation (DeO_2) slope. After maintaining the occlusion for 3 minutes, the pneumatic cuff was instantly deflated, which produced Re-oxygenation (ReO_2) slope up to a maximal level. Then the curve slowly declined to baseline, creating the hyperemic response curve.

NIRS parameters

The research parameters, including the de-oxygenation (DeO_2) slope, the re-oxygenation (ReO_2) slope, and the area under the hyperemic response curve (the reperfusion area), were recorded, and were blinded to the patient care team.(as figure 2)

Outcome Measurement

We recorded age, gender, BMI, vital signs, comorbidities, infection source, vasopressor max dose and duration, steroid use, and amount of IV fluid received during vasopressor infusion. The sequential organ failure assessment (SOFA) score and arterial lactate level were recorded at T0 and D0. Outcomes of interest were in-hospital mortality and in-hospital complications.

In-hospital complications

1. New onset of acute kidney injury (AKI) according to the KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012. [12]

The definition for AKI was defined as any of the following:

- Increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours: or
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days: or
- Urine volume < 0.5 ml/kg/h for 6 hours

2. New episodes of shock after recovery from the septic shock defined by resuming the vasopressor to maintain MAP ≥ 65 mmHg without association with the previous septic shock.

3. Nosocomial infections after recovery from septic shock, defined as the pathogen-proven infection requiring antibiotic treatment, occurs during the septic shock recovery phase

- Central Line-Associated Blood Stream Infection (CLABSI) [13]
- Catheter-Associated Urinary Tract Infection (CAUTI) [14]
- Hospital-acquired and Ventilator-associated Pneumonia [15]

4. Delirium which defined according to the confusion assessment method for the intensive care unit (CAM-ICU). [16]

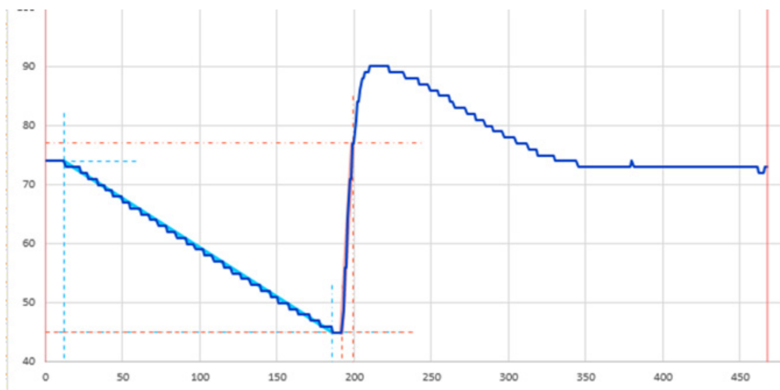

Figure 2. NIRS parameters record

Timeline

	February 2020-June 2021	January -July 2021	July 2021-January 2022	February 2022
Analyze previous study	→			
Amendment and renew project expiration	→	→		
Data collection			→	
Data analysis, discussion and presentation				→

DATA ANALYSIS PLAN

Sample size estimation

The sample size was calculated from the prognostic ability of mortality by using null hypothesis to predict mortality at Area Under the Curve of ROC was 0.61 while we predicted that the parameters in our study could better predict in-hospital mortality with AUC of 0.65. General in-hospital mortality of septic shock was 39%. [17] We set alpha error at 0.05. 121 patients were needed with power of 80%.

OUTCOME ANALYSIS PLAN

Statistical analysis was performed using SPSS version 23. The normality of distribution was checked using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (25^{th}–75^{th} percentile). For demographics and clinical characteristics of the study groups, Student's t test or the Mann–Whitney U test was used to compare continuous variables between two groups. Nominal variables were compared across groups using the chi-square test.

The univariate logistic regression analysis was used to select significant vasriables at p-value<0.1 and multivariate logistic regression analyses was performed to identify significant variables at p-value<0.05. The receiver operating characteristic (ROC) analyses were performed to assess the diagnostic ability and identify the cut-off threshold of various parameters by Youden's index. Statistical significance was considered at the threshold of p-value < 0.05.

DATA MANAGEMENT AND DATA MONITORING

Input data and monitoring method

Physical and clinical baseline characteristics of the patients (Table1)

Clinical data of recovered from septic shock patients, comparison between hospital survivors and non-survivors (Table 2)

Univariate analysis of the variables associated with hospital mortality among 97 recovered from septic shock patients (Table 3)

Multivariate analysis of the variables including de-oxygenation slope associated with in- hospital mortality among 97 recovered from septic shock patients (Table 4)

NIRS parameters in patients recovered from septic shock at D0 regarding in-hospital complications (Table 5)

Definition of Variables

Septic shock defined as patients, who met clinical criteria of sepsis, develop persistence of hypotension, and require vasopressors to optimize MAP ≥65 mm Hg, in combination with a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation

Recovery from septic shock defined as the day which patients hemodynamically stable without uses of vasopressor.

Research Instruments

Near-infrared spectroscopy, 4-wavelength sensors, depth 12.5 mm, would be placed on the thenar eminence ,selected one of the upper extremities which arterial line was not inserted, not too edema, not the same site of vasopressors infusion and confirming that the NIRS probe is attached firmly with thenar eminence.

Table 1. Baseline characteristics of variables

Variables	Values
Age (year)	Chart reviewed
Gender - Male - Female	Chart reviewed
Body mass index (kg/m^2)	Chart reviewed
Heart rate (beats/minute)	Chart reviewed
SBP (mmHg)	Chart reviewed
DBP (mmHg)	Chart reviewed
MAP (mmHg)	Chart reviewed
Source of infection - Unknown - Central nervous system - Respiratory system - Intra-abdomen - Skin - Urogenital system - Line	Chart reviewed
Type of infection - Nosocomial - Community-acquired	Chart reviewed
Underlying disease - Diabetes - Hypertension - History of myocardial infarction - Smoking - Chronic obstructive pulmonary disease - Chronic liver disease - Chronic kidney disease - Malignancy	Chart reviewed
Norepinephrine max dose (mcg/kg/min)	Chart reviewed
Second vasopressor usage	Chart reviewed
Steroid received	Chart reviewed
Positive blood culture	Chart reviewed
Lactate T0[a] (mmol/L)	Chart reviewed

Table 1. (Continued) Baseline characteristics of variables.

Variables	Values
Lactate D0[b] (mmol/L)	Chart reviewed
SOFA T0[a]	Chart reviewed
SOFA D0[b]	Chart reviewed
Vasopressor duration (hour)	Chart reviewed
Cumulative fluid intake[c] (ml)	Chart reviewed

Results are presented as means ± SD; median (IQR); number (percent). [a]T0, within 24 hours after mICU admission for septic shock; [b]D0, at recovery from septic shock; [c]Total intravascular fluid received during vasopressor infusion. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SOFA, score sequential organ failure assessment score.

Table 2. Clinical data of recovered from septic shock patients, comparison between hospital survivors and non-survivors

Variables	Hospital survivors	Non-survivors	P-value
Age (year)	Chart reviewed	Chart reviewed	
Gender - Male - Female	Chart reviewed	Chart reviewed	
Body mass index (kg/m^2)	Chart reviewed	Chart reviewed	
Heart rate (beats/minute)	Chart reviewed	Chart reviewed	
SBP (mmHg)	Chart reviewed	Chart reviewed	
DBP (mmHg)	Chart reviewed	Chart reviewed	
MAP (mmHg)	Chart reviewed	Chart reviewed	
Type of infection - Nosocomial - Community-acquired	Chart reviewed	Chart reviewed	
Norepinephrine max dose (mcg/kg/min)	Chart reviewed	Chart reviewed	
Second vasopressor usage	Chart reviewed	Chart reviewed	
Steroid received	Chart reviewed	Chart reviewed	
Positive blood culture	Chart reviewed	Chart reviewed	
Lactate T0[a] (mmol/L)	Chart reviewed	Chart reviewed	
Lactate D0[b] (mmol/L)	Chart reviewed	Chart reviewed	
SOFA score T0[a]	Chart reviewed	Chart reviewed	
SOFA score D0[b]	Chart reviewed	Chart reviewed	
Vasopressor duration (hour)	Chart reviewed	Chart reviewed	

Results are presented as means ± SD; median (IQR); number (percent). [a]T0, within 24 hours after mICU admission for septic shock; [b]D0, at recovery from septic shock; [c]Total intravascular fluid received during vasopressor infusion. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SOFA, score sequential organ failure assessment score.

Table 3. Univariate analysis of the variables associated with hospital mortality among 97 recovered from septic shock patients.

Variables	Hospital survivor (N)	Hospital survivor (N)	OR(95%CI)	p-value
- Steroid use	Chart reviewed	Chart reviewed		
- Positive hemoculture	Chart reviewed	Chart reviewed		
- Lactate clearance	Chart reviewed	Chart reviewed		
- Pulmonary infection	Chart reviewed	Chart reviewed		
- De-oxygenation T0 (%/sec)	Bedside collected	Bedside collected		
- Re-oxygenation T0 (%/sec)	Bedside collected	Bedside collected		
- Reperfusion area T0 (%•sec)	Bedside collected	Bedside collected		
- Vasopressure use(hr)	Chart reviewed	Chart reviewed		
- Lactate T0	Chart reviewed	Chart reviewed		
- SOFA score T0	Chart reviewed	Chart reviewed		

Table 3. (Continued) Univariate analysis of the variables associated with hospital mortality among 97 recovered from septic shock patients.

Variables	Hospital survivor (N)	Hospital survivor (N)	OR(95%CI)	p-value
- Lactate D0	Chart reviewed	Chart reviewed		
- SOFA score D0	Chart reviewed	Chart reviewed		
- De-oxygenation D0 (%/sec)	Bedside collected	Bedside collected		
- Re-oxygenation D0 (%/sec)	Bedside collected	Bedside collected		
- Reperfusion area D0 (%•sec)	Bedside collected	Bedside collected		
- De-oxygenation D3 (%/sec)	Bedside collected	Bedside collected		
- Re-oxygenation D3 (%/sec)	Bedside collected	Bedside collected		
- Reperfusion area D3 (%•sec)	Bedside collected	Bedside collected		
- De-oxygenation D5 (%/sec)	Bedside collected	Bedside collected		
- Re-oxygenation D5 (%/sec)	Bedside collected	Bedside collected		
- Reperfusion area D5 (%•sec)	Bedside collected	Bedside collected		
- De-oxygenation D7 (%/sec)	Bedside collected	Bedside collected		
- Re-oxygenation D7 (%/sec)	Bedside collected	Bedside collected		
- Reperfusion area D7 (%•sec)	Bedside collected	Bedside collected		
- ICU stay	Chart reviewed	Chart reviewed		

Table 4. Multivariate analysis of the variables including de-oxygenation slope associated with in- hospital mortality among 97 recovered from septic shock patients.

Variables	OR(95%CI)	p-value
Age	Chart reviewed	
Sex	Chart reviewed	
Serum lactate at recovery day	Chart reviewed	
SOFA score at recovery day	Chart reviewed	
De-oxygenation slope	Bedside collected	
Re-oxygenation slope	Bedside collected	
Reperfusion area	Bedside collected	

Table 5. NIRS parameters in patients recovered from septic shock at D0 regarding in-hospital complications.

New onset of acute kidney injury (N)		p-value
De-oxygenation slope	Bedside collected	
Re-oxygenation slope	Bedside collected	
Reperfusion area	Bedside collected	
New sepsis/ septic shock (N)		
De-oxygenation slope	Bedside collected	
Re-oxygenation slope	Bedside collected	
Reperfusion area	Bedside collected	
Nosocomial infection (N)		
De-oxygenation slope	Bedside collected	
Re-oxygenation slope	Bedside collected	
Reperfusion area	Bedside collected	
Delirium(N)		
De-oxygenation slope	Bedside collected	
Re-oxygenation slope	Bedside collected	
Reperfusion area	Bedside collected	

DISCUSSION

Currently, NIRS is widely accepted as a non-invasive tools for measuring oxygenation. NIRS with a VOT provides dynamic parameters of tissue oxygen extraction and microvascular reactivity. [18, 19] At the time of this research, there is no study of microcirculation alteration in recovery phase of septic shock. Our hypothesis is there are parameters in recovery phase of septic shock patients by using NIRS with VOT techniques can predict in-hospital mortality and complications. If this hypothesis is proven. NIRS with VOT technique would be an effectively non-invasive, easy to use tools to apply to patients and provide a better care of sepsis bundle after septic shock is recovered.

Study's strength: this is the first study to demonstrate the clinical significance of microcirculation alteration by the NIRS with the VOT technique in patients who recovered from septic shock. The study protocol is clearly explained.

Limitations: firstly, because of the widely repetitive spread of COVID-19 pandemic, ICU capacity was overwhelm with COVID-19 patients and decreased septic shock patients in normal ICU. Second limitation of this study is the tools to interpret NIRS parameters. When using NIRS by Nonin Medical's SenSmart™ Model X-100, it is necessary to have an instrument to convert graphics of NIRS to parameters as numbers e.g. re-oxygenation slope parameters and area of the reperfusion area which depends on selection of interpreters whether they select an accurate parameters or not.

CONFIDENTIALITY

Informed consent is obtained at bedside isolated room in ICU. Instead of personal information such as name-sur-name, hospital number, admission number, and identifica-tion number, an ID code is utilized and recorded. The data for this study is only kept in collected data form and is pass-word secured on the computers of the researchers. When the research is concluded, all physical data will be destroyed, and all digital data will be deleted from all computers.

DISSEMINATION POLICY

The results of a study will be submitted in peer-reviewed journals and presented at conferences in critical care medicine and anesthesiology, Ramathibodi hospital.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Gunthiga Laplertsakul; (II) Data curation: Gunthiga Laplertsakul; (III) Formal analysis: Gunthiga Laplertsakul, Pongdhep Theerawit, Yuda Sutherasan, Detajin Junhasavasdikul; (IV) Funding acquisition: Gunthiga Laplertsakul; (V) Methodology: Gunthiga Laplertsakul, Pongdhep Theerawit, Yuda Sutherasan, Detajin Junhasavasdikul; (VI) Project administration: Gunthiga Laplertsakul; (VII) Visualization: Gunthiga Laplertsakul; (VIII) Writing-original draft: Gunthiga Laplertsakul; (IX) Writing – review & editing: Gunthiga Laplertsakul, Pongdhep Theerawit.

SUPPLEMENTARY MATERIALS

none

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