Afterload-related cardiac performance predicts prognosis in critical ill patients with sepsis
A prospective observational pilot study

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Abstract
To investigate the usefulness of afterload-related cardiac performance (ACP) for assessing cardiac impairment and predicting prognosis in septic patients.

Adult patients with sepsis in the intensive care unit were included. Cardiac output, cardiac index, cardiac power index, and ACP were calculated at the time of admission (D0) and 48–72 h after admission (D3). They were correlated with Acute Physiology and Chronic Health Evaluation II and sequential organ failure assessment scores, then the prognostic values were analyzed.

A total of 41 patients with sepsis were selected. ACP showed a stronger negative correlation with Acute Physiology and Chronic Health Evaluation II and sequential organ failure assessment scores than cardiac output, cardiac index, and cardiac power index. ACP predicted 28-day mortality with an area under the curve of 0.775 and 0.976 on D0 and D3, respectively. In addition, most non-survivors had emergent cardiac impairment (ACP ≤ 80%) on D0, and cardiac function was deteriorated on D3. Survival analysis showed that the patients with a decreased ACP from D0 to D3 had the highest mortality. The decrease of ACP on D3 was an independent risk factor for mortality (hazard ratio, 11.89; P = .0028).

ACP can be used to assess the severity of cardiac impairment in sepsis. Continued decline of ACP during the first 3 days strongly suggests a poor prognosis.

Abbreviations: ACP = afterload-related cardiac performance, APACHE II = Acute Physiology and Chronic Health Evaluation II, AUC = area under the curve, CI = cardiac index, CO = cardiac output, CPI = cardiac power index, CVP = central venous pressure, D0 = the time of admission, D3 = 48–72 h after admission, HR = hazard ratio, ICU = intensive care unit, MAP = mean arterial pressure, ROC = receiver operating characteristic curve, SOFA = sequential organ failure assessment, SV = stroke volume, SVR = systemic vascular resistance.

Keywords: afterload-related cardiac performance, intensive care unit, sepsis, septic cardiomyopathy

1. Introduction
Sepsis is characterized by a deregulation of host response to infection with life-threatening organ dysfunction.[1] Septic cardiomyopathy is the reversible myocardial depression caused by sepsis[2] and increases the mortality of sepsis patients.[3–5] Early diagnosis and management after the development of septic cardiomyopathy improves outcomes.

Echocardiography[6–8] plays an important role in the diagnosis of septic cardiomyopathy which can comprehensively and intuitively evaluate cardiac systolic and diastolic functions. Ultrasound, combined with hemodynamic monitoring indicators, such as cardiac output (CO), cardiac index (CI), and cardiac power index (CPI), can better assess the degree of damage to heart pump function in sepsis. However, these parameters may overestimate heart function because reduced systemic vascular resistance (SVR) will lead to a seemingly “normal” CO in sepsis patients. Therefore, the early occurrence of septic cardiomyopathy might not be recognized, and the severity of sepsis may be underestimated.

Afterload-related cardiac performance (ACP, %) was developed and described as CO measured / CO predicted × 100%.[9] The “CO predicted” can be calculated as a function of SVR: CO predicted = β0 × SVR1.1/3 (β0 = 394.07, β1 = −0.64). After corrected by SVR, ACP could identify whether the actual CO represents a normal or an already impaired cardiac function.
Normal cardiac function is defined by ACP > 80%. Werdan et al.\textsuperscript{[9]} found the parameter ACP was superior to CI and CPI to identify cardiac injury at an early stage, so was of prognostic relevance in patients with multiorgan dysfunction syndrome caused by sepsis. Subsequently, an investigation conducted on 141 patients with community-acquired sepsis revealed that ACP was a predictive index for mortality at the time of admission to the emergency department\textsuperscript{[10]}. However, there are a few studies on the potency of ACP in patients with sepsis. More clinical research is needed to verify the reliability and application value of ACP in sepsis patients.

Therefore, this study aims to investigate whether ACP is superior to traditional cardiac parameters (CO, CI, and CPI) to recognize myocardial dysfunction at an early stage and predict a worse prognosis in patients with sepsis in the intensive care unit (ICU).

2. Methods

2.1. Study population

We performed a prospective, single-center, observational study in the intensive care unit (ICU, 20 beds) of the Fourth Hospital of Hebei Medical University from October 1, 2018 to January 31, 2019, and the final follow-up was February 26, 2019. Patients admitted in our ICU with a clinical diagnosis of sepsis were included in the study. Informed consent was obtained either from the patient or a proxy. The study protocol was approved by our Institutional Research Ethics Committee and has been pre-registered in the Chinese Clinical Trial Registry (No. ChiCTR1800016120). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Sepsis was diagnosed by Sepsis-3.0 definition,\textsuperscript{[1]} which is life threatening organ dysfunction caused by infection. Patients were excluded from the analysis if there was a history of coronary heart disease (including ischemic cardiomyopathy, angina, and myocardial infarction),\textsuperscript{[11]} heart failure (including systolic and diastolic heart failure),\textsuperscript{[12]} atrial fibrillation, age < 18 years, pregnancy, segmental wall dyskinesia, or admission time < 24 hours.

2.2. Measurements

Clinical parameters included diagnosis, vital signs (such as heart rate, mean arterial pressure [MAP], central venous pressure [CVP] and laboratory examination (such as serum troponin, plateletocrit, C-reactive protein, lactate) were collected at baseline (soon after admission) and on the third day (48–72 hours after admission), respectively. For all patients, Acute Physiology and Chronic Health Evaluation II score (APACHE II)\textsuperscript{[13]} and Sequential Organ Failure Assessment score (SOFA)\textsuperscript{[14]} were determined.

In this study, MAP and CVP were measured invasively during clinical routine. All cardiac parameters were performed by critical care ultrasound (Philips CX50). The parameter ACP was calculated as described by Werdan et al.\textsuperscript{[9]} First, a measured CO (CO\textsubscript{measured}) was obtained by echocardiography. CO\textsubscript{measured} was the product of stroke volume (SV) and heart rate. SV was calculated by the radius of left ventricular outflow tract \((r)\) and left ventricular outflow tract velocity time integral. By using echocardiography in parasternal axis view assessed radius of left ventricular outflow tract. Color Doppler was taken in apical 4 chamber view and velocity time integral was measured. All measurements were performed by the first author to avoid interobserver bias. An average of consecutive 3 recordings were taken to avoid intraobserver bias. Secondly, SVR was calculated by MAP, CVP, and CO\textsubscript{measured}. Thirdly, the predicted “normal” CO (CO\textsubscript{predicted}) values for a given SVR were calculated. Finally, ACP was calculated by the ratio of CO\textsubscript{measured} to CO\textsubscript{predicted}. The calculation process is as follows:

\[
\text{CO}\textsubscript{measured} (L/min) = \text{VTI} \times \pi r^2 \times \text{heart rate} \\
\text{SVR} (\text{dynes/cm}^2\text{s}/s) = (\text{MAP} - \text{CVP}) \times 80/\text{CO}\textsubscript{measured} \\
\text{CO}\textsubscript{predicted} (L/min) = 560.68 \times \text{SVR}^{-0.64} \\
\text{ACP} (%) = \text{CO}\textsubscript{measured} / \text{CO}\textsubscript{predicted} \times 100\
\]

Body weight-adjusted indexed values CI and CPI\textsuperscript{[15]} were calculated as follows:

\[
\text{CI} (L/min/m^2) = \text{CO}\textsubscript{measured} / \text{body surface} \\
\text{CPI} (W/m^2) = \text{CI} \times \text{MAP} \times 0.0022.
\]

2.3. Outcome

The primary outcome of this study was 28-day mortality after admission to the ICU. In case of hospital discharge before day 28, survival status was verified via phone contact after day 28.

2.4. Statistics

Statistical analysis used the software Excel (Microsoft office, Redmond, WA, USA) and SPSS 21 (SPSS Inc., Chicago, IL, USA). Numerical data are given as mean ± standard deviation (mean ± SD), and Student t test was used for 2 independent sample groups. The measurement data of non-normal distribution are expressed by median (interquartile interval) and analyzed by rank sum test. Dichotomous data are expressed by quantity (percentage) and analyzed by Pearson chi-squared test. Linear regression analysis was used for correlation analysis. Receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) were used to compare the value of each of the cardiac parameters (CO, CI, CPI, ACP) in predicting the primary outcome. Survival analysis was calculated using the Kaplan–Meier method. Cox proportional hazard regression analysis on ACP and 28-day mortality were performed. \(P < .05\) was considered to be statistically significant.

3. Result

All cardiac parameters performed by ultrasound were completed by the first author (CCZ), who has been using critical care ultrasound for > 3 years and obtained the training certificate from Chinese Critical Ultrasound Study Group.

3.1. Patient characteristics

A total of 235 patients were admitted to our intensive care unit during a period of 4 months, with 56 sepsis patients. Among them, 15 patients were excluded due to unclear ultrasound imagery (7/15), atrial fibrillation (4/15), myocardial infarction (2/15), pregnancy (1/15), and death within 24 hours after admission (1/15). For further analysis, only 41 patients with sepsis were chosen. According to the 28-day survival status,
patients were divided into 2 groups: survival group \( n = 27 \) and non-survival group \( n = 14 \). Figure 1 shows the schematic of patient enrollment.

Comparing the basic medical characteristics between the 2 groups, the critical illness scores were higher in the non-survival group, including APACHE II \( (P = .015) \) and SOFA scores \( (P = .002) \). In addition, there were differences in C-reactive protein, central venous pressure, and lactate level between the 2 groups. The other parameters did not show any significant difference (Table 1).

### 3.2. Cardiac parameters and outcome

The 28-day mortality of the whole study group was 34.2\% \( (n = 14) \). At the time of admission, non-survivors had significantly lower levels of CPI and ACP than survivors, but there was no obvious difference of CO and CI between the 2 groups. On the third day of admission, all the cardiac parameters were significantly different between survivors and non-survivors (Table 2).

Table 3 shows the correlation between severity of disease and cardiac parameters. We used APACHE II and SOFA scores to indicate the severity of disease. On the time of admission, it was evident that values of CPI and ACP correlate—versely—with APACHE II and SOFA scores, but not the values for CO and CI. On the third day of admission, although CO, CI, CPI, and ACP were all negatively correlated with APACHE II and SOFA scores, and ACP had the strongest correlation.

Comparing the ability of CI, CPI, and ACP to discriminate between survivors and non-survivors by means of ROC curve analysis, all showed significant AUC values. On the first day of admission, there was no significant difference of the 3 cardiac parameters in the predictive value for mortality (Fig. 2A), while the predictive advantage of ACP (AUC 0.976, 95\% CI 0.872–0.999; \( P < .001 \)) was obvious on the third day of admission (Fig. 2B).

With a cut-off value of 80.2\% or below on D0, ACP predicted non-survival with a sensitivity of 92.6\%, a specificity of 92.9\% (Table 4). The threshold values of CI and CPI for 28-day mortality were also showed in Table 4.

### 3.3. Correlation of ACP with outcomes

In order to determine the frequency of septic cardiomyopathy in survivors and non-survivors, the severest decrease in ACP was assessed for all patients. The severest decrease in ACP was divided into 4 grades: normal \((ACP > 80\%)\), slight impairment \((60\% < ACP < 80\%)\), moderate impairment \((40\% < ACP < 60\%)\), and severe impairment \((ACP < 40\%)\). As shown in Fig. 3, the degree of cardiac impairment was significantly different between survivors and non-survivors. On the time of admission, only 30\% of survivors had a decrease in cardiac function, and cardiac function was slightly impaired in most of these cases (26\%). On the contrary, 79\% of non-survivors showed a decrease in cardiac function, and slight impairment accounted for 64\% cases and moderate impairment accounted for 15\% cases (Fig. 3A). On the third day of admission, the frequency of cardiac impairment decreased in survivors, >80\% survivors had no relevant decrease.

### Table 1

Baseline and follow-up characteristics of patients in this study.

| Baseline parameters       | Survivors \( n = 27 \) | Non-survivors \( n = 14 \) | \( P \) value |
|---------------------------|------------------------|-----------------------------|-------------|
| Male gender, n (%)       | 17 (63.0)              | 13 (92.9)                   | .094        |
| Age (years)              | 65 (56–70)             | 62 (63–71)                  | .978        |
| APACHE II score          | 18 (14–21)             | 24 (19–31)                  | .015        |
| SOFA score               | 9 ± 3                  | 13 ± 5                      | .002        |
| Sepsis shock, n (%)      | 17 (63.0)              | 10 (76.9)                   | .588        |
| Vasopressor support, n (%) | 23 (85.2)              | 13 (92.9)                   | .477        |
| Cardiac biomarkers        |                        |                             |             |
| BNP, pg/mL               | 196 (105–487)          | 161 (119–256)               | .441        |
| Troponin, ng/mL          | 0.05 (0.02–0.19)       | 0.05 (0.01–0.17)            | .846        |
| Myoglobin, ng/mL         | 132 (69–246)           | 355 (39–1227)               | .290        |
| Infection biomarkers      |                        |                             |             |
| WBC \( (10^9)/\ell \)    | 15.41                  | 18.88                       | .360        |
| PCT, ng/mL               | 3.5 (1.4–19.5)         | 3.9 (0.6–13.3)              | .475        |
| CRP, mg/L                | 279 (172–354)          | 152 (113–247)               | .017        |
| Hemodynamic parameters   |                        |                             |             |
| CVP, mmHg                | 9 ± 3                  | 12 ± 4                      | .021        |
| MAP, mmHg                | 92 ± 12                | 76 ± 8                      | .109        |
| Lactate, mmol/L          | 1.9 (1.4–3.0)          | 3.0 (1.9–6.0)               | .023        |
| SVRI, dynes/cm²/s        | 1032 ±523              | 1149 ±437                   | .359        |
| Source of infection, n (%)|                        |                             |             |
| Thoracic infection       | 6 (22.2)               | 1 (7.1)                     | .119        |
| Abdominal infection      | 6 (22.2)               | 4 (28.6)                    | .588        |
| Blood stream infection   | 5 (18.5)               | 2 (14.3)                    | .978        |
| Skin soft-tissue infection | 1 (3.7)               | 2 (14.3)                    | .978        |
| Pneumonia                | 7 (26.0)               | 4 (28.6)                    | .978        |
| Other                    | 2 (7.4)                | 1 (7.1)                     | .978        |
| Life support, n (%)      |                        |                             |             |
| Mechanical ventilation   | 23 (85.2)              | 14 (100)                    | .290        |
| Renal support            | 4 (14.8)               | 7 (50.0)                    | .016        |
| Cardio support           | 0 (0)                  | 0 (0)                       | .016        |

For numerical data, median and 25th and 75th percentiles are presented.

APACHE = acute physiology and chronic health evaluation, BNP = B-type natriuretic peptide, CRP = C-reactive protein, CVP = central venous pressure, MAP = mean arterial pressure, PCT = procalcitonin, SOFA = sequential organ failure assessment, SVRI = systemic vascular resistance index.

* Significant \( P < .05 \).

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For Table 1, the following points should be noted:

- The table includes various baseline and follow-up characteristics of patients, such as gender, age, APACHE II and SOFA scores, and various infections.
- The table also presents the comparison between survivors and non-survivors, showing significant differences in some parameters.
- The table concludes with the source of infection and the number of patients in each category.

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For Figure 1, the following points should be noted:

- Figure 1 shows the schematic of patient enrollment.
- The figure indicates 27 survivors and 14 non-survivors.
- The figure also shows the distribution of patients with sepsis, excluding those with acute myocardial infarction, pregnancy, and death within 24 hours.

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For Table 2, the following points should be noted:

- Table 2 presents the baseline parameters of survivors and non-survivors.
- The table shows significant differences in CI, CPI, and ACP between the two groups.
- The table also includes other parameters such as APACHE II, SOFA scores, and various infections.

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For Table 3, the following points should be noted:

- Table 3 shows the correlation between severity of disease and cardiac parameters.
- The table includes various parameters such as CVP, MAP, Lactate, and SVRI.
- The table presents the source of infection and the number of patients in each category.

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For Figure 2, the following points should be noted:

- Figure 2A shows the predictive value for mortality of CI and ACP.
- Figure 2B shows the predictive value for mortality of CI and ACP.
- The figure includes a ROC curve analysis for CI, CPI, and ACP.

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For Figure 3, the following points should be noted:

- Figure 3A shows the degree of cardiac impairment.
- Figure 3B shows the frequency of septic cardiomyopathy.
- The figure includes a comparison between survivors and non-survivors.

in cardiac function. On the contrary, the frequency of cardiac impairment increased in non-survivors, >80% non-survivors developed a decrease in cardiac function, and the severity of cardiac impairment was more serious (Fig. 3B).

We further divided the patients into 4 groups according to whether ACP decreased on the time of admission (D0) and 48–72 h after admission (D3): group 1, ACP on D0 and D3 were both normal; group 2, ACP was normal on D0 but decreased on D3; group 3, ACP decreased on D0 but was back to normal on D3; group 4, ACP on D0 and D3 both decreased. Then 28-day mortality rate was compared among the 4 groups to evaluate the impact of ACP on outcome of septic patients. The results showed that the survival rates were obviously different (P < .001) in the 4 groups (Fig. 4), which was highest in group 1 (100%), and lowest in group 4 (16.7%). In the other 2 groups, patients with only normal ACP on D3 had a higher survival rate than those with only normal ACP on D0 (94.4% vs 50.0%). In addition, the severity of ACP decline on D0 had no effect on survival rate.

### Table 2
Cardiac parameters of survivors and non-survivors.

| Parameter | D1 Survivors (27/41) | D1 Non-survivors (14/41) | P value | D3 Survivors (27/41) | D3 Non-survivors (14/41) | P value |
|-----------|----------------------|--------------------------|---------|----------------------|--------------------------|---------|
| CO, L/min | 6.1 ± 1.7            | 5.2 ± 1.7                | .098    | 5.9 ± 1.7            | 4.3 ± 1.4                | .004    |
| CI, L/min/m² | 3.5 ± 1.0            | 2.9 ± 0.9                | .051    | 3.4 ± 1.0            | 2.4 ± 0.9                | .003    |
| CPI, W/m²  | 0.6 ± 0.2            | 0.5 ± 0.2                | .019    | 0.6 ± 0.2            | 0.4 ± 0.1                | <.001   |
| ACP (%)    | 87.4 ± 12.5          | 74.2 ± 11.5              | .002    | 90.7 ± 8.8           | 64.3 ± 12.1              | <.001   |

ACP = afterload-related cardiac performance, CI = cardiac index, CO = cardiac output, CPI = cardiac power index.

### Table 3
Correlation of cardiac parameters with APACHE II and SOFA scores.

| APACHE II | D0 | D3 |
|-----------|----|----|
| APACHE II |    |    |
| Correlation | ns | ns |
| P value | ns | ns |

| SOFA score | D0 | D3 |
|------------|----|----|
| Correlation | ns | ns |
| P value | ns | ns |

ACP = afterload-related cardiac performance (%), CI = cardiac index (L/min/m²), CO = cardiac output (L/min), CPI = cardiac power index (W/m²), D0 = the time of admission, D3 = 48–72 h after admission, ns = not significant.

Figure 2. Receiver-operating characteristic curves show the predictive ability of ACP, CPI, CI for 28-day mortality at times of D0 (A) and D3 (B). ACP = afterload-related cardiac performance (%), CPI = cardiac power index, CI = cardiac index, D0 = the time of admission, D3 = 48–72 h after admission.
Table 4
The threshold values of cardiac parameters for 28-day mortality.

|          | D0          | D3        |
|----------|-------------|-----------|
|          | CI          | CPI       | ACP       | CI          | CPI       | ACP       |
| Cut-off value | ≤3.78       | ≤0.61     | ≤80.20    | ≤3.62       | ≤0.55     | ≤78.10    |
| Sensitivity  | 37.0%       | 44.4%     | 70.4%     | 51.9%       | 70.4%     | 92.6%     |
| Specificity  | 92.9%       | 92.9%     | 78.6%     | 100%        | 92.9%     | 92.9%     |

ACP = afterload-related cardiac performance (%), CI = cardiac index (L/min/m²), CPI = cardiac power index (W/m²), D0 = the time of admission, D3 = 48–72 h after admission.

Figure 3. Severity of cardiac impairment in survivors (n=27) and non-survivors (n=14) as measured by the classification of ACP at times of D0 (A) and D3 (B). ACP = afterload-related cardiac performance (%), D0 = the time of admission, D3 = 48–72 h after admission.

Figure 4. Kaplan–Meier estimates of 28-day survival rate in patients with sepsis. According to whether ACP was normal (>80%) at times of D0 and D3, the patients divided into 4 groups: group 1, ACP on D0 and D3 were both normal; group 2, ACP was normal on D0 but decreased on D3; group 3, ACP decreased on D0 but was back to normal on D3; group 4, ACP on D0 and D3 both decreased. ACP = afterload-related cardiac performance (%), D0 = the time of admission, D3 = 48–72 h after admission.
(Fig. 5). While, the more ACP decreased on D3, the lower the survival rate was (Fig. 6).

Then, Cox model was run with ACP and variables that differ from baseline (C-reactive protein, central venous pressure, and lactate) as covariates. The results showed that ACP < 80% on D3 was independently associated with worse outcomes (hazard ratio [HR], 11.89; 95% CI, 1.30–108.33; P = .0028), but ACP on D0 was not. Additionally, the level of lactate was another independent risk factor for mortality (HR, 1.47; 95% CI, 1.08–2.00; P = .016), although the HR was not as high as that observed for ACP. While, the Cox model with ACP, CI, and CPI showed that ACP ≤ 80% on D0 (HR, 3.95; 95% CI, 1.24–12.64; P = .02) and D3 (HR, 31.10; 95% CI, 4.03–240.06; P = .001) were both independently associated with worse outcomes, but CI and CPI were not.

Figure 5. Kaplan–Meier estimates of 28-day survival rate in patients with sepsis. According to the grade of ACP at the time of admission: group 1, normal ACP (ACP > 80%); group 2, slight decline (60% < ACP ≤ 80%); group 3, moderate decline (40% < ACP ≤ 60%). ACP = afterload-related cardiac performance (%).

Figure 6. Kaplan–Meier estimates of 28-day survival rate in patients with sepsis. According to the grade of ACP on the third day after admission: group 1, normal ACP (ACP > 80%); group 2, slight decline (60% < ACP ≤ 80%); group 3, moderate decline (40% < ACP ≤ 60%). ACP = afterload-related cardiac performance (%).
4. Discussion

There is solid evidence that septic cardiomyopathy is a relevant contributor to organ dysfunction and worse outcomes in sepsis and septic shock.\cite{16,17} Beesley et al\cite{18} summarized relevant studies that myocardial dysfunction was prevalent in patients with sepsis. However, how to early detect and best quantify the severity of septic cardiomyopathy is still an unresolved problem. Although traditional cardiac parameters, such as CO, CI, and CPI, have been useful tools to identify myocardial dysfunction, they may overestimate the heart function because the reduced SVR may lead to a seemingly "normal" CO in septic patients. The parameter "ACP" could provide methods to improve accuracy and better quantify septic-induced cardiomyopathy.\cite{9,10,15}

Hence, the aim of this study was to investigate whether ACP is a useful tool to recognize myocardial dysfunction at an early stage and predict the prognosis of septic patients in the ICU.

In this study, it was observed that ACP in non-survivors was significantly lower than in survivors at the time of admission. CPI got the same result, but the levels of CO and CI were no different between survivors and non-survivors. The results suggest that septic patients with poor prognosis had cardiac dysfunction at an early stage, and ACP and CPI were better than CO and CI in evaluating the severity of disease and predicting poor prognosis. Consistently, it has been shown that CPI has the potential to define myocardial injury and predict outcomes in patients with different heart diseases, including cardiogenic shock, heart failure, and heart transplantation.\cite{20-22} A recent study reported that myocardial injury already existed in early stage in patients with community-acquired sepsis, and the prognosis of septic patients with cardiac dysfunction was poor.\cite{10} Different with previous studies, cardiac parameters were measured non-invasively by critical care ultrasound in the present study. Sekiguchi et al's\cite{21} study showed that due to a lack of cardiac ultrasound information, the initial assessment of cardiac function in patients with sepsis in intensive care units was limited, resulting in the hidden heart abnormalities to go undetected and untreated in time. Critical care ultrasound, due to its being non-invasive, real-time, and repeatable, has been an essential component of intensive care practice.\cite{24,25}

In order to verify the value of ACP in the severity of disease in patients with sepsis, we further analyzed the correlation between ACP and critical illness scores, including the APACHE II score and the SOFA score. APACHE II was proposed in 1985\cite{13} and is an improved version of the APACHE I score.\cite{26} Nowadays, it is the most common scoring tool used for critically ill patients. It makes a quantitative evaluation of the patient's condition in order to predict the prognosis. The higher the score is, the worse the prognosis will be. Studies have shown that the SOFA score has a good predictive ability for organ failure and mortality in septic patients admitted to ICU.\cite{12} Sepsis-3.0 guidelines indicated that a SOFA score higher than 2 or at least 2 points higher than the known baseline level were used as the diagnostic criteria for sepsis.\cite{1} In conclusion, both of the 2 scores can objectively reflect the severity of sepsis and evaluate the prognosis. In accordance with the above views, the population characteristics in this study showed that APACHE II and SOFA scores in non-survivors were significantly higher than in survivors. We found that ACP and CPI were negatively correlated with APACHE II and SOFA scores from the time of admission to the third day, although the correlation coefficients of CPI were not as high as seen for ACP. While, CO and CI showed poor correlation until the third day of admission. Consistent with our view, Werdan et al\cite{9} reported in 2011 that ACP shows a stronger correlation with APACHE II and sepsis scores than CO, CI, CPO, or CPI in septic MODS patients. Our study added the SOFA score and expanded the population to all critical ill patients with sepsis, not only septic MODS patients, the evidence further clarified that ACP was better than CO, CI, or CPI in evaluating the severity of disease in the early stage of sepsis.

ROC curve was used to assess the prognostic value of ACP for predicting 28-day mortality. The results showed that ACP had no advantage for predicting 28-day mortality at the time of admission. Until the third day of admission, the AUC area predicted by ACP for 28-day mortality was as high as 0.976, which was significantly higher than other parameters. In contrast, an investigation by Wilhelm et al\cite{10} on 141 septic patients in emergency department revealed that ACP was the only hemodynamic parameter predicting mortality, with a significantly higher AUC value than CPI at the time of admission. Although ACP with a similar AUC value (0.72 in Wilhelm et al study vs 0.775 in our study) at the time of admission in these 2 studies, but its predicting value was no better than CI and CPI in our study. We presume that this discrepancy might be attributed to the different populations and measurement methods. In details, the population in the study by Wilhelm et al\cite{10} was community-acquired sepsis admitted to the emergency department, and values were taken from pulse contour cardiac output technology, pulmonary artery catheter, or transthoracic bioimpedance analysis. While, the population in our study was hospital acquired sepsis admitted to ICU, and values were taken from critical care ultrasound.

In our study, a vast majority of the surviving patients had a normal ACP (70%) or slight cardiac impairment (26%) at the time of admission, and cardiac impairment was improved on the third day after admission. Conversely, over half of non-surviving patients had a slight decrease in ACP that was present at the time of admission, and the cardiac impairment worsened as ACP drastically reduced on the third day after admission. The decrease in ACP on the third day may be more useful than the initial measurement to identify patients at a higher risk for a worse outcome. As expected, multivariate Cox regression model showed that ACP at the third day was an independent risk factor for mortality, but ACP at the time of admission was not. C-reactive protein, central venous pressure, and lactate were selected into the Cox regression model, because the 3 factors had different baseline characteristics between survivors and non-survivors. We also found lactate was an independent risk factor for mortality. It is known that increased lactate levels are associated with worse outcomes.\cite{28-30} These results revealed that ACP is a helpful tool to quantify the severity of myocardial dysfunction at the early stage of sepsis and has a highly prognostic value for mortality on the third day of admission. The dynamic change of ACP during the first 3 days may be more useful, so that repetitive daily measurements of ACP were necessary for diagnosis and future treatment of sepsis in the ICU.

There are several limitations of this study. First, the number of patients in this study was rather small. Therefore, data need to be reproduced in a multisample research. Second, except for CO, other values including SVR, ACP, and CPI cannot be determined independently, and must be calculated by CO, MAP, and CVP. Therefore, any deviation of any parameter would affect the accuracy of the data. In addition, a number of septic patients who with tracheal intubation or more comorbidities usually have poor acoustic windows. Third, ACP formula has multiple clinical
derivatives that has to be calculated, which limits its practical applications in the clinical arena. Fourth, most patients in this study were postoperative patients with sepsis, who do not represent all septic patients. Therefore, we have initiated a study containing larger sample and diversified patients with sepsis in the ICU in a similar manner as described here.

5. Conclusion

In summary, our results show that cardiac function is impaired in patients with early stage of sepsis. ACP is a useful tool to evaluate myocardial dysfunction in septic patients, and it shows stronger negative correlations with APACHE II and SOFA scores than CO, CI, and CPI. Additionally, ACP has a higher predictive value for 28-day mortality than these traditional cardiac parameters, especially the continuous decline of ACP. Furthermore, we first observed that the decrease in ACP at the third day after admission was an independent risk factor for 28-day mortality in patients with sepsis in the ICU. Our findings suggest that compared with survivors, non-survivors have a higher degree and longer duration of cardiac function impairment. In addition, critical care ultrasound plays an important role in assessing myocardial depression in sepsis.

Author contributions

Conceptualization: Li-Xia Liu, Zhen-Jie Hu.
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