Prognostic Accuracy of the Afterload-related Cardiac Performance for 7-day Mortality Among Critical Ill Patients With Septic Shock

Wei-yan Chen
Southern Medical University
Li-li Tao
Guangzhou Medical University Second Affiliated Hospital
Qi Xu
Guangzhou Medical University Second Affiliated Hospital
Xing Wei
Guangzhou Medical University Second Affiliated Hospital
Min-sheng Chen (minshengsmu@163.com)
Zhujiang Hospital, Southern Medical University https://orcid.org/0000-0002-8271-268X

Research

Keywords: afterload-related cardiac performance, septic cardiomyopathy, mortality, cardiac index, left ventricle ejection fraction

Posted Date: September 21st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-76639/v1

Abstract

Background

Septic patients with cardiac impairment are with high mortality. Afterload-related cardiac performance (ACP), as a new tool for diagnostic septic cardiomyopathy (SCM), still needs to be evaluated its impact on the prognosis for patients with septic shock.

Methods

In this observational retrospective study, 119 patients with septic shock undertaken PiCCO monitoring were evaluated for the effects of ACP on 7-day mortality, ICU mortality and hospital mortality. The ability of ACP, cardiac index (CI) and left ventricular ejection fraction (LVEF) to discriminate between survivors and non-survivors was tested by comparing the area under the receiver operating characteristic curve (AUROC) analysis. Multivariable logistic regression and Cox proportional hazards regression analyses were performed to assess the associations of ACP with 7-day mortality. Curve estimation was used to describe the relationship between hazard ratio (HR) of death and ACP.

Results

ACP assessed at 12 hours (ACP12h) after septic shock [AUROC 0.86 (95% CI 0.79 to 0.93), $P < 0.001$] demonstrated significantly greater discrimination for 7-day mortality than CI [AUROC 0.67 (95% CI 0.57 to 0.78), $P = 0.001$] and LVEF [AUROC 0.53 (95% CI 0.43 to 0.64), $P = 0.58$] (all $P < 0.001$). Similarly, when adjusted with gender, APACHEII score, VIS and MAP as possible confounders, ACP12h still outperformed both CI12h and LVEF for discrimination of 7-day mortality (both $P < 0.001$). The superior discriminatory performance of ACP12h over both CI12h and LVEF was further maintained when considering ICU mortality and hospital mortality when considered in isolation or adjusted with the baseline prediction. Compared with normal ACP, HR for slight, moderate and severe impairment were 4.84 (1.96 to 11.96), 12.13 (4.83 to 30.43) and 32.70 (7.76 to 137.86), respectively. After adjustment for risk factor, decrease ACP still associated with increasing 7-day mortality ($P = 0.001$). Exponential relationship was observed between ACP12h and HR of 7-day death.

Conclusions

Our results suggested that ACP may serve as a new tool for diagnosing SCM. In addition, the assessment of ACP at 12 hours after septic shock in ICU significantly improves 7-day mortality, ICU mortality and hospital mortality predictions when compared to CI and LVEF.

Background

Sepsis is caused by a dysregulated host response to infection, which leads to life-threatening organ dysfunction(1). The heart is one of the most frequently affected organs. It has been known for years that severe impairment of cardiac function was not only one of the leading causes of septic shock, but also

contributes to mortality in intensive care unit (ICU)(2). However, septic cardiomyopathy (SCM) was difficult to define because of its limited means of diagnosis and inconsistent criteria in the last few decades. As a result, it was recognized only when obvious cardiac dysfunction was present in clinic. The prevalence reported varies from 10% to 70%(3, 4). The mechanism of SCM and its influence on prognosis are also not well understood.

Efficacy diagnostic methods and accurate diagnostic criteria have an important role in critical ill patients with septic shock, providing tools for research, performance monitoring, and therapy exploration. Many attempts have been made to early recognized and quantify the severity of SCM, for example left ventricular ejection fraction (LVEF), cardiac index (CI), myocardial performance index (MPI), and others. Nevertheless, “the impaired cardiac function” in septic patients is often masked by the severe reduction of afterload, which leads to a compensatory increase of cardiac output (CO) and LVEF. Several studies reported that when SCM was defined by echocardiography, LVEF was not associated with in-hospital and 30-d mortality in patients with sepsis or septic shock(5-7). In a meta-analysis, there were no significant differences in LVEF, right ventricular ejection fractions, and right ventricular dimensions between the survivor and non-survivor groups(8). Su et al demonstrated that only low CI combined with high stroke volume variation increased mortality(9). Accordingly, LVEF and CI are not ideal indicators for SCM.

In recent years, the strain measured by speckle tracking technique (STT) is considered less susceptible to changes in pre- or afterload. In a multi-center prospective cohort study, Chang et al demonstrated that global longitudinal strain was an independent prognostic indicator of ICU mortality(10). However, STT still carries a disadvantage of being a discontinuous measurement. The process of SCM is still unclear. When to take the STT is indeed an important problem that complicates the investigators. The afterload-related cardiac performance (ACP), first introduced by Werdan et al. in 2011(11), is a ratio of measured to predicted cardiac output, adjusted for systemic vascular resistance (SVR). These measures are obtained from an indicator-dilution or pulse contour analytic cardiac output monitoring device. It proposes an option for a more relevant continuous monitoring of cardiac performance than is currently available. It is reported that ACP correlated well with 30-day mortality when calculated on admission in patients with community-acquired sepsis(12). ACP may be a potential effective means for SCM diagnosis, but still need more studies to reveal the relationship between ACP and SCM.

The primary aims of this study were to assess the effect of a decrease in ACP within the first 24 hours of septic shock in discriminating against 7-day mortality, ICU mortality or hospital mortality.

Methods

Setting

This was a retrospective cohort study, approved by the Second Affiliated Hospital of Guangzhou Medical University Clinical Research and Application Institutional Review Board in Guangzhou, China. The Second Affiliated Hospital of Guangzhou Medical University is a tertiary hospital with a 32-bed multidisciplinary

ICU. The ICU has an electronic patient record system where most of the data is recorded at the time of generation.

Patients and study design

Adult patients (aged ≥ 18 years) undertaken pulse indicator continuous cardiac output technology (PiCCO^{R}, Pulsion, Munich, Germany) in the first 24-hour time period of septic shock during his/her stay in ICU between June 2016 and June 2019 were screened for study inclusion. Septic shock was defined as a subset of sepsis and clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolemia (sepsis-3)(1). Patients were excluded if they met one of the following criteria: (1) repeat ICU admissions from the same hospital episode; (2) previous history of significant underlying cardiac conditions, such as ischemic cardiac disease, congenital heart disease, severe valvular heart disease, and cardiomyopathy; (3) active diagnoses directly relating to myocardial dysfunction, such as acute myocardial infarction, myocarditis, myocardial effusion, unstable arrhythmia, and post-cardiopulmonary resuscitation status.

In our ICU, parameters estimated by PiCCO were measured and recorded every 6 hours. MAP was monitored continuously and recorded hourly.

Data collection

We extracted the following data: demographics, chronic co-morbidities [coronary heart disease (CHD), chronic kidney disease (CKD), diabetes, hypertension], Acute Physiology and Chronic Health Evaluation (APACHE) II score, Vasoactive Inotropic Score (VIS) [VIS = 100 × norepinephrine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 10 × milrinone (ng/kg/min) + 1 × dopamine (μg/kg/min) + 1 × dobutamine (μg/kg/min)], white blood cell (WBC) counts, serum procalcitonin (PCT) and Lactate levels on the first day of septic shock, LVEF estimated by transthoracic echocardiography within 48 hours of septic shock. Focus of infection attributed to septic shock was collected. We also extracted data on the type of organ support, for example, the application of mechanical ventilation and continuous renal replacement therapy (CRRT). CO, CI, central venous pressure (CVP) and MAP was collected at 0h, 6h, 12h, 18h and 24h after PiCCO monitoring. Survival status on day 7 after septic shock, ICU and hospital discharge were collected. ICU length to stay (LOS), hospital LOS and LOS of 7 days after septic shock were also collected.

Afterload-related cardiac performance (ACP)

ACP is described as $CO_{measured}/CO_{predicted\ as\ normal} \times 100$. It was calculated using the formula previously described by Werdan et al.(11): ACP (%) = 100 × CO/[560.68 × ((MAP - CVP) × 80/CO)$^{-0.645}$]. ACP was classified as normal (> 80%), slight impairment (60% ~ 80%), moderate impairment (40% ~ 60%) and severe impairment (< 40%), respectively.

Outcomes

The primary study outcome was to explore the prognostic accuracy of ACP, CI and LVEF for 7-day mortality among critical ill patients with septic shock. The secondary study outcomes included ICU mortality and in-hospital mortality.

Statistical analysis

Continuous variables with normal distribution were summarized as mean and standard deviation (SD), otherwise median and inter-quartile range (IQR, 25^{th} percentile to 75^{th} percentile). Normal distribution was tested by Kolmogorov-Smirnov test. Categorical variables were described as frequencies or percentages. Group comparisons were conducted using Fisher's exact tests for equal proportions, *t* tests for normally distributed data, and Mann-Whitney's *U* tests otherwise. The ability of ACP, CI and LVEF to discriminate between survivors and non-survivors was tested by comparing the area under the receiver operating characteristic curve (AUROC) analysis (unadjusted analysis) and adjusted with a baseline risk model (adjusted analysis). Specific AUROC (95% CI) values were generated. The cut-off value was defined by the maximum of the sum of sensitivity and specificity.

To further assess the associations of ACP with 7-day mortality, multivariable logistic regression and Cox proportional hazards regression analyses were performed. Scatter diagram was drawn and curve estimation was used to describe the relationship between hazards ratio of death and ACP.

A two-tailed p value < 0.05 was set as statistically significant. All analyses were performed using SPSS 22.0 and R. software version 4.0.2.

Results

1. **Demographic data and main measurements of patients with septic shock**

Between June 2016 and June 2019, 412 patients were undertaken PiCCO in the ICU; 216 patients did not have septic shock and 77 patients met one of exclusion criteria (Fig. 1). Among this cohort, 72 (60.5%) patients had low ACP within the first 24 hours of septic shock, of which 45 (37.8%) patients were slightly impaired, 24 (20.2%) patients were moderately impaired and 3 (2.5%) were severely impaired. The majority of patients with moderately to severely myocardial impaired (88.9%) died 7 days after septic shock and all died in hospital. While patients with normal ACP only had low mortality (12.8%) 7 days after septic shock. (Figure S1, Table S1). Only 15 (12.61%) patients had abnormal LVEF and 55 (46.22%) patients had low CI.

Patients who died 7 days after septic shock were characterized by a significantly higher APACHEII score, higher VIS and higher level of serum lactate within the first 24 hours of septic shock, and greater need for CRRT compared to patients who survived. Non-survivors had lower ACP values measured within the first 24 hours after septic shock [0h, 6h, 12h, 18h, 24h and the minimum value (ACPmin)]. While only CI measured at 12h and 18h after septic shock were significantly lower in non-survivors. There was no difference in LVEF between survivors and non-survivors. (Table 1).

Table 1 Demographic data and main measurements among septic shock patients.

	All (N=119)	7-day survivors (n=67)	7-day Non-survivors (n=52)	*P*-value
Demographics				
Age, mean (SD), y	66.8 (15.4)	64.7 (15.2)	69.4 (15.3)	0.101
Male, No. (%)	73 (61.3)	38 (56.7)	35 (67.3)	0.241
Severity of illness on the beginning of septic shock				
APACHEII score, mean (SD)	24.4 (9.4)	21.7 (8.1)	27.9 (9.9)	< 0.001
VIS, median (IQR)	111.4 (29.8-189.8)	57.7 (3.1-129.0)	161.6 (110.6-263.6)	< 0.001
Vital signs, mean (SD)				
MAP, mmHg	81.0 (29.5)	80.4 (29.7)	81.8 (29.6)	0.787
HR, beat/min	37.0 (2.7)	37.1 (2.6)	36.9 (2.8)	0.605
Body temperature, ℃	116.6 (27.9)	116.9 (28.8)	116.2 (27.0)	0.898
Focus of infection, NO. (%)				
Bloodstream infection	22 (18.5)	12 (17.9)	10 (19.2)	1.00
Pulmonary infection	48 (40.3)	28 (41.8)	20 (38.5)	0.851
Abdominal infection	24 (20.2)	16 (23.9)	8 (15.4)	0.357
Urinary infection	3 (2.5)	3 (4.5)	0 (0)	0.256
Infection of biliary tract	8 (6.7)	3 (4.5)	5 (9.6)	0.295
Skin soft-tissue infection	3 (2.5)	0 (0)	3 (5.8)	0.081
Other	11 (9.2)	5 (7.5)	6 (11.5)	0.531
Medical history and combined therapy, No. (%)				
CHD	18 (15.1)	9 (13.4)	9 (17.3)	0.612
CKD	14 (11.8)	6 (9.0)	8 (15.4)	0.28
Diabetics	12 (10.1)	7 (10.5)	5 (9.6)	0.881
Hypertension	12 (10.1)	6 (9.0)	6 (11.5)	0.643
Combined therapy, No. (%)				
Mechanical ventilation	114 (95.8)	62 (92.5)	52 (100.0)	0.067
CRRT	72 (60.5)	31 (46.3)	41 (78.9)	< 0.001

Outcomes				
ICU mortality, No. (%)	75 (63.0)	24 (36.9)	51 (94.4)	< 0.001
ICU LOS, median (IQR), d	8.0 (3.0-17.0)	13.0 (7.0-24.0)	4.0 (2.0-7.8)	< 0.001
Hospital mortality, No. (%)	78 (65.6)	26 (40.0)	52 (96.3)	< 0.001
Hospital LOS, median (IQR), d	17.0 (8.0-30.0)	25.0 (16.0-40.0)	8.0 (3.0-15.5)	< 0.001
ACP assessed at different time, mean (SD), %				
ACP0h (n=119)	76.3 (18.4)	81.0 (15.2)	70.2 (20.4)	0.001
ACP6h (n=116)	75.4 (19.1)	82.3 (18.2)	65.9 (16.0)	<0.001
ACP12h (n=110)	76.4 (18.8)	84.5 (16.7)	63.8 (14.4)	<0.001
ACP18h (n=101)	77.8 (23.5)	83.3 (17.3)	68.7 (29.2)	0.002
ACP24h (n=91)	80.9 (17.0)	86.3 (14.6)	68.7 (15.9)	<0.001
ACP_{min} (n=119)	63.3 (15.9)	71.0 (12.2)	53.4 (14.8)	<0.001
CI assessed at different time, mean (SD), L/min/m^2				
CI0h (n=119)	3.1 (1.3)	3.2 (1.1)	2.9 (1.5)	0.147
CI6h (n=116)	3.2 (1.7)	3.4 (1.9)	2.8 (1.2)	0.055
CI12h (n=110)	3.2 (1.4)	3.4 (1.4)	2.8 (1.3)	0.019
CI18h (n=103)	3.2 (1.6)	3.5 (1.7)	2.7 (1.3)	0.018
CI24h (n=91)	3.4 (1.4)	3.5 (1.5)	3.2 (1.4)	0.298
CI_{min} (n=119)	2.5 (1.1)	2.7 (0.9)	2.2 (1.2)	0.017
LVEF, mean (SD), %				
LVEF (n=91)	59.3 (8.5)	59.9 (8.4)	58.1 (8.6)	0.322
Laboratory test				
WBC, mean (SD), $\times 10^9$/L	15.9 (16.1)	15.8 (15.8)	15.9 (16.5)	0.967
PCT, mean (SD), ng/ml	41.9 (53.9)	39.6 (49.6)	44.9 (59.4)	0.595
Lactate, mean (SD), mmol/L	7.9 (6.3)	5.3 (3.8)	11.1 (7.3)	<0.001

2. **Prognostic predictive value of ACP, CI and LVEF.**

In order to find out ACP measured at which time point had the best prognostic predictive value, crude AUROCs at each time point within the first 24 hours of septic shock were calculated (Table 2). Assuming that data was missing because of death, missing data was imputed via the data from the closest time point (Figure S2). It is found that ACP assessed at 12 hours (ACP12h) had the highest AUROC. Although ACP24h had the same AUROC as ACP12h after missing data was imputed, ACP12h was more valuable for predicting the prognosis because it could predict the prognosis earlier and had less missing data.

Table 2 Discriminative abilities of ACP assessed at different time point

	ACP0h (n=119)	ACP6h (n=116)	ACP12h (n=110)	ACP18h (n=103)	ACP24h (n=91)	ACP_{min} (n=119)
7-day mortality						
Crude AUROC (95% CI)	0.67 (0.57-0.77)	0.76 (0.68-0.85)	0.84 (0.77-0.92)	0.79 (0.70-0.89)	0.80 (0.70-0.90)	0.82 (0.74-0.90)
Imputation for missing data	–	0.78 (0.69-0.86)	0.86 (0.79-0.93)	0.83 (0.75-0.91)	0.86 (0.80-0.93)	–
ICU mortality						
Crude AUROC (95% CI)	0.59 (0.49-0.70)	0.68 (0.58-0.78)	0.74 (0.65-0.83)	0.65 (0.54-0.75)	0.69 (0.59-0.80)	0.71 (0.61-0.80)
Imputation for missing data	–	0.69 (0.60-0.79)	0.76 (0.68-0.85)	0.70 (0.60-0.79)	0.76 (0.68-0.85)	–
Hospital mortality						
Crude AUROC (95% CI)	0.61 (0.51-0.71)	0.68 (0.59-0.78)	0.74 (0.65-0.83)	0.65 (0.55-0.76)	0.69 (0.58-0.80)	0.72 (0.63-0.81)
Imputation for missing data	–	0.70 (0.60-0.79)	0.76 (0.68-0.85)	0.70 (0.61-0.79)	0.76 (0.68-0.85)	–

Discrimination of 7-day mortality after septic shock was significantly higher using ACP12h than either CI12h or LVEF with incremental differences between ACP12h and CI12h, ACP12h and LVEF being statistically significant (both $P < 0.001$) (Table 3, Figure 2A). LVEF did not show significant AUROC value. With a cut-off value of 70.51% or below, ACP12h predicted non-survival with a sensitivity of 75%, a

specificity of 85.1%, a positive predictive value (PPV) of 79.59%, a negative predictive value (NPV) of 81.43%, and accuracy of 80.67%. With a cut-off value of 2.5L/min/m^2 or below, CI12h predicted non-survival with a sensitivity of 52%, a specificity of 94%, a PPV of 87.10%, a NPV of 71.59%, and accuracy of 75.63%. Similarly, when adjusted with gender ($P = 0.15$), APACHEII score ($P < 0.004$), VIS ($P < 0.001$) and MAP ($P = 0.02$) as possible confounders (Table S2), ACP12h still outperformed both CI12h and LVEF for discrimination of 7-day mortality of septic shock with incremental differences between ACP12h and CI12h, ACP12h and LVEF being statistically significant (both $P < 0.001$) (Table 3, Figure 2B).

The superior discriminatory performance of ACP12h over both CI12h and LVEF was further maintained when considering the secondary outcomes of ICU mortality and hospital mortality when considered in isolation or adjusted with the baseline prediction (Table 3, Figure 2C-F, Table S3 and S4).

Table 3 Crude and adjusted AUROCs for discrimination characteristics of ACP, CI, and LVEF among patients with septic shock (n = 119).

	ACP12h	CI12h	LVEF	Between, group difference		
				ACP12h vs. CI12h	ACP12h vs. LVEF	CI12h vs. LVEF
7-day mortality						
Crude AUROC (95% CI)	0.86 (0.79-0.93)	0.67 (0.57-0.78)	0.53 (0.43-0.64)	0.19 (0.07-0.31)	0.33 (0.21-0.45)	0.14 (0.00-0.28)
Cut-off (Spe, Se)	70.51 (0.85, 0.75)	2.50 (0.94, 0.52)	65.5 (0.89, 0.24)	--	--	--
P-value	<0.001	0.001	0.58	<0.001	<0.001	0.06
Adjusted AUROC (95% CI)[a]	0.80 (0.72-0.89)	0.62 (0.51-0.73)	0.53 (0.42-0.63)	0.18 (0.08-0.28)	0.27 (0.17-0.37)	0.09 (0.00-0.20)
P-value	<0.001	0.03	0.62	<0.001	<0.001	0.08
ICU mortality						
Crude AUROC (95% CI)	0.76 (0.68-0.85)	0.59 (0.49-0.69)	0.51 (0.40-0.62)	0.17 (0.08-0.26)	0.25 (0.15-0.35)	0.08 (0.00-0.19)
Cut-off (Spe, Se)	74.92 (0.82, 0.67)	2.50 (0.93, 0.37)	56.5 (0.32, 0.75	--	--	--
P-value	<0.001	0.11	0.83	<0.001	<0.001	0.22
Adjusted AUROC (95% CI)[b]	0.73 (0.64, 0.82)	0.59 (0.49, 0.69)	0.61 (0.51, 0.72)	0.14 (0.04, 0.24)	0.12 (0.02, 0.22)	-0.02 (-0.12, 0.00)
P-value	<0.001	0.09	0.04	0.004	0.11	0.80
Hospital mortality						
Crude AUROC (95% CI)	0.76 (0.68-0.85)	0.60 (0.50-0.70)	0.53 (0.42-0.64)	0.16 (0.07-0.25)	0.23 (0.13-0.33)	0.07 (0.00-0.18)
Cut-off (Spe, Se)	74.92 (0.83, 0.65)	2.50 (0.95, 0.37)	64.5 (0.73, 0.30)	--	--	--

P-value	<0.001	0.09	0.65	<0.001	<0.001	0.15
Adjusted AUROC (95% CI)[c]	0.76 (0.68-0.85)	0.65 (0.56-0.75)	0.47 (0.36-0.57)	0.11 (0.02-0.20)	0.29 (0.19-0.39)	0.18 (0.08-0.28)
P-value	<0.001	0.006	0.57	0.02	0.001	0.11

Abbreviation: Spe, specificity; Se, sensitivity; 95% CI: 95% confidence interval.

[a] The AUROC of the model to predict 7-day mortality using baseline risk factors (gender, APACHEII score, VIS and MAP) without ACP12h was 0.84 (95% CI, 0.77-0.91).

[b] The AUROC of the model to predict ICU mortality using baseline risk factors (gender, CRRT, APACHEII score, VIS and PCT) without ACP12h was 0.85 (95% CI, 0.78-0.92).

[c] The AUROC of the model to predict hospital mortality using baseline risk factors (gender, CRRT, APACHEII score, VIS and PCT) without ACP12h was 0.86 (95% CI, 0.80-0.93)

3. **Cox proportional hazards regression analyses of 7-day mortality according to ACP12h**

As a continuous variable, reduced HR of 7-day death was significantly associated with increased levels of ACP12h (table 4). Exponential relationship was observed between ACP12h and HR of 7-day death (Fig. 3A). After adjusting for age, gender and other risk factors (Table S5 and Table S6), reduced HR of 7-day death was still significantly associated with increased levels of ACP12h. Exponential relationship was also observed between ACP12h and HR of 7-day death (Fig. 3B).

We further analyzed ACP12h as a categorical variable in a cox model. Using patients with normal ACP as the reference group, HRs were 4.84 (1.96 to 11.96) for slight impairment, 12.13 (4.83 to 30.43) for moderate impairment and 32.70 (7.76 to 137.86) for severe impairment, respectively. The trend across classifications of ACP was significant ($P < 0.001$) (Fig. 4A). A similar finding was also observed for 7-day mortality regardless of HR adjusted for age, gender or combined with other risk factors (Fig. 4B, Table S7 and Table S8).

Table 4 Cox proportional hazards regression analyses of 7-day mortality according to ACP12h (n = 119).

Variable	Crude model	Minimally adjusted model	Fully adjusted model
Continuous variable, HR (95% CI)			
ACP12h	0.94 (0.92-0.96)	0.94 (0.92-0.95)	0.95 (0.93-0.97)
	P < 0.001	P < 0.001	P < 0.001
Classifications of ACP12h, HR (95% CI)			
normal	1.00	1.00	1.00
Slight impairment	4.84 (1.96-11.96)	5.40 (2.17-13.46)	5.01 (1.99-12.59)
	P = 0.001	P < 0.001	P = 0.001
Moderate impairment	12.13 (4.83-30.43)	13.92 (5.32-36.43)	7.12 (2.59-19.75)
	P < 0.001	P < 0.001	P < 0.001
Severe impairment	32.70 (7.76-137.86)	36.45 (8.60-154.57)	14.14 (3.07-65.11)
	P < 0.001	P < 0.001	P = 0.001
P for trend	<0.001	<0.001	0.001

Minimally adjusted model: age, gender;

Fully adjusted model: age, gender, APACHEII score, VIS, Lactate.

Discussion

In this retrospective study, the prevalence of SCM within the first 24 hours of septic shock reported as high as 60% through ACP assessment. In comparison with CI or LVEF, a decrease in ACP assessed at 12 hours after septic shock demonstrated superior prognostic accuracy for 7-day mortality, ICU mortality and hospital mortality among patients with septic shock in ICU. Furthermore, we found that decreased ACP levels were associated with increased HR of 7-day death. Exponential relationship was observed between ACP12h and HR of 7-day death.

Due to limited means and inconsistent criteria of SCM, the prevalence reported varies among studies(3, 6, 13). LVEF has been increasingly acknowledged to be a non-sensitive and non-specific predictor of mortality because of its dependent on pre- and afterload(6, 14-17). In our study, SCM was diagnosed by LVEF in only 12% of patients under past criteria. There was no difference between survivors and non-survivors. Therefore, it is not suitable to rely on a LVEF-based definition for SCM. CI has been proposed as helpful tools to detect impaired cardiac function in sepsis. Nevertheless, studies found that patients with septic shock often had a normal or elevated CI due to the decrease in SVR(9, 18). In recent years, more sophisticated techniques such as STT was proved to be an accurate marker of intrinsic cardiac function. Studies have found that 50~70% patients with septic shock undertaken STT had abnormal strain, which

was consistent with our studies(19-21). It is established that ACP is a more sensitive diagnostic method of SCM than CI and LVEF.

However, the optimal timing of ACP assessment remains a question. Previous studies had heterogeneous option on the diagnostic timing of SCM. In Lanspa et al.'s study(19), STT was obtained within 6 hours of ICU admit, and 60% of patients with severe sepsis or septic shock had abnormal strain. In Dalla et al's study(20), STT was obtained within 48 hours of ICU admit, and 50% of patients with severe sepsis or septic shock had preserved LVEF, but abnormal strain. Compared with STT, ACP has the advantage of continuous monitoring but the disadvantage of not accounting for preload. In our study, ACP assessed at 12 hours after septic shock had the best discrimination of 7-day mortality after septic shock. This might be related to the fact that ACP at this time point reflects the intrinsic cardiac function due to volume has been restored after adequate fluid resuscitation. To the best of our knowledge, this is the first study to compare different time points at assessing cardiac function by ACP in the patients with septic shock.

ACP has been demonstrated to be a useful predictor of 30-day mortality in patients with community-acquired sepsis(12). Our data showed that ACP was a better predictor for 7-day mortality, ICU mortality and hospital mortality than CI and LVEF. It established that the use of ACP to define SCM was an appropriate data-base starting point, and would likely have broad external validity in ICU patients with septic shock. Remarkably, the calculated cut-off value of ACP of 70% for predicting death within 7 days of septic shock, and 75% for predicting ICU and hospital mortality agrees well with the threshold proposed for SCM by Werdan et al(11). The high specificity of 94% and high PPV of 87.10% indicates that ACP might be especially useful to identify patients with an impaired cardiac function, which seem to have the worse prognosis for 7-day survival after septic shock. This study's finding confirmed that LVEF provided no additional predictive use for prognosis. Similar to the results of previous studies, CI had no additional predictive use for ICU mortality and hospital mortality, but only for 7-day mortality.

Wilhelm et al. revealed that patients with an ACP value above 80% had a significant higher survival rate(12). Our findings were consistent with previous findings demonstrating increased risk of death at 7-day after septic shock as patients with severe classification of ACP. Our findings showed that with an increase in ACP, the risk of death at 7-day decreased exponentially.

This study had a number of strengths. Continuous cardiac function within the first 24 hours of septic shock were assessed through ACP caculation. ACP values at 12 hours after septic shock were selected for prediction, overcoming the disadvantage that ACP could not account for preload. In addition, although the sample size was small, patients were strictly screened and missing data was imputed via the data from the closest time point, which improved the accuracy of the results. In our study, 7-day mortality which was selected as the early outcome could better reflect the predictive value of ACP, because the condition of patients in ICU was complex and SCM has the characteristics of 1~2 weeks recovery.

Limitations

Several limitations must be considered in our study. First, this was a small retrospective cohort study, limited factors could be studied. Second, our finding was based on data obtained from patients undertaken PiCCO monitoring, which might lead to selection bias. The third limitation was that the diagnostic accuracy of ACP for SCM still needs to be identified through golden standard.

Clinical perspective

There are few studies on ACP at present. ACP as a new diagnostic method of SCM has not yet been widely accepted. More large-scale studies are needed to provide evidence for this, particularly those that identify the diagnostic accuracy of ACP for cardiac function by comparison with the golden standard. Furthermore, ACP, as a continuous bedside monitoring indicatior, will be useful to explore the impact factors of SCM, investigate the occurrence and development of SCM, guide individual treatment, and ultimately improve outcome of septic shock.

Conclusion

In conclusion, our results suggest that the ACP may serve as a new tool for diagnosing SCM. In addition, the assessment of ACP at 12 hours after septic shock in ICU significantly improves 7-day mortality, ICU mortality and hospital mortality predictions when compared to CI and LVEF.

Abbreviations

ACP, afterload-related cardiac performance; SCM, septic cardiomyopathy; CI, cardiac index; LVEF, left ventricular ejection fraction; AUROC, area under the receiver operating characteristic curve; HR, hazard ratio; ICU, intensive care unit; CO, cardiac output; STT, speckle tracking technique; SVR, systemic vascular resistance; PiCCO, pulse indicator continuous cardiac output technology; MAP, mean arterial pressure; CHD, coronary heart disease; CKD, chronic kidney disease; APACHEII, Acute Physiology and Chronic Health Evaluation; VIS, vasoactive inotropic score; PCT, procalcitonin; WBC, white blood cell; CRRT, continuous renal replacement therapy; CVP, central venous pressure; LOS, length of stay; SD, standard deviation; PPV, positive predictive value; NPV, negative predictive value;

Declarations

Acknowlegements

None.

Funding

This study was partly supported by the New Technology, New business Clinical Research and Application Fund from the Second Affiliated Hospital of Guangzhou Medical University (No: 2018-XJS-E-05).

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Min-sheng Chen help develop the study design and oversaw the project, including data collection, data analysis, interpretation of the results, revise and approved the manuscript for publication. Wei-yan Chen develop the study design, analyzed the data, and draft the manuscript. Li-li tao, Qi Xu and Xing Wei contributed to the data collection and interpretation of the results. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Second Affiliated Hospital of Guangzhou Medical University Clinical Research and Application Institutional Review Board in Guangzhou, China. Need for individual informed consent was waived as this was a retrospective analysis of data collected prospectively for routine care, and there was no breach of privacy or anonymity.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Cardiology, Heart Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China. [2]Intensive Care Unit, the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. [3]Guangdong Provincial Biomedical Engineering Technology Research Center for Cardiovascular Disease, Guangzhou, China. [4]Sino-Japanese Cooperation Platform for Translational Research in Heart Failure, Guangzhou, China. [5]Laboratory of Heart Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 2016-02-23;315(8):801.
2. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. CURR OPIN CRIT CARE. [Journal Article; Review]. 2009 2009-10-01;15(5):392-7.

3. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, et al. Septic Cardiomyopathy. CRIT CARE MED. 2018;46(4):625-34.
4. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. CRIT CARE MED. [Journal Article]. 2008 2008-06-01;36(6):1701-6.
5. Etchecopar-Chevreuil C, François B, Clavel M, Pichon N, Gastinne H, Vignon P. Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. INTENS CARE MED. 2008;34(2):250-6.
6. Sato R, Kuriyama A, Takada T, Nasu M, Luthe SK. Prevalence and risk factors of sepsis-induced cardiomyopathy: A retrospective cohort study. MEDICINE. 2016;95(39):e5031.
7. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, et al. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. MAYO CLIN PROC. 2012;87(7):620-8.
8. Huang SJ, Nalos M, McLean AS. Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis. CRIT CARE. [Journal Article; Meta-Analysis]. 2013 2013-05-27;17(3):R96.
9. Su W, Shui H, Lan C, Yang M, Hsieh C, Jang S, et al. Cardiovascular Parameters Associated With Troponin I as Indicators for 14-Day Mortality in Patients With Septic Shock. The American journal of the medical sciences. 2018;356(3):244-53.
10. Chang WT, Lee WH, Lee WT, Chen PS, Su YR, Liu PY, et al. Left ventricular global longitudinal strain is independently associated with mortality in septic shock patients. Intensive Care Med. [Journal Article; Research Support, Non-U.S. Gov't]. 2015 2015-10-01;41(10):1791-9.
11. Werdan K, Oelke A, Hettwer S, Nuding S, Bubel S, Hoke R, et al. Septic cardiomyopathy: hemodynamic quantification, occurrence, and prognostic implications. CLIN RES CARDIOL. [Journal Article]. 2011 2011-08-01;100(8):661-8.
12. Wilhelm J, Hettwer S, Schuermann M, Bagger S, Gerhardt F, Mundt S, et al. Severity of cardiac impairment in the early stage of community-acquired sepsis determines worse prognosis. CLIN RES CARDIOL. 2013;102(10):735-44.
13. Ehrman RR, Sullivan AN, Favot MJ, Sherwin RL, Reynolds CA, Abidov A, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. CRIT CARE. 2018;22(1).
14. Endo T, Kushimoto S, Yamanouchi S, Sakamoto T, Ishikura H, Kitazawa Y, et al. Limitations of global end-diastolic volume index as a parameter of cardiac preload in the early phase of severe sepsis: a subgroup analysis of a multicenter, prospective observational study. Journal of intensive care. 2013;1(1):11.
15. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. CRIT CARE MED. 2008;36(6):1701-6.

16. Ng PY, Sin WC, Ng AK, Chan WM. Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). CRIT CARE. [Controlled Clinical Trial; Journal Article]. 2016 2016-05-14;20(1):145.
17. Palmieri V, Innocenti F, Guzzo A, Guerrini E, Vignaroli D, Pini R. Left Ventricular Systolic Longitudinal Function as Predictor of Outcome in Patients With Sepsis. Circulation. Cardiovascular imaging. 2015;8(11):e3865, e3865.
18. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. ANN INTERN MED. [Journal Article]. 1984 1984-04-01;100(4):483-90.
19. Lanspa MJ, Pittman JE, Hirshberg EL, Wilson EL, Olsen T, Brown SM, et al. Association of left ventricular longitudinal strain with central venous oxygen saturation and serum lactate in patients with early severe sepsis and septic shock. Critical care (London, England). 2015;19(1):304.
20. Dalla K, Hallman C, Bech-Hanssen O, Haney M, Ricksten S. Strain echocardiography identifies impaired longitudinal systolic function in patients with septic shock and preserved ejection fraction. CARDIOVASC ULTRASOUN. 2015;13:30.
21. Orde SR, Pulido JN, Masaki M, Gillespie S, Spoon JN, Kane GC, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. Critical care (London, England). 2014;18(4):R149.

Figures

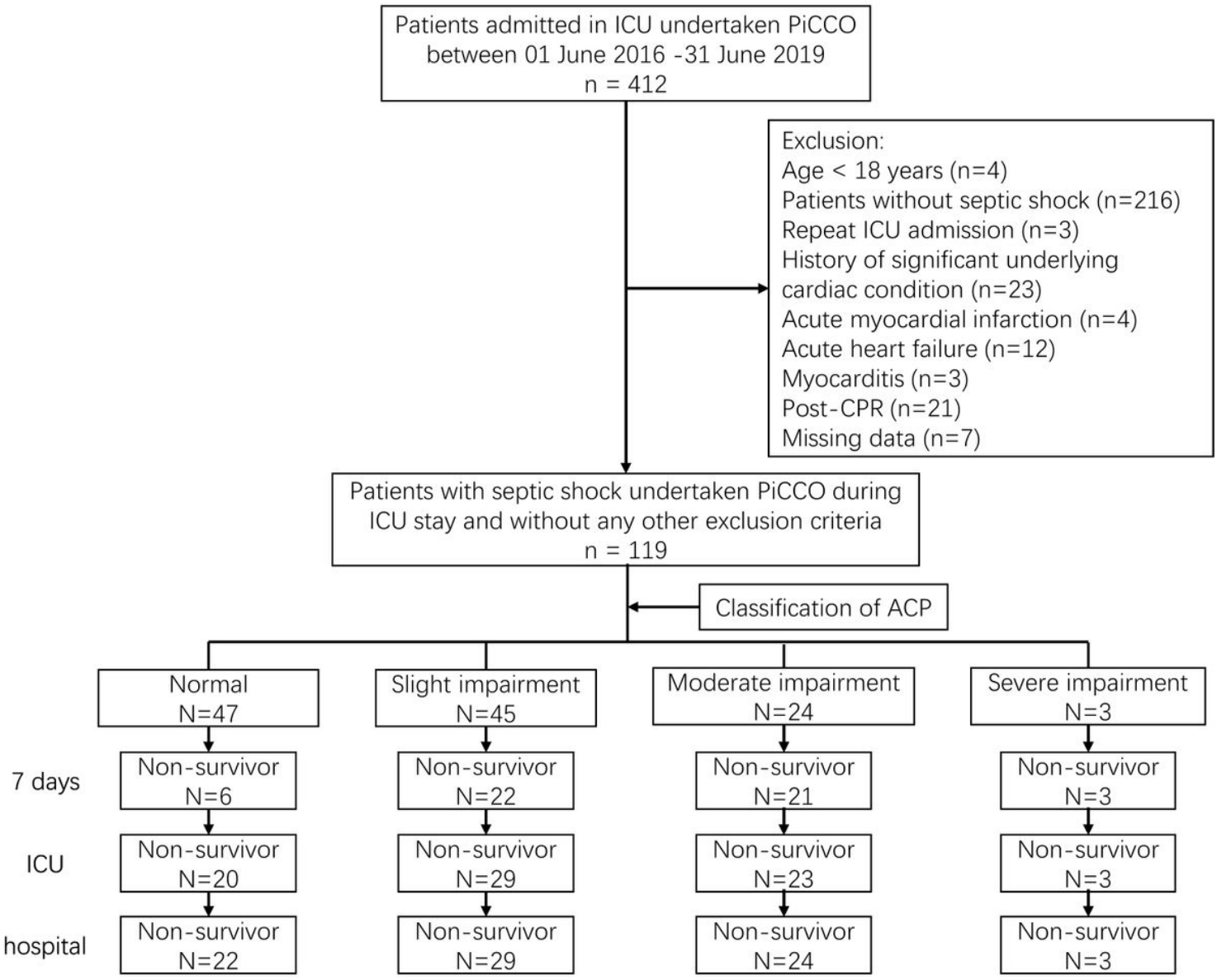

Figure 1

Patient flow chart. ICU, intensive care unit; PiCCO, pulse indicator continuous cardiac output technology; CPR, cardiopulmonary resuscitation; ACP, afterload-related cardiac performance;

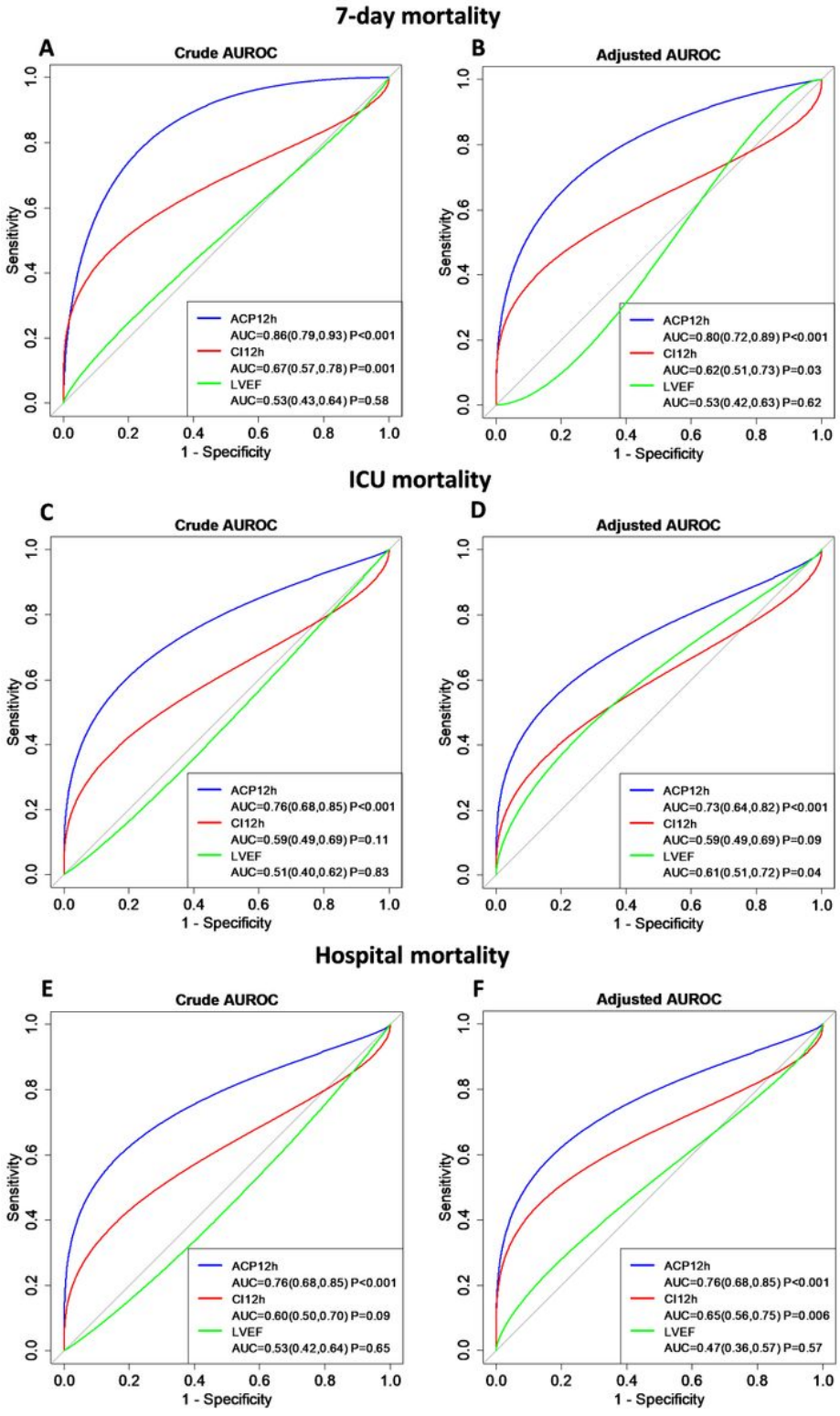

Figure 2

Area under the receiver operating characteristic curves (AUROCs) for 7d mortality, ICU mortality or hospital mortality for ACP, CI, and LVEF.

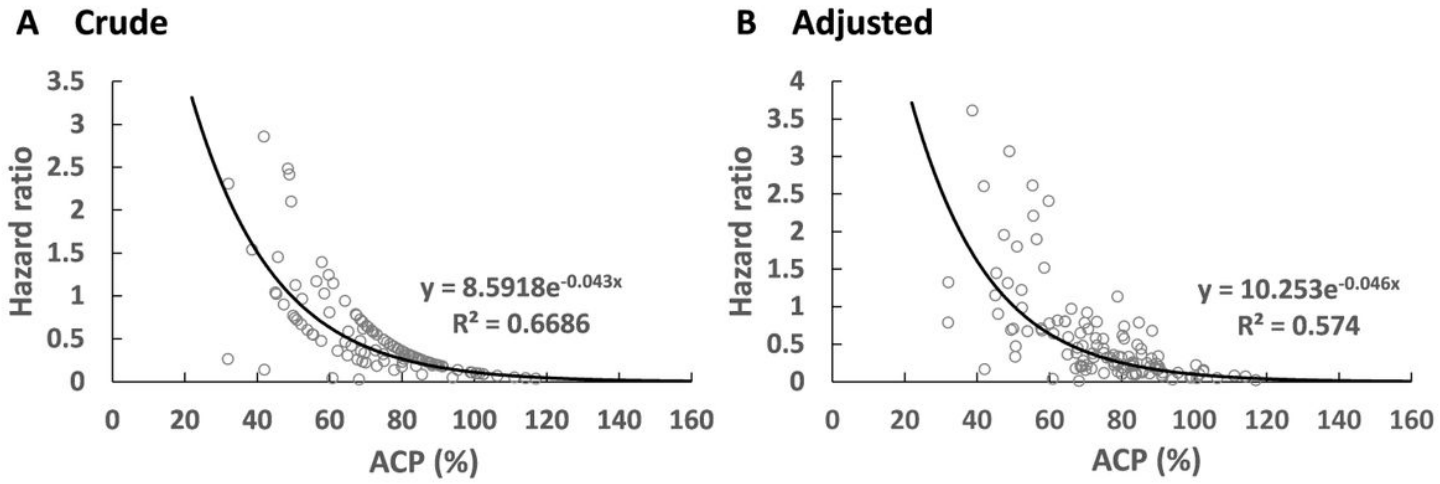

Figure 3

Cox proportional hazards regression analyses of 7-day mortality according to classification of ACP12h in patients with septic shock. A, crude model; B, adjusted model, after adjustment for baseline risk of 7-day mortality (age, gender, APACHEII score, vasoactive inotropic score, lactate).

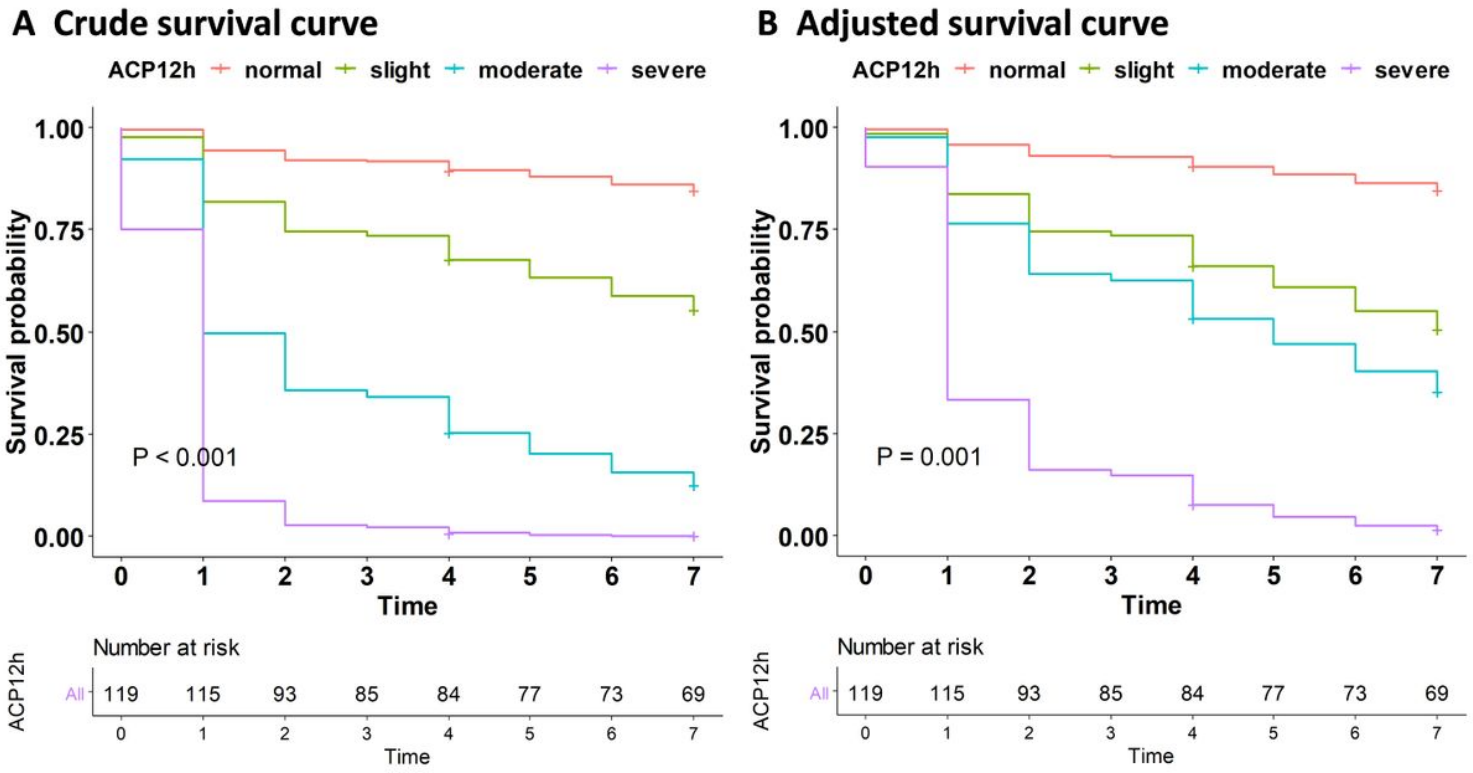

Figure 4

Correlation of ACP12h and hazard ratio of 7-day mortality in patients with septic shock. A, crude model; B, adjusted model, after adjustment for baseline risk of 7-day mortality (age, gender, APACHEII score, vasoactive inotropic score, lactate).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementfile.docx