ORIGINAL ARTICLE

Organ Functions in Septic Patients Receiving Fluid Resuscitation Guided by Dynamic versus Static Parameters: A Randomized Controlled Trial

Thiti Sricharoenchai, MD[1], Nanthawan Okas, MD[2,3]

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand; [2] Department of Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand; [3] Department of Medicine, Chawang Crown Prince Hospital, Nakhon Si Thammarat, Thailand

Background: A sequential organ failure assessment (SOFA) score of 2 or more reflects 10% mortality risk in septic patients. Although dynamic hemodynamic parameters can better predict fluid responsiveness than static parameters, standard methods have not been recommended.

Objective: The primary objective was to compare SOFA change from diagnosis to 72 hours between patients receiving dynamic ultrasound measurement of inferior vena cava (IVC) variation-guided and those receiving static central venous pressure (CVP)-guided fluid resuscitation. Secondary objectives were SOFA at 72 hours of sepsis and SOFA change from diagnosis to seven days, proportion of patients receiving vasopressor(s), 30-day vasopressor-free days (VFDs), and pulmonary edema within seven days.

Materials and Methods: A single-blinded randomized controlled trial was conducted in Thammasat University Hospital between September 2019 and March 2020. Septic patients were stratified by APACHE II score less than 25 or 25 and above, then randomized using blocks of 2 and 4 to dynamic IVC-guided or static CVP-guided.

Results: Of 104 patients, 52 in each group had comparable baseline characteristics. Median (IQR) SOFA changes during 72 hours were –2 (–3.5 to 5) versus –1 (–3 to 3.5) in dynamic IVC variation-guided vs. static CVP-guided, respectively, p=0.865. While medians (IQR) of SOFA at 72 hours and SOFA change during seven days were 5 (2 to 13) versus 7 (3.5 to 13), p=0.286, and –2 (–3.5 to 13) versus –3 (–4 to 1.5), p=0.180, those receiving vasopressor(s) were 82.7% versus 96.2%, p=0.026, median (IQR) 30-day VFDs were 28.5 (0 to 29.4) versus 22.5 (0 to 28.6), p=0.008; and pulmonary edema within seven days was 11.5% versus 13.5%, p=0.767.

Conclusion: Effects of dynamic IVC- and static CVP-guided fluid resuscitation in septic patients on SOFA score change from diagnosis to 72 hours and to seven days, 72-hour SOFA score, and pulmonary edema within seven days were not different, but those receiving vasopressor(s) may be lower, and 30-day VFDs may be higher in dynamic IVC variation-guided.

Keywords: SOFA score; Ultrasound: Central venous pressure; Fluid resuscitation; Sepsis

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Sepsis remains a public health problem in terms of high mortality and high cost of treatment[1,2]. Early goal-directed therapy (EGDT), which was introduced in 2001, could reduce the mortality rate in patients with sepsis[3]. The principle of sepsis treatment consists of intravenous (IV) fluid administered during the first six hours of resuscitation, the rational use of antibiotics, infection control, vasopressor administration, and airway management[4]. As for intravascular volume measurement during the first six hours of treatment, the recommendation is to maintain the central venous pressure (CVP) at 8 to 12 mmHg as a treatment goal[4]. However, several studies showed that CVP was not a good predictor for fluid responsiveness[5,6] because it is a static measurement at a single time point and cannot represent the volume status, and so it is unable to reflect the cardiovascular response to fluid administration. By contrast, dynamic indices were demonstrated as reliable predictors for fluid responsiveness in patients with sepsis by several studies[7-9].

Therefore, the Surviving Sepsis Campaign 2016, the international guidelines for the management of sepsis and septic shock, which were the

Correspondence to:

Sricharoenchai T.

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Thammasat University, 99/209 Moo 18, Paholyotin Road, Khlong Nueng, Khlong Luang, Pathum Thani 12120, Thailand.

Phone: +66-2-9269794, Fax: +66-2-9269793

Email: thiti_x@tu.ac.th

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current guidelines at the time of the present study, recommended that the dynamic indices were preferred to assess the response of the cardiovascular system to fluid therapy[10]. However, each dynamic index has different limitations; the international guidelines have not provided strong recommendations on any particular type of dynamic index. Thus, the adoption of dynamic indices is decided based on clinical situation, available resources, expertise, and preferences of individual attending physicians.

A sequential organ failure assessment (SOFA) score of 2 or more in patients with sepsis reflected that the overall risk of death was approximately 10%[11]. Given that the cardiovascular parameter is one component of the SOFA score, the stable hemodynamics inherently make the SOFA score lower and thus are associated with improved clinical outcomes of patients with sepsis or septic shock. The evidence of this hypothesis was demonstrated in a study of Belgian intensive care unit (ICU) showing a positive correlation between change of the SOFA score within 48 hours and mortality rate[12].

To the authors' knowledge, there is no study in Thailand comparing the alterations of organ functions attributed to dynamic indices or static indices as indicators for fluid resuscitation in patients with sepsis. This study aimed to compare the clinical outcomes between the ultrasound (US) of dynamic inferior vena cava (IVC) variation-guided and static CVP-guided fluid resuscitation in patients with sepsis, i.e., the change of the SOFA score from the recognition of sepsis to 72 hours as the primary objective, and the SOFA score at 72 hours, the change of the SOFA score from the recognition of sepsis to seven days, the proportion of patients receiving vasopressor(s), the vasopressor-free days (VFDs) within 30 days, and the incidence of pulmonary edema within seven days, as the secondary objectives.

Materials and Methods

Study design, setting, and participants

This study was a single-blinded randomized controlled trial in patients with sepsis at the medical ICU, general medical wards, or the emergency department of Thammasat University Hospital (TUH) between September 2019 and March 2020. The inclusion criteria were: 1) age of 18 years or older, 2) suspected infection, 3) SOFA score of 2 or more, 4) systolic blood pressure (SBP) less than 90 mmHg or SBP decrease of greater than 40 mmHg from the original level or mean arterial pressure (MAP) less than 70 mmHg, and 5) requirement of IV fluid to maintain stable hemodynamics. The exclusion criteria were 1) pregnancy, 2) pulmonary edema due to cardiovascular diseases, 3) inability to be in a supine position, e.g., spine deformities, 4) difficult or inaccurate US measurement of IVC diameter, e.g., IVC compression from any causes, or 5) limitation of central venous catheterization, e.g., structural abnormalities of the internal jugular vein or superior vena cava. All recruited patients were stratified by Acute Physiology and Chronic Health Evaluation II (APACHE II) of less than 25 or 25 and above, then allocated via a Sealed Envelope™ program with blocks of 2 and 4 to either the dynamic IVC variation-guided or static CVP-guided group with a one-to-one ratio by NO. The sequences of allocation in a sealed box were revealed one by one for randomization. The guiding method of fluid resuscitation was shielded from each patient by a curtain.

This study was conducted to investigate the cardiovascular response to IV fluid resuscitation and the ensuing change in organ functions and other clinical outcomes in patients with sepsis. The patients were randomized to dynamic IVC variation-guided or static CVP-guided IV fluid resuscitation. The primary outcome was the change in the SOFA score from the onset of sepsis to 72 hours later. The secondary outcomes were the SOFA score at 72 hours, the change in the SOFA score from the onset of sepsis to seven days later, the proportion of patients receiving vasopressor(s), as well as the VFDs within 30 days, and pulmonary edema within seven days. The VFDs within 30 days was refined from "vasopressor duration" to provide a more accurate and comprehensive evaluation of vasopressor support.

Interventions

1) Static CVP-guided group: The patient had a central venous catheter inserted into the right or left internal jugular vein. The CVP of each patient was initially measured immediately after the catheterization, with a CVP value of less than 8, and 8 mmHg or greater being treated as responsiveness and non-responsiveness to fluid resuscitation, respectively. The CVP threshold of 8 mmHg was used based on Surviving Sepsis Campaign Guidelines 2012[4] and the preference of attending physicians. Patients with fluid-responsiveness were resuscitated by crystalloids [mainly 0.9% sodium chloride (NaCl)] 0.5 liter (L) in 15 minutes, then CVP was measured. Fluid administration and CVP measurements had been performed cyclically and repeatedly in the same way until the resuscitation endpoint, i.e., the patient

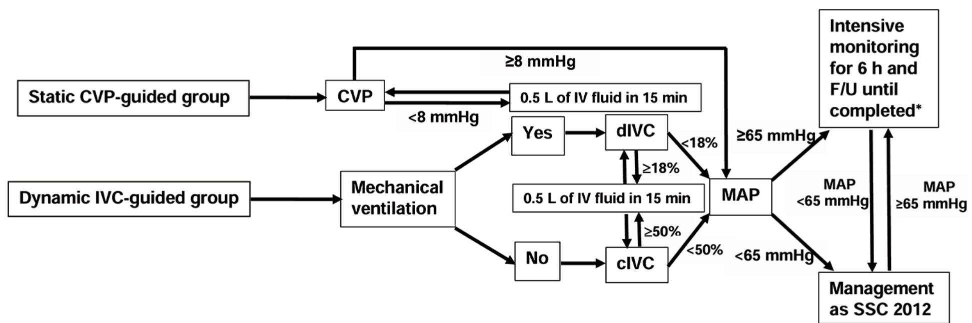

Figure 1. Study protocol diagram.

APACHE II=acute physiology and chronic health evaluation II; cIVC=inferior vena cava collapsibility index; CVP=central venous pressure; dIVC=inferior vena cava distensibility index; F/U=follow-up; h=hours; IV=intravenous; IVC=inferior vena cava; L=liter; MAP=mean arterial pressure; min=minutes; mmHg=millimeters of mercury; SSC=Surviving Sepsis Campaign Guidelines

* F/U until completed: follow up of the patients until they recovered from shock, were transferred or died within 30 days

had a MAP of at least 65 mmHg and lactate clearance at least 10% in six hours, was met. Then patient who had a MAP less than 65 mmHg along with fluid non-responsiveness were administered vasopressor(s) or inotropic agent(s) according to Surviving Sepsis Campaign Guidelines 2012[4], monitored intensively for six hours, and were tracked until shock resolution [i.e., MAP of 65 mmHg or greater and appropriate tissue perfusion without vasopressor(s)] and discharge, transfer or death within 30 days. Patients would receive standard treatment from TUH, whether or not they recovered from sepsis, until discharge, transfer, or death.

2) Dynamic IVC variation-guided group: This group had two subgroups of patients with mechanical ventilation versus spontaneous breathing. The diameter of the IVC was measured subcostally using US at 3 to 4 cm from the junction between the IVC and right atrium[13] in a supine patient. The measurement of IVC diameter variation with respiration by US was initially done at the beginning of the study in both subgroups. Mechanically ventilated patients were measured for IVC distensibility index = [(maximum diameter (Dmax) – minimum diameter (Dmin))/Dmin] × 100%, with less than 18% and 18% or greater being treated as fluid non-responsiveness, and fluid responsiveness, respectively[14]. In mechanically ventilated patients, the IVC diameter had a minimum and a maximum dimension during full expiration and full inspiration, respectively. Measurements of IVC collapsibility index [(Dmax–Dmin)/Dmax] × 100% for spontaneously breathing patients were performed with a value of less than 50% and 50% or greater being treated as fluid non-responsiveness and fluid responsiveness, respectively[15]. On the contrary, the IVC diameter had a minimum and a maximum dimension during full inspiration and full expiration, respectively, for spontaneously breathing patients. US was adopted to measure the variation of IVC diameter with respiration because of the practicability and attainability of US in the authors' center. The measurement of respiratory variation of IVC diameter using US was performed by NO under the supervision of an intensivist. LOGIQ C5 Premium Ultrasound Machine (GE Healthcare, Chicago, Illinois, USA) was used for measurement of IVC diameter. Certain mechanically ventilated patients might have received sedative agents (midazolam or fentanyl) and neuromuscular blocking agents (atracurium or cisatracurium) so as to maintain the lowest respiratory effort, and thus the validity of the IVC distensibility index was promoted. Crystalloids (also mostly 0.9% NaCl solution) of 0.5 L in 15 minutes were continuously administered to patients with fluid responsiveness, and IVC distensibility index or IVC collapsibility index measurements were done cyclically and repeatedly until fluid non-responsiveness (i.e., IVC distensibility index less than 18% or IVC collapsibility index less than 50%) was met in the same pattern as the static CVP-guided group. The patients achieving fluid non-responsiveness were administered vasopressor(s), inotropic agent(s), and other treatment, monitored intensively, and were tracked until shock resolution and discharge, transfer, or death within 30 days, identical to those of the static CVP-guided group. The study protocol diagram is shown in Figure 1.

Data collection

This study collected: 1) Demographic data: age, sex, height, weight, and concurrent underlying disease(s), 2) Clinical characteristics and treatment

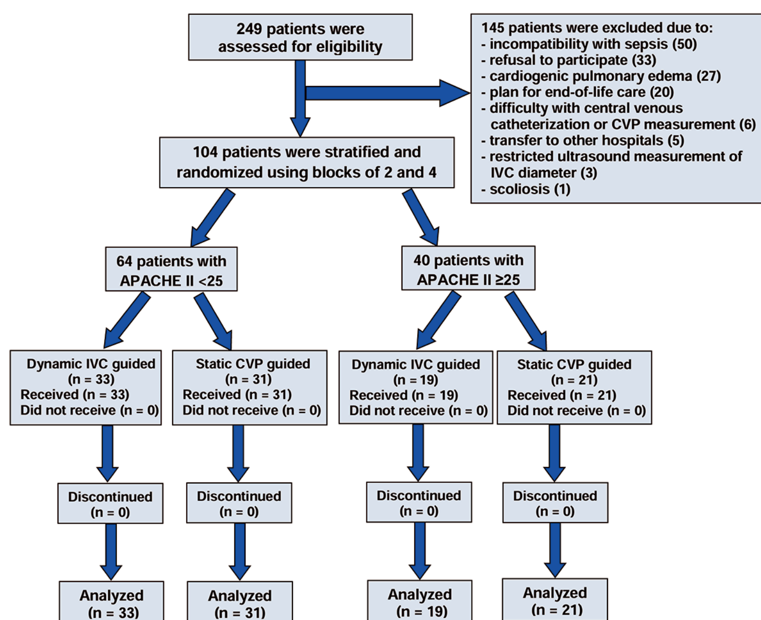

Figure 2. CONSORT flow diagram of study procedure.

APACHE II=acute physiology and chronic health evaluation II; CONSORT=Consolidated Standards of Reporting Trials; CVP=central venous pressure; IVC=inferior vena cava

of sepsis: body temperature, MAP, pulse, respiratory rate, SOFA score, acute physiologic and chronic health evaluation (APACHE) II score and lactate level at the initiation of study, source of infection, the time of diagnosis of sepsis and initiation of antibiotics, amount of IV fluid received before randomization and during 72 hours of sepsis, and ICU admission, 3) Outcomes of treatment of sepsis: SOFA score at 72 hours and seven days after treatment of sepsis, vasopressor requirement and VFDs within 30 days. Patients who died within 30 days were assigned zero. For survivors, the outcome was calculated as 30 minus the total duration (in days) of vasopressor support. This approach accounts for the competing risk of mortality and prevents the paradoxical interpretation of early death as a shorter duration of vasopressor, survival status at 30 days, hospital length of stay, and pulmonary edema within seven days.

Statistical analysis

The sample size was estimated based on a pilot study in 20 patients with sepsis who were treated at TUH between August and October 2018. The results showed that the patients in the static CVP-guided group had a mean SOFA score change of –0.55 (with standard deviation (SD) of 0.6) from recognition of sepsis to 72 hours later, compared with –1 (with SD of 0.9) in the dynamic IVC variation-guided group. The sample size was 47 per group after testing the hypothesis with the independent two-sample t-test to detect the minimum mean SOFA score change difference of 2.7 with a power of 0.8. Thus, the total sample size was 94. However, to compensate for an attrition rate of 10%, the total sample size was increased to 104.

The clinical characteristics and physiological changes when the patients were diagnosed with sepsis were analyzed for each intervention group using descriptive statistics, i.e., frequency and percentage for categorical variables, mean with SD, and median with interquartile range (IQR) for normally and non-normally distributed continuous variables, respectively. Chi-square test or Fisher's exact test, as appropriate, was used to compare the categorical outcomes between the dynamic IVC variation-guided and the static CVP-guided groups for the total population, and subgroups stratified by an APACHE II score (i.e., less than 25 versus 25 and above). The Mann-Whitney U test was used to compare the continuous outcomes with non-normally distributed data between the two groups for all patients, and subgroups stratified by an APACHE II score as well. Univariable median regression analysis was used to analyze the relationship between the fluid resuscitation guidance method and each continuous outcome. While univariable risk ratio

Table 1. Clinical characteristics of patients

Characteristics	Dynamic IVC variation-guided group (n=52)	Static CVP-guided group (n=52)	p-value
Age (years); median (IQR)	74 (63.5 to 81)	70 (55 to 78)	0.113[a]
Male; n (%)	28 (53.9)	28 (53.9)	1.000[b]
Body mass index (kg/m^2); median (IQR)	21.1 (19.5 to 23.6)	22.2 (20 to 23.6)	0.239[a]
Underlying disease; n (%)			
Hypertension	27 (51.9)	34 (65.4)	0.163[b]
Diabetes mellitus	17 (32.7)	24 (46.2)	0.160[b]
Stroke	10 (19.2)	11 (21.2)	0.807[b]
Chronic kidney disease	5 (9.6)	10 (19.2)	0.163[b]
Coronary artery disease	6 (11.5)	7 (13.5)	0.767[b]
Chronic obstructive pulmonary disease	4 (7.7)	1 (1.9)	0.363[c]
Suspected organ infection; n (%)			
Respiratory system	16 (30.8)	22 (42.3)	0.222[b]
Abdomen	17 (32.7)	9 (17.3)	0.070[b]
Urinary tract	10 (19.2)	8 (15.4)	0.604[b]
Skin and soft tissue	5 (9.6)	2 (3.9)	0.437[c]
Systemic infection	1 (1.9)	3 (5.8)	0.618[c]
Bone and joint	0 (0.0)	1 (1.9)	1.000[c]
Neurological system	0 (0.0)	1 (1.9)	1.000[c]
Others	0 (0.0)	1 (1.9)	1.000[c]
Unknown source	3 (5.8)	5 (9.6)	0.715[c]
Physiological variables			
Body temperature (°C); median (IQR)	37.4 (36.7 to 38.8)	37.8 (37 to 38.7)	0.511[a]
Initial MAP (mmHg); median (IQR)	60.5 (51 to 70)	60 (53 to 73.5)	0.543[a]
Pulse (beats per minute); mean (±SD)	109.9 (±25.0)	111.2 (±26.7)	0.800[d]
Respiratory rate (breaths per minute); median (IQR)	24 (22 to 30)	24 (22 to 28)	0.940[a]
Platelet count (cells/mm^3); median (IQR)	178,500 (106,500 to 274,000)	156,000 (107,500 to 219,500)	0.535[a]
Initial lactate (mmol/L); median (IQR)	2.9 (1.8 to 5.2)	4 (2.1 to 7.1)	0.116[a]
Initial SOFA score; median (IQR)	6 (4 to 9)	7 (6 to 11)	0.081[a]
APACHE II score; mean (±SD)	22.4 (±7.4)	23.4 (±6.8)	0.510[d]
Time from diagnosis of sepsis to antibiotic initiation (minutes); median (IQR)	70 (27.5 to 128.5)	75 (32.5 to 120)	0.961[a]
Amount of IV fluid before randomization* (mL); median (IQR)	2,200 (1,715 to 2,829)	2,000 (1,450 to 2,745)	0.515[a]
Amount of IV fluid in 72 hours (mL); median (IQR)	8,270 (6,000 to 9,786.5)	8,745 (5,945 to 10,565)	0.682[a]
ICU admission; n (%)	15 (28.9)	15 (28.9)	1.000[b]

°C=degree celsius; APACHE II=acute physiology and chronic health evaluation II; cells/mm^3=cells per cubic millimeter; CVP=central venous pressure; ICU=intensive care unit; IV=intravenous; IVC=inferior vena cava; kg/m^2=kilograms per square meter; MAP=mean arterial pressure; mL=milliliters; mmHg=millimeters of mercury; mmol/L=millimole(s) per liter; SOFA=sequential organ failure assessment

Continuous variables are presented as median (interquartile range, IQR) for non-normally distributed data and mean (±standard deviation, SD) for normally distributed data. Categorical variables are presented as number (percentage).

(a) Mann-Whitney U test, (b) Chi-square test, (c) Fisher's exact test, (d) Independent Student t-test

* This outcome was derived from 101 patients (49 in dynamic IVC variation-guided group and 52 in static CVP-guided group).

regression analysis or Poisson regression analysis was used to analyze the relationship between fluid resuscitation guidance method and each categorical outcome, as appropriate. The analysis was done on an intention-to-treat basis. The statistical significance was achieved when 2-sided p-value was less than 0.05 for comparison of data between the two intervention groups and regression analyses. Statistical analyses were performed using Stata SE, version 14.0 (StataCorp LP, College Station, TX, USA) with all findings derived from the present study dataset.

Results

Out of 249 patients screened for eligibility criteria,104 cases were included from the medical ICU, general medical wards, and the emergency department of TUH between September 2019 and March 2020. Fifty-two cases were assigned to the dynamic IVC variation-guided group and the other 52 cases to the static CVP-guided group. All patients were included in the final analysis. The procedure of recruitment, intervention, and analysis is shown in a Consolidated Standards of Reporting

Table 2. Primary and secondary outcomes for the total cohort, and subgroups stratified by an APACHE II score

Outcomes	Dynamic IVC variation-guided group (n=52)	Static CVP-guided group (n=52)	p-value
Primary outcome			
SOFA score change from diagnosis to 72 hours; median (IQR)	−2 (−3.5 to 5)	−1 (−3 to 3.5)	0.865[a]
Subgroup analyses*			
• APACHE II of less than 25	−2 (−3 to 0)	−2 (−4 to 2)	0.903[a]
• APACHE II of 25 and above	1 (−4 to 14)	0 (−2 to 5)	0.625[a]
Secondary outcomes			
SOFA score at 72 hours; median (IQR)	5 (2 to 13)	7 (3.5 to 13)	0.286[a]
Subgroup analyses*			
• APACHE II of less than 25	3 (1 to 7)	5 (2 to 13)	0.136[a]
• APACHE II of 25 and above	13 (4 to 24)	10 (6 to 14)	0.567[a]
SOFA score change from diagnosis to seven days; median (IQR)	−2 (−3.5 to 13)	−3 (−4 to 1.5)	0.180[a]
Subgroup analyses*			
• APACHE II of less than 25	−2 (−3 to 1)	−3 (−4 to 1)	0.379[a]
• APACHE II of 25 and above	9 (−5 to 15)	−3 (−4 to 8)	0.222[a]
Patients receiving vasopressor(s); n (%)	43 (82.7)	50 (96.2)	0.026[b]**
Subgroup analyses*			
• APACHE II of less than 25	24 (72.7)	29 (93.6)	0.027[b]**
• APACHE II of 25 and above	19 (100)	21 (100)	Cannot be calculated
VFDs within 30 days (days); median (IQR)	28.5 (0 to 29.4)	22.5 (0 to 28.6)	0.008[a]**
Subgroup analyses*			
• APACHE II of less than 25	28.9 (26.3 to 30)	26.9 (0 to 28.6)	0.009[a]**
• APACHE II of 25 and above	0 (0 to 29.2)	0 (0 to 28.4)	0.446[a]
Pulmonary edema within seven days; n (%)	6 (11.5)	7 (13.5)	0.767[b]
Subgroup analyses*			
• APACHE II of less than 25	2 (6.1)	4 (12.9)	0.419[c]
• APACHE II of 25 and above	4 (21.1)	3 (14.3)	0.689[c]

APACHE II=acute physiology and chronic health evaluation II; CVP=central venous pressure; IVC=inferior vena cava; SOFA=sequential organ failure assessment; VFDs=vasopressor-free days

Continuous variables are presented as median (interquartile range, IQR) because all of them are non-normally distributed data. Categorical variables are presented as number (percentage).

(a) Mann-Whitney U test, (b) Chi-square test, (c) Fisher's exact test

* Subgroup analyses included 64 patients with an APACHE II score of less than 25 (33 in dynamic IVC-guided, 31 in static CVP-guided) and 40 patients with a score of 25 and above (19 in dynamic IVC-guided, 21 in static CVP-guided).

** Statistical significance

Trials (CONSORT) flow diagram as Figure 2. The baseline characteristic data between the two groups were not different for age, sex, body mass index (BMI), underlying diseases, sources of infection, physiological variables, including initial SOFA score and APACHE II score, platelet count, initial serum lactate, time from diagnosis of sepsis to initiation of antibiotics, amount of IV fluid administration before randomization and during 72 hours of sepsis, and ICU admission. Details of baseline characteristics and treatment of sepsis are presented in Table 1.

The present study found no significant differences between the two groups in terms of the change in the medians (IQRs) of SOFA score from the diagnosis of septic shock to 72 hours later and seven days later, the median of SOFA score at 72 hours, or the incidence of pulmonary edema within seven days after the diagnosis of sepsis. The proportion of patients receiving vasopressor(s) in the dynamic IVC variation-guided group was significantly lower than that in the static CVP-guided group, while the median of the 30-day VFDs in the dynamic IVC variation-guided group was significantly higher than that in the static CVP-guided group. Subgroup analyses demonstrated that patients with an APACHE II score of less than 25 in the dynamic IVC variation-guided group were administered fewer vasopressor(s) in terms of a lower proportion of patients requiring them, and achieved higher 30-day VFDs, but these findings were not found in those with

Table 3. Association between fluid resuscitation guidance method and continuous outcomes

Outcomes	Median difference[a] (95% CI)	p-value
Primary outcome		
SOFA score change from diagnosis to 72 hours	−1 (−2.9 to 0.9)	0.295
Secondary outcomes		
SOFA score at 72 hours	−2 (−5.5 to 1.5)	0.264
SOFA score change from diagnosis to seven days	1 (−3 to 5)	0.621
VFDs within 30 days (days)	8 (−5.6 to 21.6)	0.245

CI=confidence interval; SOFA=sequential organ failure assessment; VFDs=vasopressor-free days

(a) Median differences of outcomes for dynamic inferior vena cava (IVC) variation-guided group compared with static central venous pressure (CVP)-guided group were derived from univariable median regression analyses.

Table 4. Association between fluid resuscitation guidance method and binary outcomes

Outcomes	Risk ratio[a] (95% CI)	p-value
Secondary outcomes		
Patients receiving vasopressor(s)	0.9 (0.6 to 1.3)	0.468[b]
Pulmonary edema within seven days	0.9 (0.3 to 2.4)	0.767[c]

CI=confidence interval

(a) Risk ratios of outcomes for dynamic inferior vena cava (IVC) variation-guided group compared with static central venous pressure (CVP)-guided group. (b) Univariable Poisson regression analysis, (c) Univariable risk ratio regression analysis

an APACHE II score of 25 and above. On the other hand, subgroup analyses of other outcomes showed comparable findings between the two groups across both APACHE II subgroups. All outcomes in detail are shown in Table 2.

Based on the univariable median regression analyses, all continuous outcomes, i.e., changes of median SOFA score from the onset of sepsis to 72 hours and to seven days, median SOFA scores at 72 hours after sepsis, and VFDs within 30 days, were not significantly different between the two groups. Median differences (95% confidence interval) of continuous outcomes are presented in Table 3. Furthermore, the risks of vasopressor requirement and pulmonary edema within seven days of sepsis were comparable between the two groups, based on the univariable Poisson regression and risk ratio regression analyses, as shown in Table 4.

Discussion

The present study showed that there were no differences between the patients with sepsis in the dynamic IVC variation-guided and static CVP-guided groups in the changes of median SOFA scores at 72 hours or at seven days, the median SOFA scores at 72 hours, or the risk of pulmonary edema within seven days. The proportion of patients receiving vasopressor(s) was lower in the dynamic IVC variation-guided group. However, the risks of vasopressor requirement were not significantly different between the two groups. The dynamic IVC variation-guided group showed higher 30-day VFDs than the static CVP-guided group, although the median 30-day VFDs were comparable. These discrepancies are likely due to the differing statistical approaches, including assumption models and outlier handling techniques, of the various tests employed (chi-square test, univariable Poisson regression analysis, Mann-Whitney U test, and median regression analysis).

The patients who received IV fluid resuscitation guided by the dynamic IVC variation measured by US had higher 30-day VFDs than those in the other group. This supports the notion that the dynamic indices can reliably predict a hemodynamic response to IV fluid administration[7-9] rather than static indices, in correspondence with the Surviving Sepsis Campaign Guidelines 2021[16]. The IV fluid amount that exceeds the capacity of the heart and kidneys to excrete water throughout the body results in pulmonary edema. The present study showed no significant difference of SOFA score change between patients receiving dynamic parameter-guided and static parameter-guided fluid resuscitation methods. Another study by Lanspa et al. also found no difference in medians of delta SOFA score at 48 hours, or the amount of IV fluid given during the study protocol between echocardiography-guided and EGDT groups for IV fluid administration in patients with septic shock in the USA[17]. Moreover, a study evaluating the effects of fluid therapy guidance methods in children (aged 1 month to 11 years) with septic shock showed that the echocardiography-guided therapy group had an earlier median withdrawal time of vasopressor or inotrope and a shorter shock reversal time than the Surviving Sepsis Campaign-guided therapy group[18]. This finding implied that the vasopressor duration of the dynamic parameter-guided therapy group was shorter than the static parameter-guided therapy group, corresponding to the present study finding (i.e., higher 30-day VFDs, which indicate shorter vasopressor duration), although the study was performed in children. These results reflect that dynamic parameter-guided fluid therapy is an accurate predictor for fluid responsiveness across a wide range of age groups.

A cohort study by Latham et al. evaluated the left ventricular stroke volume between patients with severe sepsis or septic shock who received fluid resuscitation guided by stroke volume and by usual care in 2014, based on the discretion of attending physicians. The study demonstrated that the stroke volume-guided fluid resuscitation decreased the vasopressor duration, but not the proportion of patients receiving vasopressor, compared with usual care-guided fluid resuscitation[19]. The effect on vasopressor duration in that study is consistent with the authors' result, confirming that dynamic parameters can better predict fluid responsiveness and thus reduce the vasopressor duration. However, the dynamic parameter in the Latham et al. study did not affect the proportion of patients receiving vasopressor, which is different from the authors' finding. This might be potentially explained by differences in factors, for example, patients' volume statuses (reflecting possible different time points in the course of disease when hospitalized), clinical practices and decisions for vasopressor administration, and importantly, study designs, between their study and the authors'.

Another study by Richard et al. demonstrated that the probability of receiving a vasopressor within 28 days was comparable between septic shock patients whose fluid administration was guided by pulse pressure variation or change in stroke volume versus those whose fluid administration was guided by CVP[20]. This finding was different from the present study finding, which may be partially accounted for by different characteristics of patients, individual medical practices for individual levels of patient care and monitoring between their practices and the authors' practices. That study also showed that median durations of pulmonary edema were not different between the two groups[20], which was considered to be in the same direction as the authors' outcome, although they were not the same outcomes.

A recent systematic review and meta-analysis revealed that US measurement of the IVC diameter variation had a good accuracy for predicting fluid responsiveness in critically ill patients with a pooled sensitivity and specificity of 0.75 and 0.83, respectively[21]. This promoted the validity of using dynamic parameters for the prediction of fluid responsiveness, although the cut-off thresholds of IVC diameter variation were different among individual studies.

There are limitations in this study: 1) It was not possible to blind the investigators because they directed the procedure of IV fluid therapy guidance with the dynamic IVC variation or static CVP measurement. However, the primary care providers were the attending physicians, who cared for the patient independently and were not related to the study. Therefore, there was no bias for treatment in either group. 2) The US measurement of dynamic IVC diameter variation was an operator-dependent procedure. However, the investigator (NO) was trained and supervised for the procedure by an expert and has examined a large number of patients, thus, the US findings were reasonably reliable. 3) The initiation time of vasopressor for each patient was not documented, thus, the time to vasopressor initiation cannot be compared between the two groups to evaluate this specific aspect of fluid resuscitation guidance methods. Nevertheless, the significant difference in 30-day VFDs provides a robust surrogate for the overall efficiency of the fluid resuscitation strategies. Finally, 4) there were missing data for some patients before participation in the present study. However, they were minimized to a few patients and likely did not affect the outcomes. The strengths of the present study were: 1) this was a randomized controlled trial, which could balance baseline characteristics and began in the early phase of sepsis, thus the results are convincingly reliable to be caused by the methods of IV fluid resuscitation guidance, 2) the methods of IV fluid resuscitation guidance are not complicated or too difficult to practice and the equipment is not that expensive or luxurious, therefore, they can be simply and generally adopted in medical practice, and 3) the study collected data from general medical wards and the emergency department in TUH, thus, the data were derived from various types of medical patients, which may enhance the generalizability.

Conclusion

Dynamic IVC variation-guided fluid resuscitation did not affect SOFA score change from diagnosis of sepsis to 72 hours and seven days later, SOFA score at 72 hours, or incidence of pulmonary edema within seven days, but this may reduce the proportion of patients requiring vasopressor(s) and increased VFDs within 30 days in patients with sepsis, compared with static CVP-guided fluid resuscitation.

What is already known about this topic?

IV fluid resuscitation is an essential component of treatment to maintain stable hemodynamics in patients with sepsis. Although dynamic parameters can better

predict fluid responsiveness than static parameters, standard methods for IV fluid resuscitation guidance have not been recommended by the current Surviving Sepsis Campaign Guidelines.

What does this study add?

The present study demonstrated that IV fluid resuscitation guided by a dynamic parameter in patients with sepsis did not affect the change of organ functions in 72 hours and seven days, organ functions at 72 hours, and pulmonary edema within seven days, but may reduce the proportion of patients requiring vasopressor(s) and increase 30-day VFDs, compared with that by a static parameter.

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Authors' contributions

Conceptualization: TS and NO; Data curation: TS and NO; Formal analysis: TS and NO; Investigation: TS and NO; Methodology: TS and NO; Project administration: TS and NO; Resources: TS and NO; Software: TS and NO; Supervision: TS; Validation: TS; Visualization: TS and NO; Writing-original draft preparation: TS; Writing-review & editing: TS and NO.

Data availability statement

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.19280768.

Ethics approval and consent to participate

The present study was performed in consonance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethics approval for research conduct, including documentation of consent from individual patients or their proxies, and an information sheet was provided by the Human Research Ethics Committee of Thammasat University (Medicine) (approval number: 140/2562) on 9th August 2019. A documented informed consent with consent for publication was obtained from each patient or their legally authorized proxy. No identifiable data of individual persons are shown.

Clinical trial registration

The present study was retrospectively registered at UMIN Clinical Trials Registry (Registration number: UMIN000053677, on February 21, 2024, available at https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000061249). The delay in registration was due to administrative oversight during the transition from data collection to data curation, analysis, and manuscript preparation. While the study protocol and primary outcome remained unchanged throughout the study period, one secondary outcome was refined from "vasopressor duration" to "VFDs within 30 days" to ensure greater accuracy and comprehensiveness.

Use of artificial intelligence

During the preparation of this manuscript, the authors used Google Gemini of the 3 series to refine the language and readability of the text. The authors reviewed and edited the content as needed and take full responsibility for the final version of the publication.

Conflicts of interest

The authors declare no conflict of interest.

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