

## Original Article

# Central venous-to-arterial partial pressure of carbon dioxide difference indicates the prognosis of cancer patients with sepsis

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**Abstract:** This study aimed to investigate whether central venous-to-arterial partial pressure of carbon dioxide difference (Pcv-aCO<sub>2</sub>) indicates the prognosis of cancer patients with sepsis post-operation. Total 157 cases of cancer patients with post-operation infection were enrolled, 127 cases were diagnosed with sepsis and received early capacity recovery. These patients were divided into two groups: Group A (Pcv-aCO<sub>2</sub> < 6 mmHg) and B (Pcv-aCO<sub>2</sub> ≥ 6 mmHg). ROC curve analysis showed that three largest areas for ROC curve included Pcv-aCO<sub>2</sub> (0.733), SOFA (0.768) and qSOFA (0.728). There was significant difference in survival between Group A and B (26.77±5.12 vs 19.60±12.13). Furthermore, we determined prognostic factors influencing the survival and identified Pcv-aCO<sub>2</sub> as the significant factor of the survival by COX regression or logistic regression analysis. In conclusion, we added two indexes of qSOFA and SOFA for early detection and early diagnosis of sepsis with the introduction of the Sepsis-3.0 guidelines. The combination of Pcv-aCO<sub>2</sub> with qSOFA and SOFA will help the diagnosis and prognosis of cancer patients with sepsis.

**Keywords:** Central venous-to-arterial partial pressure of carbon dioxide difference, sepsis, cancer, capacity recovery, sequential organ failure assessment score, quick SOFA

## Introduction

After surgical operation and septic shock, sepsis is one of the most common causes of death among patients with tumour. The rapid onset of sepsis can sequentially lead to significant organ failure over a short term, resulting in multiple organ dysfunction syndrome. Upon the admission of sepsis patients to the Intensive Care Unit (ICU), hemodynamic monitoring is important to ensure the stability of the patient's hemodynamic state, improve the oxygen supply of tissues and organs, enhance oxygen metabolism, and reduce oxygen consumption. Early Goal Directed Therapy (EGDT) has been regarded as standardized early anti-shock fluid resuscitation therapy strategy [1-5]. However, owing to the diversity and complexity of the disease, a considerable part of septic shock patients have high mortality rate and significant organ failure and hemodynamic disorder after EGDT [6].

The sequential organ failure assessment (SOFA) and Quick SOFA (qSOFA) scores have been introduced into the diagnostic criteria to improve the evaluation of early organ function in the early stage of shock [7]. Central venous-to-arterial partial pressure of carbon dioxide difference (Pcv-aCO<sub>2</sub>) has been proposed as an indicator of cardiac index [8]. Therefore, we hypothesized that Pcv-aCO<sub>2</sub> can be used to evaluate the effects of resuscitation therapy, organ perfusion, and oxygen metabolism on patients with septic shock. This study aimed to explore the value of Pcv-aCO<sub>2</sub> for guiding fluid therapy and evaluating the prognosis of patients with septic shock.

## Subjects and methods

### Subjects

The subjects were selected from 157 cancer patients hospitalized at Tianjin Medical Univer-

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**Table 1.** Comparison of general clinical data between Group A and B

	Survival (day)	Hemoglobin (g/L)	Albumin (g/L)	Cardiac index	Age (years)	BMI
Group A	26.77±5.12	124.53±4.93	21.53±0.82	2.76±0.43	70.89±7.05	22.87±2.90
Group B	19.60±12.13*	124.75±5.23	21.63±1.07	2.75±0.52	68.79±7.96	22.24±2.76
t value	3.386	-0.206	-0.488	0.018	1.325	1.094
p value	0.001	0.837	0.626	0.986	0.188	0.277

\*p < 0.05 indicated significant difference.

**Table 2.** Comparison of other clinical data between Group A and B

	Outcome	Infection site	Primary disease	Primary disease classification	Incision classification	Gender
Z value	-3.108*	-0.200	-0.861	-0.728	-1.222	-0.113
p value	0.002	0.842	0.389	0.466	0.222	0.910

\*p < 0.05 indicated significant difference.

**Table 3.** Comparison of O<sub>2</sub>ER at 6 h and 24 h between Group A and B

	O <sub>2</sub> ER at 6 h (%)	O <sub>2</sub> ER at 24 h (%)	Pcv-aCO <sub>2</sub> at 6 h (mmHg)
Group A	24.73±2.39	24.01±2.96	5.28±0.39
Group B	24.71±2.73	52.96±7.36*	7.03±0.66*
t value	0.039	-22.577	-14.688
p value	0.969	0.000	0.000

\*p < 0.05 indicated significant difference.

sity Cancer Hospital intensive care unit (ICU) from January 2014 to December 2015, who had infection post-operation. They included 69 females and 88 males, their age was 65.89±7.35 years. After sufficient assessment, 127 cases of patients were diagnosed with sepsis.

The diagnostic criteria of abdominal infection included the gallbladder, biliary tract, liver, spleen, pancreas, peritoneum, subphrenic organizations or other parts of tissues intra-abdominal infections. The following standards are included in the diagnostic criteria: Standard One: Culture pathogens through surgery or from abdominal puncture aspirate fluids. Standard Two: Infection verified by surgical or histological examination or complicated with abdominal abscess post-operation. Standard Three: Two of the following symptoms or signs that can be explained by no other reason: fever, nausea, vomiting, abdominal pain or jaundice. In addition, they should have one of the following conditions: Pathogens were cultured in a surgical drainage (closed suction, open and T tube drainages); Pathogens were found from surgery or aspiration fluid by microscopy; Blood culture positive or abnormal images were from special

examination such as ultrasound, CT scan, magnetic resonance or abdominal X-ray examination.

The diagnostic criteria of septic shock were: a. Acute physiology and chronic

health evaluation II (APACHEII) score > 15 points; b. Hemodynamic abnormalities after surgery: systolic blood pressure < 90 mmHg, or a > 40 mmHg basic blood pressure decline, pulse pressure < 20 mmHg, urinary amount < 0.5 ml/Kg/hr, heart rate > 100 beats/min, central venous pressure (CVP) < 5 mmHg, blood lactate > 2.0 mmol/L, Central venous oxygen saturation (ScvO<sub>2</sub>) < 60%.

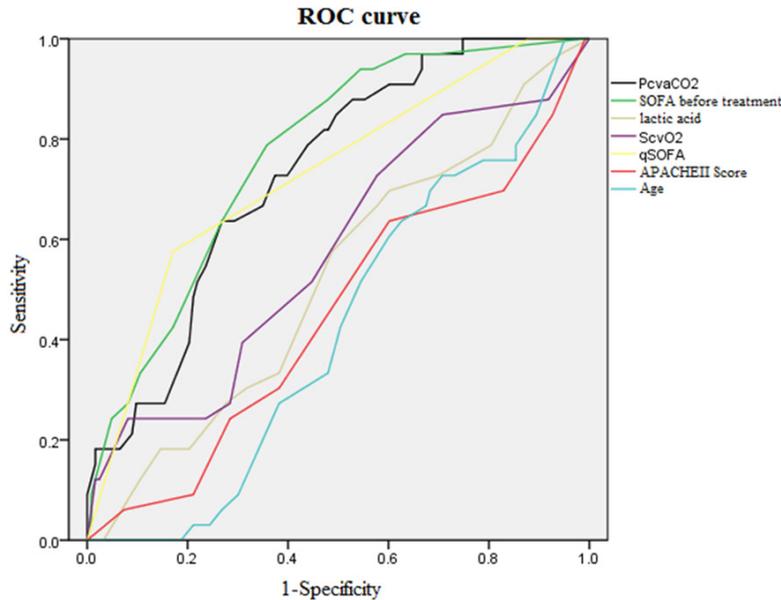
Patients were excluded if they met the following exclusion criteria: Age < 18 years old; Shock status except septic shock; Chronic diseases (chronic obstructive pulmonary disease and chronic kidney disease) because of the acute exacerbation of organ dysfunction; Taking salicylic acid, biguanide hypoglycemic agents and other drugs that can affect blood lactic acid concentration; had undergone a broad spectrum of antibiotic therapy previously; died in ICU or discharged from ICU within 24 hours.

### Procedures

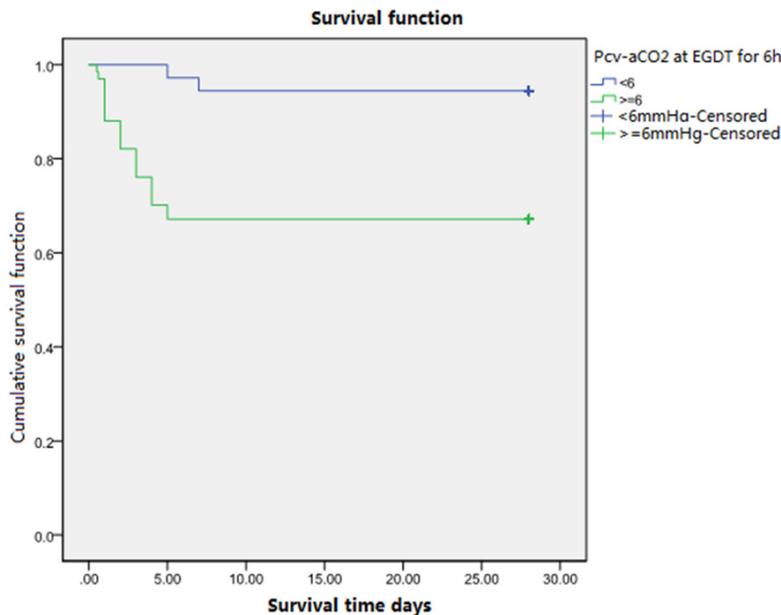
Among 157 patients, 127 were initially diagnosed as sepsis, who received capacity recovery for 6 hours. 103 patients met EGDT standard, and they were divided into two groups based on Pcv-aCO<sub>2</sub> value: Group A (Pcv-aCO<sub>2</sub> < 6 mmHg; 36 cases) and B (Pcv-aCO<sub>2</sub> ≥ 6 mmHg; 67 cases). The differences of oxygen extraction (O<sub>2</sub>ext or O<sub>2</sub>ER) were compared in two groups at the time of the capacity recovery for 6 and 24 hours. COX regression analysis was performed to determine the relevant factors that may impact the survival of the patients.

The age of all patients, APACHE II score before treatment, heart rate (HR), mean arterial pres-

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**Figure 1.** The ROC Curve of qSOFA, Pcv-aCO<sub>2</sub> and other prognostic indicators. Pcv-aCO<sub>2</sub> (0.733), SOFA (0.768), qSOFA (0.728), APACHEII score (0.450), lactic acid (0.520), ScvO<sub>2</sub> (0.576), Age (0.423), and the largest ROC areas were Pcv-aCO<sub>2</sub>, SOFA, qSOFA.



**Figure 2.** The survival curve analysis of Group A and B. The survival of patients in Group A was better than that of Group B ( $p=0.002$ ).

sure (map) and systolic blood pressure (SBP), respiratory rate (RR), urine volume per hour, central venous pressure (CVP), blood lactic acid (LAC), central venous oxygen saturation (ScvO<sub>2</sub>), oxygenation index (PaO<sub>2</sub>/FiO<sub>2</sub>), serum creatinine, total bilirubin, platelet and Glasgow

Coma Score (GCS) were recorded. Oxygen metabolism index were calculated, including oxygen delivery (DO<sub>2</sub>), oxygen consumption (VO<sub>2</sub>), arterial oxygen content (CaO<sub>2</sub>), central venous oxygen content (cvo<sub>2</sub>) and O<sub>2</sub>ER. Organ function correlation index QSOFA were calculated.

### Statistical analysis

SPSS19.0 statistics software was used for data analysis. The measurement data were presented as mean  $\pm$  standard deviation (mean  $\pm$  SD), and data between two groups were compared by independent sample *t* test. Spearman rank correlation analysis was performed.  $p < 0.05$  indicated statistical significance.

## Results

### Clinical data of the two groups

The capacity resuscitation treatment was conducted early for 127 patients initially diagnosed of sepsis, of which 103 patients met EGDT standards. We then divided 103 patients into Group A (Pcv-aCO<sub>2</sub> < 6 mmHg) and B (Pcv-aCO<sub>2</sub>  $\geq$  6 mmHg) according to Pcv-aCO<sub>2</sub> at 6 hours after EGDT.

General and other clinical data of Group A and B were shown in **Tables 1** and **2**.

There were 36 patients in Group A (16 females, 20 males) and 67 patients in Group B (29 females, 38 males). The outcome included improved or death: 33 cases improved and 3 cases died in Group A; 45 cases improved and 22 cases died in Group B. The infected area

included the lungs, abdomen and unexplained: 27 for lungs, 8 for abdominal, 1 unexplained in Group A; 51 for lungs, 16 for abdominal cavity in Group B. The primary diseases were: 12 for lung cancer, 7 for esophageal cancer, 7 for gastric cancer, 2 for colorectal cancer, 1 for liver cancer, 6 for pancreatic cancer, 2 for gallbladder cancer, 2 for renal cell carcinoma in Group A; 16 for lung cancer, 19 for esophageal cancer, 9 for gastric cancer, 5 for colorectal cancer, 6 for liver cancer, 4 for pancreatic cancer, 2 for gallbladder cancer, 3 for kidney cancer, 2 for small intestine cancer, 1 for urinary tract tumor in Group B. In Group A, 12 had chest incision; 17 had abdominal incision; 7 had thoracic and abdominal combined incision. In Group B, 15 had chest incision; 32 had abdominal incision; 19 had thoracic and abdominal combined incision. The clinical data showed no significant differences between the two groups except for survival and outcome.

We compared oxygen metabolism indicators of capacity resuscitation for 6 and 24 hours between the two groups. We found no significant difference in O<sub>2</sub>ER between Group A and B at EGDT for 6 hours, but O<sub>2</sub>ER of Group B increased significantly compared to Group A at EGDT for 24 hours (**Table 3**).

### *Correlation analysis of prognostic indicators*

We analysed the correlation between Pcv-aCO<sub>2</sub> and prognostic indicators. The areas under the ROC were Pcv-aCO<sub>2</sub> (0.733), SOFA (0.768), qSOFA (0.728), APACHE II score (0.450), lactic acid (0.520), ScvO<sub>2</sub> (0.576), Age (0.423), and the largest areas were Pcv-aCO<sub>2</sub>, SOFA and qSOFA (**Figure 1**).

Kaplan-Meier survival analysis showed that the survival of patients in Group A was significantly better than that of Group B (**Figure 2**). The results of Cox regression survival analysis were: Pcv-aCO<sub>2</sub> ( $p=0.020$ , B value =-2.369, 95.0% CI 0.013~0.692), SOFA before treatment ( $p=0.374$ , B value =0.088, 95.0% CI 0.899~1.326), qSOFA before treatment ( $p=0.216$ , B values =0.615, 95.0% CI 0.698~4.897), APACHE II score ( $p=0.091$ , B value =0.239, 95.0% CI 0.598~1.038), Hemoglobin ( $p=0.536$ , B value =-0.027, 95.0% CI 0.895~1.060), Albumin ( $p=0.370$ , B value =-0.241, 95.0% CI 0.464~1.331). The results of logistic regression analysis were: Pcv-aCO<sub>2</sub> ( $p=0.012$ ,

OR value =-3.293), SOFA before treatment ( $p=0.235$ , OR value =0.167), qSOFA before treatment ( $p=0.333$ , OR value =0.645), APACHE II score ( $p=0.069$ , OR value =-0.356), Hemoglobin ( $p=0.480$ , OR value =-0.041), Albumin ( $p=0.474$ , OR value =-0.237). Therefore, only Pcv-aCO<sub>2</sub> was the significant factor that affected the survival ( $p < 0.05$ ).

### **Discussion**

Sepsis is a common cause of death in critically ill patients. For peritoneal cancer patients, long-term poor nutritional status can cause hypoalbuminemia and decreased immune function after surgery, complicated with intra-abdominal infections. These conditions lead to continuous aggravation of abdominal infection, which can eventually result in septic shock. The mortality rate of sepsis is 30-50%. Early identification and evaluation of septic shock, the implementation of capacity resuscitation, improvement of tissue perfusion, and prevention of secondary multiple organ dysfunction are essential to improve the prognosis. The mortality of patients remains high even after fulfilling EGDT.

The standard of ScvO<sub>2</sub>  $\geq$  70% separated part of the patients from harmful hypoperfusion with shock [9]. However, ScvO<sub>2</sub>  $\geq$  70% does not prevent the progress of multiple organ dysfunction [10]. Furthermore, continued high ScvO<sub>2</sub> level is even directly related to the high mortality rate in patients with shock [11, 12]. Notably, the combination of lactic acid and ScvO<sub>2</sub> indicators determined the end point of capacity resuscitation, but they failed to achieve better results [13]. Pcv-aCO<sub>2</sub> is the difference between PcvCO<sub>2</sub> and PaCO<sub>2</sub>, and its normal range is 2-6 mmHg. Mixed venous blood flow through the lungs, and gas exchange are excreted from the lungs. Increased Pcv-aCO<sub>2</sub> can reflect reduced blood flow because the discharge capacity of CO<sub>2</sub> is very strong. Pv-aCO<sub>2</sub> has a negative correlation with cardiac output (CO), thus hemodynamic status of a patient can be evaluated by Pcv-aCO<sub>2</sub>. Vallee et al. reported that Pcv-aCO<sub>2</sub>  $>$  6 mmHg may be a useful indicator of capacity resuscitation when ScvO<sub>2</sub>  $>$  70% [14]. Futier et al. showed that Pcv-aCO<sub>2</sub>  $>$  5 mmHg but not ScvO<sub>2</sub>  $>$  70% was associated with postoperative complications [15]. Therefore, in this study we explored the clinical value of Pcv-aCO<sub>2</sub> for capacity resuscitation of septic shock patients.

In this study, we selected 157 postoperative patients complicated with infections. According to the latest Sepsis-3.0 guideline, we chose qSOFA and SOFA to screen the patients with sepsis and 127 cases were diagnosed with sepsis and capacity resuscitation was immediately carried out. According to the guidelines, the EGDT target for 103 patients is reached in six hours. The 103 patients were divided into Group A (Pcv-aCO<sub>2</sub> ≤ 6 mmHg) and B (Pcv-aCO<sub>2</sub> > 6 mmHg). We found that the survival of Group A was longer than that of Group B, and the overall patient outcome was better in Group A than in Group B. Furthermore, we determined the relevant factors influencing the survival and identified Pcv-aCO<sub>2</sub> as the significant factor of the survival by COX regression or logistic regression analysis.

In summary, we added two index of qSOFA and SOFA for early detection and early diagnosis of sepsis with the introduction of the Sepsis-3.0 guidelines. We introduced Pcv-aCO<sub>2</sub> as an important complement to traditional hemodynamic parameters to improve the treatment success rate of patients with sepsis. In the clinical we can combine Pcv-aCO<sub>2</sub> with qSOFA and SOFA to determine the diagnosis and prognosis of cancer patients with sepsis.

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### Disclosure of conflict of interest

None.

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