Original Article

# Hepatic Perfusion Alterations in Septic Shock Patients: Impact of Early Goal-directed Therapy

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## Abstract

**Background:** Early goal-directed therapy (EGDT) has become an important therapeutic management in early salvage stage of septic shock. However, splenic organs possibly remained hypoperfused and hypoxic despite fluid resuscitation. This study aimed to evaluate the effect of EGDT on hepatic perfusion in septic shock patients.

**Methods:** A prospective observational study was carried out in early septic shock patients who were admitted to Intensive Care Unit within 24 h after onset and who met all four elements of the EGDT criteria after treatment with the standard EGDT procedure within 6 h between December 1, 2012 and November 30, 2013. The hemodynamic data were recorded, and oxygen metabolism and hepatic functions were monitored. An indocyanine green clearance test was applied to detect the hepatic perfusion. The patients' characteristics were compared before treatment (T0), immediately after EGDT (T1), and 24 h after EGDT (T2). This study is registered at ClinicalTrials.org, NCT02060773.

**Results:** Twenty-one patients were included in the study; however, the hepatic perfusion data were not included in the analysis for two patients; therefore, 19 patients were eligible for the study. Hemodynamics data, as monitored by pulse-indicator continuous cardiac output, were obtained from 16 patients. There were no significant differences in indocyanine green plasma disappearance rate (ICG-PDR) and 15-min retention rate (R15) at T0 (11.9 ± 5.0%/min and 20.0 ± 13.2%), T1 (11.4 ± 5.1%/min and 23.6 ± 14.9%), and T2 (11.0 ± 4.5%/min and 23.7 ± 15.3%) (all $P > 0.05$). Both of the alterations of ICG-PDR and R15 showed no differences at T0, T1, and T2 in the patients of different subgroups that achieved different resuscitation goal numbers when elected ($P > 0.05$).

**Conclusion:** There were no hepatic perfusion improvements after EGDT in the early phase of patients with septic shock.

**Trial Registration:** Clinicaltrials.gov NCT02060773 (https://clinicaltrials.gov/ct2/show/NCT02060773).

**Key words:** Early Goal-directed Therapy; Fluid Resuscitation; Hepatic Perfusion; Indocyanine Green; Septic Shock

## Introduction

Septic shock remains an important issue in critical illness because of its high mortality rate, which has been reported to be as high as 50%.[1,2] At present, fluid resuscitation, antimicrobial therapy, source control, vasopressors, inotropic therapy, and mechanical ventilation have become important aspects of treatment for early septic shock. Rivers *et al*.[3] demonstrated that the institution of early goal-directed therapy (EGDT) could significantly reduce mortality in patients with severe sepsis or septic shock. However, despite EGDT, high mortality (42.3%) and hypoperfusion rates remain in these patients. Thus, EGDT, as an early resuscitation end-point, may not be sufficient for patients with septic shock.

In recent years, whether tissue perfusion in patients with septic shock improves after EGDT has become a hot issue. Brügger *et al*.[4] showed that in a porcine model, celiac trunk, hepatic artery, superior mesenteric artery, and carotid artery blood flows were higher in control group than those in endotoxin group. Although regional flow of the superior mesenteric artery and celiac trunk axes increased after fluid challenges, they still did not return to baseline. Thus, splenic organs possibly remained hypoperfused and hypoxic despite fluid resuscitation.[5]

Sepsis-associated liver dysfunction, with an astonishing incidence of 34.7%,[6] is an aspect of multiple organ

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dysfunction syndrome and is usually associated with a poor prognosis.[7] Although the liver plays a pivotal role in regulating a wide range of key metabolic, homeostatic, and host-defense activities, liver dysfunction is commonly viewed only as a consequence of shock and initial tissue hypoperfusion. In fact, the injured liver may be considered one of the main actors in multiple organ failure genesis and amplification.[8] However, the lack of reliable diagnostic tools does not allow for early liver dysfunction detection.[9] Some authors have argued for the use of a dynamic test, such as the evaluation of the indocyanine green plasma disappearance rate (ICG-PDR), to assess liver function. ICG is an organic anion that is exclusively eliminated by the liver and can estimate hepatic cell function and blood flow. This technique may detect septic liver dysfunction earlier than bilirubin and appears to correlate with patient outcomes.[10,11] However, this technique has not been used to evaluate hepatic function in patients with septic shock during EGDT. Hence, it is important to monitor alterations of hepatic perfusion and function in septic patients through ICG-PDR for guiding early liquid therapy.

In light of these observations, we carried out a prospective trial assessing patients with septic shock who had undergone ICG-PDR evaluations to determine the effects of EGDT on hepatic perfusion. We hypothesized that hepatic perfusion would be impaired and might persist despite achievement of global resuscitation goals.

## Methods

This prospective, observational trial was approved by the Ethical Committee of the Southeast University Hospital (No. 2012ZKllKY25.0) and was registered on clinicaltrials.gov (No. NCT02060773).

### Study population

Eligible adult patients who presented to the Intensive Care Unit (ICU) with septic shock as defined by the International Sepsis Definitions Conference criteria[12] from December 1, 2012 to November 30, 2013, were assessed for possible enrollment according to the inclusion criteria: (1) fulfillment of two of the four systemic inflammatory response syndrome criteria; (2) systolic blood pressure (SBP) no higher than 90 mmHg, mean arterial pressure (MAP) no higher than 70 mmHg, 40 mmHg SBP reduction from baseline (after a crystalloid-fluid challenge of 20–30 ml/kg of body weight over a 30-min period), blood lactate concentration of 4 mmol/L or more, or oliguria; and (3) EGDT criteria were not met (central venous pressure [CVP] no higher than 8 mmHg, MAP no higher than 65 mmHg, urine output no higher than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$, or central venous oxygen saturation no higher than 70%).

The exclusion criteria included the following conditions: EGDT not met within 6 h after the EGDT standard procedure treatment; below 18 or above 90 years of age; pregnancy; if over 24 h of time elapsed after septic shock onset; chronic liver disease; terminal stage of disease; brain death; other types of shock; brain injury; or iodine or ICG allergies.

### General management

All patients were managed according to the set guidelines. Each patient was equipped with an arterial catheter and a central venous catheter (CareFlow™, Becton Dickinson Critical Care Systems, Singapore). In addition, the patients assigned to the trial were also monitored with a pulse-induced continuous cardiac output (PiCCO) catheter (4F, PV2014L16N, Pulsion Medical Systems, Germany). Treatment for septic shock was standardized,[4] including vasopressors (norepinephrine with epinephrine as a rescue therapy) to MAP, in addition to repeated fluid challenges with crystalloids, natural albumin, and artificial colloids (hydroxyethyl starch solutions) to achieve a CVP of 8–12 mmHg, to maintain a MAP of at least 65 mmHg and to ensure that the urine output was at least 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$. Hydrocortisone (50 mg every 6 h) was added in severe cases (a norepinephrine dose >0.5–0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$). During the initial resuscitation phase, we attempted to maintain central venous oxygen saturation ($ScvO_2$) levels at 70% and if the $ScvO_2$ was <70%, red blood cells were transfused to achieve a hematocrit level of at least 30%. If the $ScvO_2$ was <70% after CVP, MAP and hematocrit were optimized, dobutamine was administered. If needed, mechanical ventilation was provided under light sedation (propofol up to 80 mg/h) and analgesia (morphine up to 2 mg/h or remifentanil up to 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In mechanically ventilated patients, tidal volumes were limited to 6–8 ml/kg.

### Measurements

Temperature, heart rate (HR), MAP, and CVP were measured in all patients. Body weight was recorded as the usual body weight of the patients or obtained from their families. Cardiac output, systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), extravascular lung water index (EVLWI), and $ScvO_2$ were also obtained in the patients monitored with a PiCCO catheter. The arterial and central venous blood samples were withdrawn simultaneously, and blood gases, hemoglobin saturation, hemoglobin, and lactate concentrations were measured. The oxygen delivery index ($DO_2I$) was calculated using standard formulas. Alanine transaminase, aspartate transaminase, γ-glutamyltransferase (γ-GT), total bilirubin (TBIL), albumin, and the urine output per hour were also recorded. All of the above variables were assessed before treatment (T0), immediately after EGDT (T1), and 24 h after EGDT (T2). The Acute Physiology and Chronic Health Evaluation II (APACHE II)[13] and the Sequential Organ Failure Assessment (SOFA) scores[14] were computed at study inclusion. The patients were followed for 28 days or until death.

### Hepatic perfusion measurements and analyses

The ICG elimination tests were conducted as described by Sakka *et al*.[15] using the noninvasive liver function monitoring system (LiMON, Pulsion Medical Systems,

Germany). Each patient received an ICG finger clip that was connected to a liver function monitor. A 0.5 mg/kg dose of ICG (Dandong Medical and Pharmaceutical Industry, China) was given through a central vein as a bolus and immediately flushed with 10 ml of normal saline. The ICG-PDR and 15-min retention rate (R15) were calculated before and after the infusions.

### Exploratory subgroup analyses

We evaluated whether there were hepatic perfusion alterations among T0, T1, and T2 time points in the different subgroups, which was in accordance with different numbers of the achieved resuscitation goals (MAP ≥65 mmHg, CVP ≥8 mmHg, $ScvO_2$ ≥70%, and urine output ≥0.5 ml·kg$^{-1}$·h$^{-1}$) as proposed by the surviving sepsis campaign[12] when patients were enrolled.

### Statistical analysis

Data were analyzed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 for Windows (GraphPad Prism Software Inc., La Jolla, CA, USA). We computed descriptive statistics for all of the study variables. We used the Kolmogorov-Smirnov test and stratified distribution plots to verify the distribution normality of the continuous variables. Data that were normally distributed are presented as mean ± standard deviation (SD) whereas those that were not distributed normally are presented as median ($P_{25}$, $P_{75}$). Categorical variables are presented as numbers (%). We assessed differences in the patient hemodynamics, oxygen metabolism data, and hepatic function and perfusion among T0, T1, and T2 time points by one-way analysis of variance, followed by Bonferroni corrections for multiple comparisons. We used the Mann-Whitney *U*-test to evaluate the vasopressor dose differences among T0, T1, and T2 time points. We evaluated the relationships between the hepatic perfusion variables and the tissue perfusion variables using Pearson's correlation coefficient. To evaluate the relationships with patient outcomes, we constructed receiver operating characteristic curves and computed their area and Youden's index to identify the best cutoff value. For all analyses, $P < 0.05$ was considered statistically significant.

## Results

### Baseline characteristics

During the study, a total of 176 patients with septic shock were admitted into ICU, including 31 patients who already met the EGDT criteria and one patient who was missing. Among the enrolled patients, 123 cases were excluded for various reasons as shown in Figure 1. Twenty-one patients were included in the study; however, we could not access the ICG-PDR data for one patient, and one patient was discharged without being cured. Thus, these two patients were excluded. Finally, 19 patients were eligible for the study.

The main characteristics for the 19 patients are presented in Table 1. The achieved EGDT time was 303 ± 56 min. Liver perfusion was monitored in all 19 patients, but the patient's hemodynamics, which was synchronously monitored by PiCCO, was only recorded for 16 patients. There were seven male patients and 12 female patients in the study, and the mean APACHE II and SOFA scores were 19.9 ± 8.1 and 9.7 ± 3.2, respectively. There were no allergies or side effects among the enrolled patients following the ICG injections.

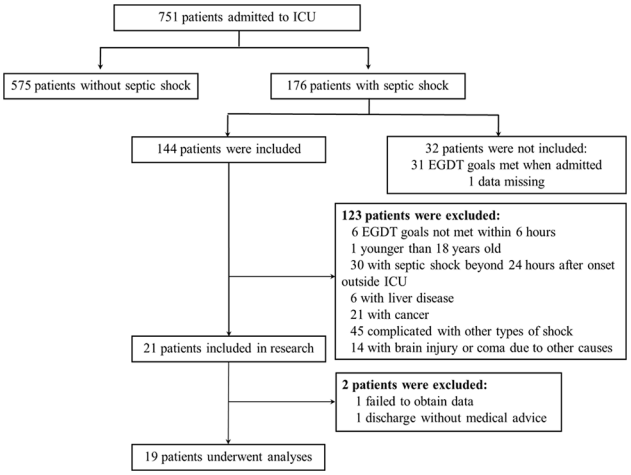


**Figure 1:** Overview of patient enrollment. ICU: Intensive Care Unit; EGDT: Early goal-directed therapy.

**Table 1: The baseline characteristics of all patients in this study (*n* = 19)**

| Characteristics | Values |
|---|---|
| Age (years), mean ± SD | 74.6 ± 12.3 |
| Gender (male/female), *n* | 7/12 |
| APACHE II score, mean ± SD | 19.9 ± 8.1 |
| SOFA score, mean ± SD | 9.7 ± 3.2 |
| Temperature (°C), mean ± SD | 38.2 ± 1.3 |
| HR (beats/min), mean ± SD | 102 ± 21 |
| MAP (mmHg), mean ± SD | 66 ± 10 |
| WBC counts (×10$^9$/L), mean ± SD | 14.9 ± 8.2 |
| Lactate (mmol/L), median ($P_{25}$, $P_{75}$) | 3.2 (1.7, 4.8) |
| Infection site*, *n* (%) | |
| Lung | 14 (73.7) |
| Intra-abdominal | 5 (26.3) |
| Biliary tract | 6 (31.6) |
| Vasoactive agents* | |
| Norepinephrine (μg·kg$^{-1}$·min$^{-1}$, *n* = 14), median ($P_{25}$, $P_{75}$) | 0.12 (0.07, 0.17) |
| Dopamine (μg·kg$^{-1}$·min$^{-1}$, *n* = 7), mean ± SD | 8.7 ± 5.3 |
| Previous history*, *n* (%) | |
| Hypertension | 12 (63.2) |
| Diabetes | 7 (36.8) |
| Coronary heart disease | 1 (5.3) |
| Chronic kidney disease | 1 (5.3) |
| Tumors | 2 (10.5) |
| Survivor/nonsurvivor, *n* | 14/5 |

*Patients merged with other conditions. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; HR: Heart rate; MAP: Mean arterial pressure; WBC: White blood cell; SD: Standard deviation.

## Global hemodynamics in patients with septic shock after early goal-directed therapy

The patients' hemodynamics were markedly improved after EGDT. The HR values at T1 and T2 were significantly decreased compared with T0 ($F$ = 7.518, $P$ < 0.05). In addition, MAP increased from 65 ± 9 mmHg at T0 to 81 ± 8 mmHg at T1 ($F$ = 43.120, $P$ < 0.0001) and to 91 ± 12 mmHg at T2 ($F$ = 43.120, $P$ < 0.0001). Moreover, CVP increased to 12.4 ± 3.5 mmHg at T1 compared with T0 (9.0 ± 4.4 mmHg; $F$ = 17.690, $P$ < 0.0001). The stroke volume also significantly increased to 70.8 ± 20.5 ml at T1 compared with T0 (53.7 ± 17.0 ml; $F$ = 11.560, $P$ = 0.0042). As shown in Table 2, there were no significant differences in SVR, SVRI, or EVLWI between T0, T1, and T2 ($P$ > 0.05).

Crystalloid was the first choice for fluid resuscitation in the patients with septic shock [Table 3]. For the patients whose MAP could not be maintained above 65 mmHg after adequate fluid resuscitation, norepinephrine was chosen as the preferred vasopressor, the dose of which increased significantly at T1 compared with T0 ($U$ = 59.50, $P$ = 0.0149) [Table 2].

## Systematic oxygen metabolism and tissue perfusion in patients with septic shock after early goal-directed therapy

Oxygen metabolism in patients with septic shock improved significantly at 24 h after EGDT. As shown in Table 4, the $ScvO_2$ and $DO_2I$ also significantly increased to 82.6 ± 5.4% ($F$ = 5.423, $P$ = 0.0146) and 543.8 ± 132.8 ml·min$^{-1}$·m$^{-2}$ ($F$ = 3.855, $P$ = 0.0099), respectively, at T2 compared with T0. The urine output also significantly increased at both T1 and T2 compared with T0 ($P$ = 0.0002 and $P$ = 0.0004, respectively), contrary to the lactate trend ($P$ = 0.0003 and $P$ < 0.001, respectively). In addition, there was a slight delay in the oxygen metabolism improvement in the septic patients.

## Hepatic perfusion in the septic shock patients after early goal-directed therapy

Both ICG-PDR and R15 values in patients with septic shock before EGDT were beyond the normal range. As shown in Table 5, the ICG-PDR declined at T1 and T2 compared with T0; however, these differences were not statistically significant (T0 vs. T1: $P$ = 0.7626; T0 vs. T2: $P$ = 0.6344). The G-PDR values between T1 and T2 were also not significantly different ($P$ = 0.8201). In addition, R15 values increased at T1 and T2 compared with T0; however, these differences were not statistically significant (T0 vs. T1: $P$ = 0.1168; T0 vs. T2: $P$ = 0.2288). R15 values between T1 and T2 were also not significantly different ($P$ = 0.9915). Furthermore, there were no significant differences in the hepatic perfusion alterations at T0, T1, and T2 in the different subgroups that achieved different resuscitation goal numbers [Figure 2].

## Hepatic function in patients with septic shock after early goal-directed therapy

There were no significant liver function changes in patients with septic shock during EGDT. The albumin levels increased, however, from 24.3 ± 4.9 g/L (T0) to

**Table 3: Fluids administered for patient with septic shock during resuscitation ($n$ = 19)**

| Fluid | T0–T1 | T1–T2 |
|---|---|---|
| Crystalloid (ml) | 1566.3 ± 892.4 | 1468.4 ± 647.7 |
| Colloid | | |
| Hydroxyethyl starch (130/0.4) (ml) | 350 (0, 500) | 0 (0, 0) |
| Dextran-40 (ml) | 0 (0, 500) | 0 (0, 0) |
| 20% albumin (g) | 0 (0, 0) | 20 (0, 40) |

Data are shown as mean ± SD or median ($P_{25}$, $P_{75}$). T0–T1: Pre-EGDT to immediately after EGDT; T1–T2: Immediately after EGDT to 24 h after EGDT; SD: Standard deviation; EGDT: Early goal-directed therapy.

**Table 2: The main hemodynamic variables and vasopressor use in all patients ($n$ = 19)**

| Variables | T0 | T1 | T2 | $P$ | | |
|---|---|---|---|---|---|---|
| | | | | T0 vs. T1 | T0 vs. T2 | T1 vs. T2 |
| HR (beats/min) | 102 ± 21 | 92 ± 22 | 92 ± 17 | 0.0001 | 0.0118 | 0.9913 |
| MAP (mmHg) | 65 ± 9 | 81 ± 8 | 91 ± 12 | <0.0001 | <0.0001 | 0.0011 |
| CVP (mmHg) | 9.0 ± 4.4 | 12.4 ± 3.5 | 11.0 ± 3.2 | <0.0001 | 0.0146 | 0.0333 |
| CO (L/min)* | 5.3 ± 1.8 | 6.3 ± 2.3 | 6.5 ± 2.1 | 0.0629 | 0.0292 | 0.8837 |
| Cardiac index (L·min$^{-1}$·m$^{-2}$)* | 3.2 ± 1.1 | 3.8 ± 1.3 | 4.0 ± 1.2 | 0.0615 | 0.0355 | 0.8278 |
| SV (ml)* | 53.7 ± 17.0 | 70.8 ± 20.5 | 72.3 ± 17.0 | 0.0042 | 0.0009 | 0.9355 |
| SVI (ml/m$^2$)* | 32.7 ± 9.3 | 43.0 ± 10.4 | 44.1 ± 8.2 | 0.0032 | 0.0008 | 0.9177 |
| SVR (dyn·s$^{-1}$·cm$^{-5}$)* | 964 ± 358 | 975 ± 315 | 1068 ± 293 | 0.9935 | 0.5176 | 0.1483 |
| SVRI (dyn·s$^{-1}$·m$^{-2}$·cm$^{-5}$)* | 1555 ± 529 | 1585 ± 519 | 1741 ± 489 | 0.9810 | 0.4290 | 0.1544 |
| EVLWI (ml/kg)* | 9.0 ± 6.3 | 9.0 ± 4.8 | 8.8 ± 4.3 | 0.9996 | 0.9915 | 0.9892 |
| Norepinephrine | | | | | | |
| Patient numbers | 14 (73.7) | 17 (89.5) | 18 (94.7) | | | |
| Dose (μg·kg$^{-1}$·min$^{-1}$) | 0.12 (0.07, 0.17) | 0.17 (0.12, 0.32) | 0.18 (0.08, 0.32) | 0.0149 | 0.1219 | 0.8760 |

*These variables were only recorded for 16 patients. Data are shown as mean ± SD, median ($P_{25}$, $P_{75}$), or $n$ (%). T0: Pre-EGDT; T1: Immediately after EGDT; T2: 24 h after EGDT; HR: Heart rate; MAP: Mean atrial pressure; CVP: Central venous pressure; CO: Cardiac output; SV: Stroke volume; SVI: Stoke volume index; SVR: Systemic vascular resistance; SVRI: Systemic vascular resistance index; EVLWI: Extravascular lung water index; EGDT: Early goal-directed therapy; SD: Standard deviation.

**Table 4: The systematic oxygen metabolism and tissue perfusion in all patients of this study ($n$ = 19)**

| Variables | T0 | T1 | T2 | *P* | | |
|---|---|---|---|---|---|---|
| | | | | T0 vs. T1 | T0 vs. T2 | T1 vs. T2 |
| pHa | 7.386 ± 0.082 | 7.370 ± 0.078 | 7.371 ± 0.065 | 0.3986 | 0.7246 | 0.9976 |
| $ScvO_2$ (%) | 77.9 ± 7.6 | 80.9 ± 4.5 | 82.6 ± 5.4 | 0.3014 | 0.0146 | 0.1543 |
| $DO_2I$ (ml·min$^{-1}$·m$^{-2}$)* | 445.6 ± 129.3 | 510.8 ± 183.8 | 543.8 ± 132.8 | 0.2472 | 0.0099 | 0.6849 |
| Lac (mmol/L) | 3.2 (1.7, 4.8) | 1.4 (1.1, 2.0) | 1.0 (0.8, 1.6) | 0.0003 | <0.0001 | 0.9913 |
| Urine output (ml·kg$^{-1}$·h$^{-1}$) | 0.4 (0.1, 1.0) | 1.4 (0.9, 1.8) | 1.3 (0.9, 2.1) | 0.0002 | 0.0004 | >0.9999 |

*This variable was only recorded for 16 patients. Data are shown as mean ± SD or median ( $P_{25}$, $P_{75}$). T0: Pre-EGDT; T1: Immediately after EGDT; T2: 24 h after EGDT; pHa: pH of artery; $ScvO_2$: Central venous oxygen saturation; $DO_2I$: Oxygen delivery index; Lac: Lactate; EGDT: Early goal-directed therapy; SD: Standard deviation.

**Table 5: The main variables of hepatic perfusion and hepatic function in patients with septic shock after EGDT**

| Variables | T0 | T1 | T2 | *P* | | |
|---|---|---|---|---|---|---|
| | | | | T0 vs. T1 | T0 vs. T2 | T1 vs. T2 |
| ICG-PDR (%/min) | 11.9 ± 5.0 | 11.4 ± 5.1 | 11.0 ± 4.5 | 0.7626 | 0.6344 | 0.8201 |
| R15 (%) | 20.0 ± 13.2 | 23.6 ± 14.9 | 23.7 ± 15.3 | 0.1168 | 0.2288 | 0.9915 |
| ALT (U/L) | 30.0 (15.5, 97.0) | 26.0 (17.5, 55.5) | 24.0 (12.8, 52.2) | >0.9999 | 0.2004 | 0.4699 |
| AST (U/L) | 42.0 (30.8, 101.3) | 33.5 (25.8, 70.2) | 41.5 (23.8, 80.2) | >0.9999 | 0.7302 | >0.9999 |
| γ-GT (U/L) | 42.5 (28.8, 134.3) | 35.0 (24.0, 121.5) | 32.5 (16.5, 63.5) | 0.0035 | <0.0001 | 0.6341 |
| TBIL (μmol/L) | 13.8 (9.1, 32.8) | 13.0 (10.2, 61.9) | 13.0 (10.1, 43.4) | >0.9999 | 0.7302 | >0.9999 |
| Albumin (g/L) | 24.3 ± 4.9 | 22.0 ± 5.6 | 26.7 ± 3.2 | 0.0928 | 0.1096 | 0.0009 |

Data are shown as mean ± SD or median ( $P_{25}$, $P_{75}$). T0: Pre-EGDT; T1: Immediately after EGDT; T2: 24 h after EGDT; ICG-PDR: Indocyanine green plasma disappearance rate; R15: 15-min retention rate; ALT: Alanine transaminase; AST: Aspartate transaminase; γ-GT: γ-glutamyltransferase; TBIL: Total bilirubin; EGDT: Early goal-directed therapy; SD: Standard deviation.

26.7 ± 3.2 g/L (T2; $F$ = 9.731, $P$ = 0.0001), which may be more associated with a complement of the fluid resuscitation than self-synthesis. TBIL remained unchanged during EGDT ($P$ > 0.05), and other liver function variables had a downward trend; however, these variables were not significantly different from one another ($P$ > 0.05) except for γ-GT (T0 vs. T1: $F$ = 22.200, $P$ = 0.0035; $P$ < 0.0001 when T0 vs. T2) [Table 5].

### Hepatic and systematic tissue perfusion correlations

There were no significant correlations between ICG-PDR, R15, urine output, and lactate levels (all $P$ > 0.05) [Figure 3].

### Mortality relationships

The value of ICG-PDR in predicting 28-day mortality rate of patients with septic shock was limited whereby the area under the curve (AUC) was 0.69, which was higher than AUCs of $\Delta PDR_{T1-T0}$, $\Delta PDR_{T2-T0}$, and $\Delta PDR_{T2-T1}$ (0.49, 0.57, and 0.66, respectively). The sensitivity and specificity of ICG-PDR ≤9.4%/min in predicting the 28-day mortality were 100% and 50%, respectively [Figure 4a].

In addition, the AUCs of R15 and $\Delta R15_{T2-T1}$ were 0.69 in predicting 28-day mortality rate of patients with septic shock, which was higher than the AUCs of $\Delta R15_{T1-T0}$ and $\Delta R15_{T2-T0}$ (0.57 and 0.61, respectively). The sensitivity and specificity of R15 >18.6% in forecasting the 28-day mortality rate were 100% and 50%, respectively. In addition, the sensitivity and specificity of $\Delta R15_{T2-T1}$>−3.5% in predicting the mortality rate were 100% and 42.9%, respectively [Figure 4b].

## Discussion

To the best of our knowledge, there was few study that evaluated hepatic perfusion alterations in patients with septic shock during EGDT with the ICG clearance test. The results showed that there were no early phase hepatic perfusion improvements after EGDT in the observed patients with septic shock as ICG-PDR and R15 remained similar during EGDT.

Interestingly, an important observation of this study was that the hepatic perfusion decreased significantly in septic patients, which was independent of the global hemodynamic and tissue perfusion improvements. As shown in the present study, even in the subgroup analysis, which achieved different resuscitation goal numbers when patients were enrolled, there were significant hepatic perfusion alterations during EGDT. Furthermore, the lack of fluctuation in the other hepatic function variables ruled out the influence of hepatocyte damage. During sepsis and severe sepsis, the intrahepatic blood flow redistribution channels can move the blood from contracted vessels to dilated vessels, which creates a net decrease in the perfused sinusoidal area.[16] However, fluid resuscitation results in only marginally increased microvascular liver perfusion levels.[17] In addition, De Backer *et al*.[18] demonstrated that the proportion of perfused small vessels alterations was similar in patients who achieved their MAP, CVP, and $ScvO_2$ resuscitation goals and in patients who did not. These findings were in line with those observed in our study. Thus, it was important to monitor hepatic perfusion during resuscitation in patients with septic shock.

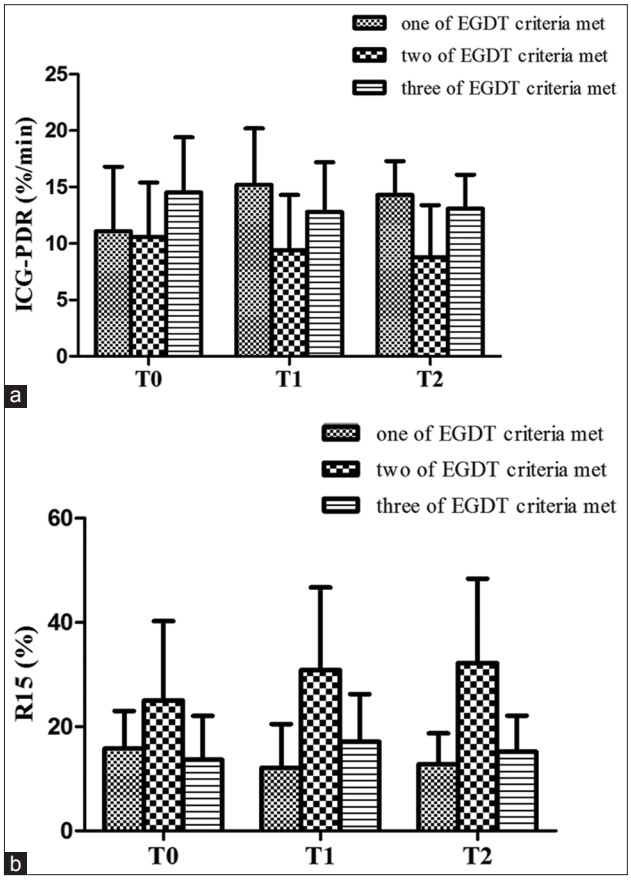


**Figure 2:** The alterations of ICG-PDR (a) and R15 (b) between T0, T1, and T2 in different subgroups which achieving different numbers of resuscitation goals. One of EGDT criteria met: $n = 3$; two of EGDT criteria met: $n = 10$; three of EGDT criteria met: $n = 6$. EGDT: Early goal-directed therapy; T0: Pre-EGDT; T1: Immediately after EGDT; T2: 24 h after EGDT; ICG-PDR: Indocyanine green plasma disappearance rate; R15: 15-min retention rate.

Moreover, an irrelevant relationship was found between ICG-PDR, R15, urine output, and lactate levels. Sepsis causes severe changes in the microcirculatory blood flow in all of the splanchnic organs that cannot be predicted from changes in systemic or regional flows. This was elegantly demonstrated in a porcine fecal peritonitis model that produced septic shock. During shock, systemic, superior mesenteric artery, and microcirculatory liver flow all decreased by approximately 50%. Fluid resuscitation resulted in a threefold increase in systemic and mesenteric flow, but the microvascular liver perfusion only increased by 16%.[17]

One interpretation of these results was that the volume of the fluid administered during the resuscitations was not adequate. In our study, the fluid volume was in line with that of a previous study.[19] Although different MAP targeting groups did not result in significant differences in mortality of septic shock patients and there were also no significant differences of fluid administered between those groups,[19] effects of fluid and MAP on splanchnic organ perfusion were not predictable. In addition, the liver circulation is considered unique because it consists of a dual blood supply. The intrahepatic blood flow is controlled by a balance between the vasoconstrictive endothelin and vasodilative gaseous molecules, which not only act on smooth muscle cells that feed the hepatic arteriolar and portal venular segments but also through pericytes in the hepatic sinusoids.[20] Thus, different types of vasopressors may result in different liver perfusion effects. It has been demonstrated that epinephrine, but not norepinephrine, could impair the splanchnic circulation in severe septic shock cases,[21] whereas dopamine increased the global oxygen demand and impaired the hepatic energy balance.[22] Moreover, in patients with norepinephrine-dependent septic shock, continuous low-dose vasopressin infusion resulted in hepatic perfusion damage;[23] however, terlipressin blunted the progressive decrease in the MAP without any detrimental effects on hepatosplanchnic perfusion, oxygen exchange, and metabolism.[24] Consequently, it was important to monitor the multiple factors that affected the hepatic perfusion alterations during resuscitation.

Finally, hepatic perfusion directed fluid resuscitation in patients with septic shock may have some limitations. This research indicated that ICG-PDR, R15, and their changes during EGDT were not good predictors for 28-day mortality in patients with septic shock. Previous studies, however, showed that the ICG-PDR was associated with increased ICU mortality in severe cases and the mortality rate in cases where the ICG-PDR ≤8%/min was as high as 80%.[25] Unlike global hemodynamics, the ICG-PDR was shown to be significantly different in survivors compared with nonsurvivors in septic patients after fluid resuscitation.[26] The above two studies enrolled critically ill patients and sepsis patients, and the majority of the patients in the latter study was complicated with pneumonia. Moreover, there were also differences in the resuscitation goals. All of the factors above led to differences in liver perfusion and disease severity as well as the inconsistent results of our study. In addition, it is still unknown whether hepatic microcirculatory blood flow improvements in patients with septic shock are dependent upon large fluid infusion amounts. Therefore, hepatic perfusion-guided fluid resuscitation in septic patients may not be a preferred choice.

This study had several limitations. First, the majority of the infection sites in the patients was lung infections; however, this was in accord with the results of Extended Prevalence of Infection in Intensive Care (EPIC II) study.[27] Second, this research was conducted in a single-center, and the ICG-PDR was only monitored within 24 h after EGDT. A large-scale and multi-centered study is needed to detect whether a much longer time is required for hepatic hypoperfusion improvement in septic patients. Finally, the ICG-PDR is unable to distinguish the relative contribution of hepatic blood flow alterations to hepatocellular injury. In our study, other hepatic function variables were monitored to rule out an influence on hepatocyte damage.

In conclusion, the ICG-PDR was significantly decreased in the observed patients with septic shock. There were no hepatic perfusion improvements, however, in the early

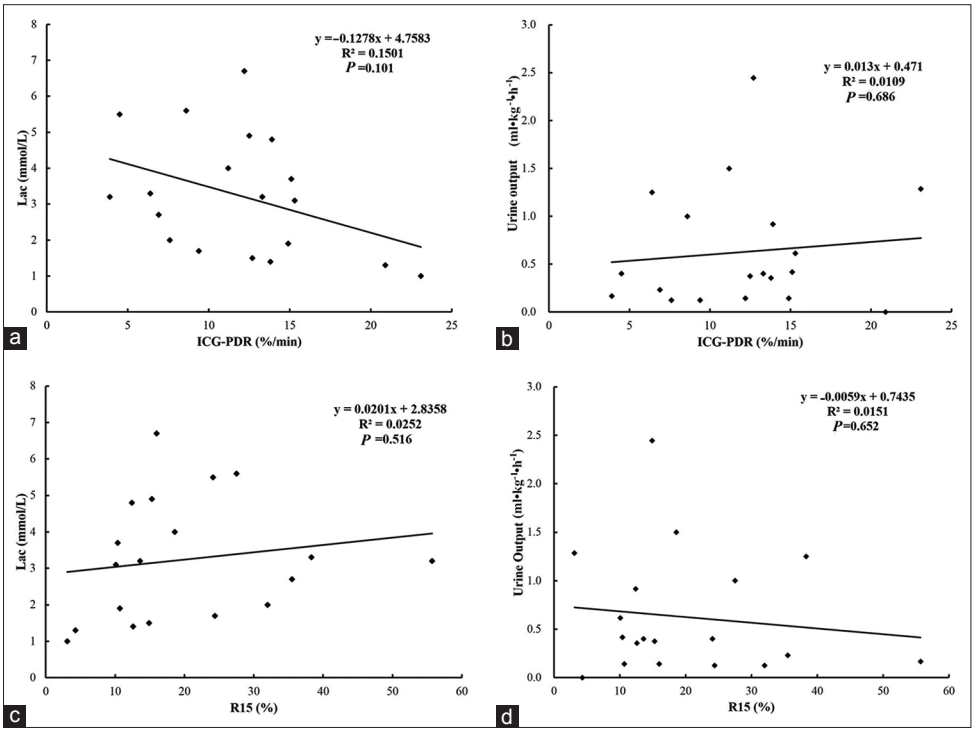


**Figure 3:** Correlations between ICG-PDR, R15, and lactate, urine output at T0 in patients with septic shock ($n$ = 19). (a) Correlation between ICG-PDR and lactate at T0. (b) Correlation between ICG-PDR and urine output at T0. (c) Correlation between R15 and lactate at T0. (d) Correlation between R15 and urine output at T0. ICG-PDR: Indocyanine green plasma disappearance rate; R15: 15-min retention rate; Lac: Lactate.

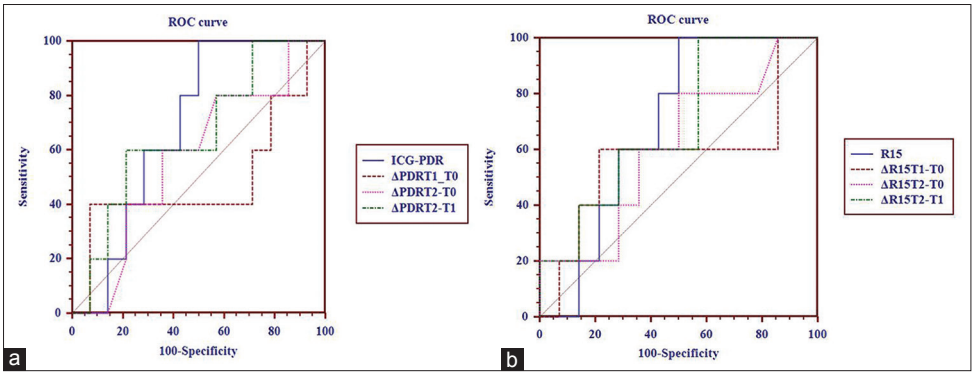


**Figure 4:** The ROC curves of ICG-PDR and R15 for predicting the 28-day mortality rate of patients with septic shock ($n$ = 19). (a) The ICG-PDR, $\Delta PDR_{T1-T0}$, $\Delta PDR_{T2-T0}$, and $\Delta PDR_{T2-T1}$ AUCs that were calculated to predict the 28-day mortality rate of patients with septic shock were 0.69 (95% *CI*: 0.44–0.87), 0.49 (95% *CI*: 0.26–0.72), 0.57 (95% *CI*: 0.33–0.79), and 0.66 (95% *CI*: 0.41–0.86). (b) The AUCs of R15, $\Delta R15_{T1-T0}$, $\Delta R15_{T2-T0}$ and $\Delta R15_{T2-T1}$ that were calculated to predict the 28-day mortality rate of patients with septic shock were 0.69 (95% *CI*: 0.44–0.87), 0.57 (95% *CI*: 0.33–0.79), 0.61 (95% *CI*: 0.36–0.82), and 0.69 (95% *CI*: 0.44–0.87). ROC: receiver operating characteristic; ICG-PDR: Indocyanine green plasma disappearance rate; R15: 15-min retention rate; $\Delta PDR_{T1-T0}$: The ICG-PDR difference between T1 and T0; $\Delta PDR_{T2-T0}$: The ICG-PDR difference between T2 and T0; $\Delta PDR_{T2-T1}$: The ICG-PDR difference between T2 and T1; $\Delta R15_{T1-T0}$: The R15 difference between T1 and T0; $\Delta R15_{T2-T0}$: The R15 difference between T2 and T0; $\Delta R15_{T2-T1}$: The R15 difference between T2 and T1; *CI*: Confidential interval; AUC: Area under the curve.

post-EGDT phase while the systematic tissue hypoperfusion was rectified. Moreover, the hepatic perfusion authenticity might not be reflected by the variables, which implied systemic perfusion. Thus, hepatic perfusion directed fluid resuscitation in patients with septic shock may have some limitations.


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## Conflicts of interest

There are no conflicts of interest.

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